Sataloff's Comprehensive Textbook of Otolaryngology Head & Neck Surgery

Rhinology/ Allergy and Immunology

Series Editor
Robert T Sataloff

Volume Editors
Marvin P Fried
Abtin Tabaee

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TEXTBOOK OF OTOLARYNGOLOGY
HEAD AND NECK SURGERY

Series Editor: **Robert T Sataloff** MD DMA FACS

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Vol. 2

Volume Editors

Marvin P Fried MD FACS
Professor and University Chairman
Department of Otorhinolaryngology—Head and Neck Surgery
Montefiore Medical Center
The University Hospital for Albert Einstein College of Medicine
Bronx, New York, USA

Abtin Tabaee MD FARS FACS
Associate Professor of Otolaryngology
Department of Otolaryngology
Weill Cornell Medical College
New York, New York, USA

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Jaypee Brothers Medical Publishers (P) Ltd

Headquarters
Jaypee Brothers Medical Publishers (P) Ltd.
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
E-mail: jaypee@jaypeebrothers.com

Overseas Offices
J.P. Medical Ltd.
83, Victoria Street, London
SW1H 0HW (UK)
Phone: +44-20 3170 8910
Fax: +44(0)20 3008 6180
E-mail: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc.
City of Knowledge, Bld. 237, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
E-mail: cservice@jphmedical.com

Jaypee Medical Inc.
The Bourse
111 South Independence Mall East
Suite 835
Philadelphia, PA 19106, USA
Phone: +1 267-519-9789
E-mail: jpmed.us@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.
17/1-B, Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
E-mail: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.
Bhotahity, Kathmandu, Nepal
Phone: +977-9741283608
E-mail: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

Sataloff's Comprehensive Textbook of Otolaryngology: Head and Neck Surgery: Rhinology/Allergy and Immunology (Vol. 2)

First Edition: **2016**

ISBN: 978-93-5152-456-4

Printed at

Dedication

This book is dedicated to my wife, Rita, and my daughters, Jaimie and Karen, and their families who have always been there for me. They are my foundation. To those who have taught me and have been and are my colleagues, I am truly grateful.

Marvin P Fried

It is with eternal gratitude that I dedicate this book to the nurturing guidance of my mentors, the love and support of my wife, family and friends, and most of all, to the wisdom, sacrifice and dedication of my parents. It is through their collective words and deeds that the foundations of my career and life are based.

Abtin Tabaee

Contributors

Waleed M Abuzeid MD
Assistant Professor
Department of Otolaryngology—
Head and Neck Surgery
Montefiore Medical Center and Albert
Einstein College
Bronx, New York, USA

Robert T Adelson MD
Albany ENT and Allergy
Albany, New York, USA

Mohammad Al Bar MD
University of Miami
Miller School of Medicine
Miami, Florida, USA

Jeremiah A Alt MD PhD
Assistant Professor
Division of Otolaryngology
University of Utah
Salt Lake City, Utah, USA

Vijay K Anand MD
Clinical Professor of Otolaryngology
Department of Otorhinolaryngology
Weill Medical College of Cornell
University
New York, New York, USA

Martin Anderson MD
Resident
Department of Otolaryngology
Saint Louis University
St Louis, Missouri, USA

Jastin Antisdel MD
Assistant Professor
Department of Otolaryngology
Saint Louis University
School of Medicine
St Louis, Missouri, USA

Leonardo Balsalobre MD MPH
Sao Paulo Ear, Nose, and
Throat/Skull Base Center
Complexo Hospitalar Edmundo
Vasconcelos
São Paulo, São Paulo, Brazil

Jacqueline A Bello MD
Professor of Clinical Radiology
Department of Radiology
Montefiore Medical Center and Albert
Einstein College of Medicine
Bronx, New York, USA

Michael S. Benninger MD
Chairman, Professor of Surgery
Head and Neck Institute
The Cleveland Clinic
Cleveland, Ohio, USA

Seth M Brown MD MBA FACS
Assistant Clinical Professor
Department of Surgery
Division of Otolaryngology
University of Connecticut School of
Medicine
Farmington, Connecticut, USA

Raewyn G Campbell MD
Instructor, Division of Rhinology
Department of Otorhinolaryngology—
Head and Neck Surgery
University of Pennsylvania
Philadelphia, Pennsylvania, USA

Roy R Casiano MD FACS
Professor and Vice Chairman
Department of Otolaryngology
University of Miami
Miller School of Medicine
Miami, Florida, USA

Peter J Catalano MD
Professor
Department of Otolaryngology
Tufts University
Chief of Otolaryngology
St. Elizabeth Medical Center
Boston, Massachusetts, USA

Mohamad R Chaaban MD
University of Alabama at Birmingham
Medical Director
Lanier Nasal and Sinus Institute
Birmingham, Alabama, USA

Rakesh Chandra MD
Associate Professor
Department of Otolaryngology
Vanderbilt University
Nashville, Tennessee, USA

Jerry Chao MD
Assistant Professor
Department of Anesthesiology
Montefiore Medical Center and
Albert Einstein College of Medicine
Bronx, New York, USA

Philip G Chen MD
Assistant Professor
Department of Otolaryngology—
Head and Neck Surgery
University of Texas Health Science
Center San Antonio
San Antonio, Texas, USA

Nipun Chhabra MD
Otolaryngologist, OSF Healthcare
Peoria, Illinois, USA

Alexander G Chiu MD
Professor and Chair
Department of Otolaryngology—
Head and Neck Surgery
University of Arizona
Tucson, Arizona, USA

Patrick Colley MD
Department of Otolaryngology—
Head and Neck Surgery
Mount Sinai Health Systems
New York, New York, USA

Jacquelynne P Corey MD FACS FAAOA
Professor, Department of Surgery
Section of Otolaryngology—
Head and Neck Surgery
University of Chicago
Chicago, Illinois, USA

Ryan A Crane MD
Resident, Department of
Otolaryngology—Head and Neck Surgery
University of Cincinnati
Cincinnati, Ohio, USA

Dustin M Dalgorf MD FRCSC
Clinical Lecturer
Department of Otolaryngology—
Head and Neck Surgery
University of Toronto
Toronto, Ontario, Canada

Subinoy Das MD
Adjunct Clinical Assistant Professor
Department of Otolaryngology—
Head and Neck Surgery
The Ohio State University
Columbus, Ohio, USA

Gabriele de Vos MD
Assistant Professor
Department of Medicine
Division of Allergy and Immunology
Albert Einstein College of Medicine
Bronx, New York, USA

Adam S DeConde MD
Assistant Clinical Professor
Department of Surgery
Division of Otolaryngology—
Head and Neck Surgery
University of California, San Diego
San Diego, California, USA

John M DelGaudio MD
Professor and Vice Chair
Chief of Rhinology and Sinus Surgery
Residency Program Director
Department of Otolaryngology
Emory University
Atlanta, Georgia, USA

Richard L Doty MD
Director and Professor
Smell and Taste Center
Department of Otorhinolaryngology—
Head and Neck Surgery
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania, USA

Eugenie Du MD
Resident
Department of Otorhinolaryngology—
Head and Neck Surgery
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York, USA

James Duncavage MD
Professor, Department of Otolaryngology
Vanderbilt University Medical Center
Nashville, Tennessee, USA

Jean Anderson Eloy MD FACS
Professor and Vice Chairman
Director, Rhinology and Sinus Surgery
Director, Otolaryngology Research
Co-Director, Endoscopic Skull Base
Surgery Program
Department of Otolaryngology—
Head and Neck Surgery
Rutgers New Jersey Medical School
Newark, New Jersey, USA

Joaquim Farinhas MD
Associate Professor of Clinical Radiology
Department of Radiology
Montefiore Medical Center
Bronx, New York, USA

Berrylin J Ferguson MD
Professor, Division of Sinonasal
Disorders and Allergy
Department of Otolaryngology
University of Pittsburgh School of
Medicine
Pittsburgh, Pennsylvania, USA

Juan C Fernandez-Miranda MD
Associate Professor of
Neurological Surgery
Director, Surgical Neuroanatomy Lab
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Carrie E Flanagan MD
Ear, Nose, and Throat
Andrews Air Force Base
Maryland, USA

Rebecca E Fraioli MD
Otolaryngology—Head and Neck Surgery
Montefiore Greene Medical Arts
Bronx, New York, USA

Marvin P Fried MD FACS
Professor and University Chairman
Department of Otorhinolaryngology—
Head and Neck Surgery
Montefiore Medical Center
The University Hospital for Albert
Einstein College of Medicine
Bronx, New York, USA

Mark E Friedel MD MPH
Clinical Associate
Department of Otorhinolaryngology
University of Pennsylvania
Advanced Ear, Nose and Throat
Voorhees, New Jersey, USA

Paul A Gardner MD
Assistant Professor of
Neurological Surgery
Director, Center for Skull Base Surgery
University of Pittsburgh
School of Medicine
Pittsburgh, Pennsylvania, USA

Jamie L Gentile MD
Resident Physician
Department of Otolaryngology—
Head and Neck Surgery
University of Cincinnati
Cincinnati, Ohio, USA

Rachel Georgopoulos MD
Department of Otolaryngology
Temple University
Philadelphia, Pennsylvania, USA

Marc J Gibber MD
Assistant Professor
Department of Otolaryngology—
Head and Neck Surgery
Montefiore Medical Center
Bronx, New York, USA

Arel Golombeck MD
Assistant Professor
Department of Radiology
Mount Sinai Hospital
New York, New York, USA

Satish Govindaraj MD FACS
Associate Professor
Department of Otolaryngology—
Head and Neck Surgery
Icahn School of Medicine at
Mount Sinai
New York, New York, USA

Sezelle Gereau Haddon MD
Integrative Otolaryngology
Mount Sinai Beth Israel
Integrative Medicine
New York, New York, USA

Richard J Harvey MD
Professor and Program Head
Radiology and Skull Base
Applied Medical Research Center
University of New Southwest and
Macquarie University
Sydney, Australia

Samuel N Helman
Medical Student
Albert Einstein College of Medicine
Bronx, New York, USA

Brian L Hendricks MD
Resident
Department of Otolaryngology—
Head and Neck Surgery
University of Cincinnati
Cincinnati, Ohio, USA

Mira Herman MD
Resident
Department of Radiology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York, USA

Diego Rodrigo Hermann MD
Ear, Nose and Throat Surgeon
Department of Ear, Nose and
Throat and Skull Base
Centro de Otorrinolaringologia
de São Paulo
São Paulo, São Paulo, Brazil

Yan W Ho MD
Resident, Department of Otolaryngology—
Head and Neck Surgery
The Icahn School of Medicine at
Mount Sinai
New York, New York, USA

Nicole M Hsu MD
Resident, New York Presbyterian Hospital
New York, New York, USA

Peter H Hwang MD
Professor and Chief
Division of Rhinology and
Endoscopic Skull Base Surgery
Department of Otolaryngology—
Head and Neck Surgery
Stanford University School of Medicine
Stanford, California, USA

Alexis H Jackman MD
Assistant Professor
Department of Otorhinolaryngology—
Head and Neck Surgery
Albert Einstein College of Medicine/
Montefiore Medical Center
Bronx, New York, USA

Joseph B Jacobs MD
Professor
Department of Otolaryngology
New York University Langone
Medical Center
New York, New York, USA

Elina Jerschow MD
Assistant Professor
Department of Medicine
Allergy/Immunology Division
Albert Einstein College of
Medicine/Montefiore Medical Center
Bronx, New York, USA

Ashutosh Kacker MD
Professor of Clinical Otolaryngology
Department of Otolaryngology—
Head and Neck Surgery
Weill Cornell Medical College
New York, New York, USA

Azeem S Kaka MD
Resident
Department of Otolaryngology—
Head and Neck Surgery
The Ohio State University
Columbus, Ohio, USA

Rachel Kaye MD
House Staff, PGY-4
Department of
Otorhinolaryngology—
Head and Neck Surgery
Montefiore Medical Center
Bronx, New York, USA

David W Kennedy MD
Rhinology Professor
Otorhinolaryngology—
Head and Neck Surgery
Hospital of the
University of Pennsylvania
Philadelphia, Pennsylvania, USA

Robert C Kern MD
George A Sisson
Professor of Otolaryngology
Chair, Department of Otolaryngology—
Head and Neck Surgery
Professor, Otolaryngology—
Head and Neck Surgery and
Medicine-Allergy-Immunology
Northwestern University Feinberg
School of Medicine
Chicago, Illinois, USA

Osaama H Khan MD
Western Hospital, University of Toronto
Toronto, Ontario, Canada

Esther Kim MD
Walter Reed National
Military Medical Center
Bethesda, Maryland, USA

Richard A Kraut DDS
Chairman, Department of Dentistry
Montefiore Medical Center
Bronx, New York, USA

Daniel Krieger MD
Chief Resident, Department of Radiology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York, USA

John H Krouse MD PhD
Professor and Chairman
Department of Otolaryngology—
Head and Neck Surgery
Temple University
Philadelphia, Pennsylvania, USA

Arjuna B Kuperan MD
Rhinology Fellow, Department of
Otolaryngology—Head and Neck Surgery
University of Miami
Miami, Florida, USA

Jeffrey T Laitman PhD DMedSc (Hon) FAAAS FAAA FALA
Distinguished Professor
Professor and Director of Anatomy and
Functional Morphology
Professor of Otolaryngology
Professor of Medical Education
Director of Gross Anatomy
Center for Anatomy and Functional
Morphology
Icahn School of Medicine at Mount Sinai
New York, New York, USA

Kent Lam MD
Department of Otolaryngology—
Head and Neck Surgery
Northwestern University Feinberg
School of Medicine
Chicago, Illinois, USA

Andrew P Lane MD
Professor
Department of Otolaryngology—
Head and Neck Surgery
Johns Hopkins School of Medicine
Baltimore, Maryland, USA

Donald C Lanza MD MS
Director
Sinus and Nasal Institute of Florida
Foundation
Saint Petersburg, Florida, USA

Adrienne M Laury MD
Assistant Professor
Department of Otolaryngology
Brooke Army Medical Center
JBSA—Fort Sam Houston
San Antonio, Texas, USA

William Lawson MD
Professor
Department of Otolaryngology
Mount Sinai Hospital
New York, New York, USA

Jenna Le MD
Resident
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York, USA

Philip Lebowitz MD
Professor of Clinical Anesthesiology
Department of Anesthesiology
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York, USA

Richard A Lebowitz MD
Associate Professor
Department of Otolaryngology
New York University School of Medicine
New York, New York, USA

Jimmy Lee MD
Department of Ophthalmology and
Visual Sciences
Montefiore Medical Center
Bronx, New York, USA

Stella Lee MD
Assistant Professor
Department of Otolaryngology
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Seth M Lieberman MD
Assistant Professor
Department of Otolaryngology
New York University Langone
Medical Center
New York, New York, USA

Giant Lin MD
Private Practice
Mount Arlington, New Jersey, USA

Sandra Y Lin MD
Associate Professor
Department of Otolaryngology—
Head and Neck Surgery
Johns Hopkins School of Medicine
Baltimore, Maryland, USA

Patricia A Loftus MD
Resident
Department of Otorhinolaryngology—
Head and Neck Surgery
Albert Einstein College of Medicine
Bronx, New York, USA

Songhui Ma MD
Clinical Instructor
Department of Medicine
Mount Sinai School of Medicine
New York, New York, USA

Samuel Márquez MD
Assistant Professor
Department of Cell Biology
Department of Otolaryngology
SUNY Downstate Medical Center
Brooklyn, New York, USA

Andrew McClelland MD PhD
Chief Resident
Diagnostic Radiology
Residency Program
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York, USA

Edward D McCoul MD
Clinical Instructor
Department of Otolaryngology
University of Washington
Seattle, Washington, USA

Caitlin McMullen MD
Resident
Department of Otorhinolaryngology—
Head and Neck Surgery
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York, USA

Ralph Metson MD
Clinical Professor
Department of Otology and Laryngology
Harvard Medical School
Boston, Massachusetts, USA

Justine BF Millar MD
Doctor
Department of Otolaryngology
St. Vincents Hospital
Darlinghurst NSW, Australia

James W Mims MD
Associate Professor
Department of Otolaryngology
Wake Forest University School of
Medicine
Winston-Salem, North Carolina, USA

Sam P Most MD FACS
Professor
Department of Otolaryngology—
Head and Neck Surgery
Stanford University School of Medicine
Stanford, California, USA

Gurston G Nyquist MD
Assistant Professor
Department of Otolaryngology
Thomas Jefferson University
Philadelphia, Pennsylvania, USA

Richard R Orlandi MD
Professor
Division of Otolaryngology—
Head and Neck Surgery
University of Utah
Salt Lake City, Utah, USA

Whitney Pafford MD
Ear, Nose, Throat and Sinus Associates
Lima, Ohio, USA

Anthony S Pagano MD
Clinical Instructor
Mount Sinai Hospital
Icahn School of Medicine at Mount Sinai
New York, New York, USA

James N Palmer MD
Professor and Director
Division of Rhinology
Department of Otorhinolaryngology—Head and Neck Surgery
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania, USA

Purvi Parikh MD
Clinical Instructor
Department of Medicine and Pediatrics
New York University School of Medicine
New York, New York, USA

Steven Y Park MD
Assistant Professor
Department of Otorhinolaryngology
Albert Einstein College of Medicine
Bronx, New York, USA

Charles Parker MD
Resident, Department of Otolaryngology—Head and Neck Surgery
University of Cincinnati
Cincinnati, Ohio, USA

James Phillips MD
Department of Surgery
Division of Otolaryngology—Head and Neck Surgery
University of Alabama at Birmingham
Birmingham, Alabama, USA

Michael Platt MD
Boston University School of Medicine
Boston Medical Center
Boston, Massachusetts, USA

Steven D Pletcher MD
Associate Professor
Department of Otolaryngology—Head and Neck Surgery
University of California, San Francisco
San Francisco, California, USA

David M Poetker MD MA
Associate Professor
Division of Otolaryngology
Zablocki VA Medical Center
Milwaukee, Wisconsin, USA

Roheen Raithatha MD
Clinical Instructor
Department of Otolaryngology
Icahn School of Medicine at Mount Sinai
New York, New York, USA

Jeremy T Reed MD
Assistant Professor
Department of Otolaryngology
Uniformed Services University of the Health Sciences
Bethesda, Maryland, USA

Dale H Rice MD
Professor
Department of Otolaryngology—Head and Neck Surgery
University of Southern California
Los Angeles, California, USA

Kenneth Rodriguez MD
Chief of Rhinology, Allergy, and Anterior Skull Base Surgery
Department of Otolaryngology—Head and Neck Surgery
University Hospitals Case Medical Center
Assistant Professor of Otolaryngology—Head and Neck Surgery
Case Western Reserve University School of Medicine
Cleveland, Ohio, USA

Marc R Rosen MD
Professor
Department of Otolaryngology—Head and Neck Surgery and Neurological Surgery
Thomas Jefferson University
Philadelphia, Pennsylvania, USA

David L Rosenstreich MD
Professor
Departments of Medicine, Microbiology and Immunology and Otorhinolaryngology
Albert Einstein College of Medicine and Montefiore Medical Center
Bronx, New York, USA

Bradley A Schiff MD
Associate Professor
Department of Otorhinolaryngology—Head and Neck Surgery
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York, USA

Robert Schwarcz MD
Associate Adjunct Surgeon
New York Eye and Ear Infirmary of Mount Sinai
New York, New York, USA

Theodore H Schwartz MD
Professor
Neurological Surgery
Weill Cornell Medical College
New York, New York, USA

Allen M Seiden MD
Professor
Department of Otolaryngology—Head and Neck Surgery
University of Cincinnati College of Medicine
Cincinnati, Ohio, USA

Brent A Senior MD
Professor
Otolaryngology—Head and Neck Surgery
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina, USA

Michael Setzen MD
Clinical Associate Professor
Otolaryngology—Head and Neck Surgery
New York University School of Medicine
New York, New York, USA

Josef Shargorodsky MD
Coastal Ear, Nose and Throat
Jersey Shore University Medical Center
Neptune, New Jersey, USA

Raj Sindwani MD FACS FRCS(C)
Vice Chairman and Section Head
Rhinology, Sinus and Skull Base Surgery
Head and Neck Institute
The Cleveland Clinic Foundation
Cleveland, Ohio, USA

Ameet Singh MD
Assistant Professor of Surgery (Otolaryngology) and Neurosurgery
Co-Director
Endoscopic Pituitary and Skull Base Surgery
The George Washington University
Washington, DC, USA

Timothy L Smith MD MPH
Professor
Department of Otolaryngology—Head and Neck Surgery
Oregon Health and Science University
Portland, Oregon, USA

James B Snow, Jr MD
Professor
Philosophy Department
Loyola University
Baltimore, Maryland, USA

Carl H Snyderman MD MBA
Professor
Departments of Otolaryngology and Neurological Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Alla Y Solyar MD
Sinus and Nasal Institute of Florida
St. Petersburg, Florida, USA

Susan Sotardi MD
Albert Einstein College of Medicine
Bronx, New York, USA

Ari Spiro MD
Resident
Department of Radiology
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York, USA

Aldo Cassol Stamm MD
Director
Sao Paulo Ear, Nose and Throat and Skull Base
Hospital Professor Edmundo Vasconcelos
Sao Paulo, Sao Paulo, Brazil

James A Stankiewicz MD
Professor and Chair
Department of Otolaryngology—Head and Neck Surgery
Loyola University of Chicago
Chicago, Illinois, USA

Michael G Stewart MD MPH
Professor and Chairman
Weill Cornell Medical College
New York, New York, USA

Janalee K Stokken MD
Otolaryngology
Rhinology Fellow
Cleveland, Ohio, USA

Jeffrey D Suh MD
Assistant Professor
Department of Head and Neck Surgery
University of California, Los Angeles
Los Angeles, California, USA

Abtin Tabaee MD FARS FACS
Associate Professor of Otolaryngology
Department of Otolaryngology
Weill Cornell Medical College
New York, New York, USA

Brian Thorp MD
Otolaryngologist
University of North Carolina
Chapel Hill, North Carolina, USA

Elina M Toskala MD PhD
Professor
Department of Otolaryngology—Head and Neck Surgery
Temple University
Philadelphia, Pennsylvania, USA

Oscar Trujillo MD
Department of Otolaryngology—Head and Neck Surgery
Weill Cornell Medical College
New York, New York, USA

Satyen Undavia MD
Private Practice
Havertown, Pennsylvania, USA

Christopher Vanison MD
Resident Physician
Otolaryngology—Head and Neck Surgery
Northwestern Memorial Hospital
Chicago, Illinois, USA

Eduardo de Arnaldo Silva Vellutini MD
Neurosurgeon
DFV Neuro
São Paulo, São Paulo, Brazil

Andrea S Wang MD
Assistant Professor
Weill Cornell Medical College
New York, New York, USA

Eric W Wang MD
Assistant Professor
Department of Otolaryngology
University of Pittsburgh
School of Medicine
Pittsburgh, Pennsylvania, USA

Calvin C Wei MD
Department of Otolaryngology—Head and Neck Surgery
Mount Sinai St. Luke's—Roosevelt Hospital
New York, New York, USA

Sarah K Wise MD
Assistant Professor
Director of Resident Education
Otolaryngology—Head and Neck Surgery
Emory University
Atlanta, Georgia, USA

Troy Woodard MD
Department of Otolaryngology
Head and Neck Institute
The Cleveland Clinic
Cleveland, Ohio, USA

Bradford A Woodworth MD
James J. Hicks Associate Professor of Surgery
Department of Surgery
Division of Otolaryngology
University of Alabama at Birmingham
Birmingham, Alabama, USA

Peter-John Wormald MD
Professor and Chairman
Department of Otolaryngology—Head and Neck Surgery
University of Adelaide
Adelaide, South Australia, Australia

Bozena B Wrobel MD
Assistant Professor
Department of Otolaryngology—Head and Neck Surgery
University of Southern California
Los Angeles, California, USA

Whitney Zirkle MD
Chicago, Illinois, USA

Foreword

Sataloff's Comprehensive Textbook of Otolaryngology: Head and Neck Surgery is a component of the most extensive compilation of information in otolaryngology—head and neck surgery to date. The six volumes of the comprehensive textbook are part of a 12-volume, encyclopedic compendium that also includes a six-volume set of detailed, extensively illustrated atlases of otolaryngologic surgical techniques. The vision for the *Comprehensive Textbook* was realized with the invaluable, expert collaboration of eight world-class volume editors. Chapter authors include many of the most prominent otolaryngologists in the world, and coverage of each subspecialty is extensive, detailed and scholarly.

Anil K Lalwani, MD edited the volume on otology/neurotology/skull base surgery. Like all six of the volumes in the *Comprehensive Textbook*, the otology/neurotology/skull base surgery volume is designed not only as part of the multivolume book, but also to stand alone or in combination with the atlas of otological surgery. Dr Lalwani's volume covers anatomy and physiology of hearing and balance, temporal bone radiology, medical and surgical treatment of common and rare disorders of the ear and related structures, occupational hearing loss, aural rehabilitation, cochlear and brainstem implantation, disorders of the facial nerve, and other topics. Each chapter is not only replete with the latest scientific information, but also accessible and practical for clinicians.

The rhinology/allergy and immunology volume by Marvin P Fried and Abtin Tabaee is the most elegant and inclusive book on the topic to date. Drs Fried and Tabaee start with a history of rhinology beginning in ancient times. The chapters on evolution of the nose and sinuses, embryology, sinonasal anatomy and physiology, and rhinological assessment are exceptional. The volume includes discussions of virtually all sinonasal disorders and allergy, including not only traditional medical and surgical therapy but also complementary and integrative medicine. The information is state-of-the-art.

Anthony P Sclafani's volume on facial plastic and reconstructive surgery is unique in its thoroughness and practicality. The volume covers skin anatomy and physiology, principles of wound healing, physiology of grafts and flaps, lasers in facial plastic surgery, aesthetic analysis of the face and other basic topics. There are extensive discussions on essentially all problems and procedures in facial plastic and reconstructive surgery contributed by many of the most respected experts in the field. The volume includes not only cosmetic and reconstructive surgery, but also information on diagnosis and treatment of facial trauma.

The volume on laryngology edited by Dr Michael S Benninger incorporates the most current information on virtually every aspect of laryngology. The authors constitute a who's who of world experts in voice and swallowing. After extensive and practical discussions of science and genetics, the volume reviews diagnosis and treatment (traditional and complementary) of laryngological disorders. Chapters on laser physics and use, voice therapy, laryngeal dystonia, cough, vocal aging and many other topics provide invaluable "pearls" for clinicians. The volume also includes extensive discussion of surgery for airway disorders, office-based laryngeal surgery, laryngeal transplantation and other topics.

For the volume on head and neck surgery, Drs Patrick J Gullane and David P Goldstein have recruited an extraordinary group of contributors who have compiled the latest information on molecular biology of head and neck cancer, principles of radiation, immunobiology, medical oncology, common and rare head and neck malignancies, endocrine neoplasms, lymphoma, deep neck space infections and other maladies. The surgical discussions are thorough and richly illustrated, and they include definitive discussions of free flap surgery, facial transplantation and other subjects.

Dr Christopher J Hartnick's vision for the volume on pediatric otolaryngology was expansive, elegantly scholarly and invaluable clinically. The volume begins with information on embryology, anatomy, genetics, syndromes and other complex topics. Dr Hartnick's contributors include basic discussions of otolaryngologic examination in a pediatric patient, imaging, hearing screening and aural rehabilitation, and diagnosis and treatment of diseases of the ear, nose, larynx, oral cavity, neck and airway. Congenital, syndromic and acquired disorders are covered in detail, as are special, particularly vexing problems such as chronic cough in pediatric patients, breathing and obstructive sleep apnea in children, pediatric voice disorders, and many other subjects. This volume will be invaluable to any otolaryngologist who treats children.

All of us who have been involved with the creation of the six-volume *Sataloff's Comprehensive Textbook of Otolaryngology: Head and Neck Surgery* and its companion six-volume set of surgical atlases hope and believe that our colleagues will find this new offering to be not only the most extensive and convenient compilation of information in our field, but also the most clinically practical and up-to-date resource in otolaryngology. We are indebted to Mr Jitendar P Vij (Group Chairman) and Mr Ankit Vij (Group President) of M/s Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India, for their commitment to this project, and for their promise to keep this work available not only online but also in print. We are indebted also to the many otolaryngologists who have contributed to this work not only by editing volumes and writing chapters, but also by asking questions that inspired many of us to seek the answers found on these pages. We also thank especially the great academic otolaryngologists who trained us and inspired us to spend our nights, weekends and vacations writing chapters and books. We hope that our colleagues and their patients find this book useful.

Robert T Sataloff MD DMA FACS
Professor and Chairman
Department of Otolaryngology—Head and Neck Surgery
Senior Associate Dean for Clinical Academic Specialties
Drexel University College of Medicine
Philadelphia, Pennsylvania, USA

Preface

The field of rhinology has undergone a dramatic evolution in the past two decades. Landmark events that have occurred during this period include the widespread adoption of advanced technologies, the expansion of endoscopic techniques to complex skull base pathologies, and a dedicated focus on clinical and basic science research. This process has been, in large part, fueled by the increasing sub-specialization of the field, including the continued growth of fellowship programs and clinician-scientists dedicated to rhinology.

As the breadth of the field has expanded, so too have our horizons. It is interesting that the trends in rhinology have moved in different directions for various aspects of the field. For example, the indications and capabilities of endoscopic approaches for skull base tumors have increasingly expanded; at the same time, there has been a greater interest in minimally invasive techniques for inflammatory sinusitis, including balloon dilation technology. Integral to the development of novel surgical techniques and technology is a greater emphasis on a more holistic approach to surgical outcome analysis, including an emphasis on patient-scored quality-of-life measures. In parallel, the striking increase in the number and quality of basic science research articles is beginning to address fundamental questions, including the pathophysiologic basis of inflammatory sinusitis. This is an exciting time in rhinology as the field collectively looks back on its recent advances and towards the future to the remaining unanswered questions.

In creating this volume, our primary goal has been to provide a comprehensive reference for the field of rhinology, including the fundamental underpinnings of anatomy, physiology, and radiology; a practical approach to the evaluation of patient with sinonasal disorders; a description of the full spectrum of rhinologic disorders, including the different subtypes of rhinitis and sinusitis; and a comprehensive approach to medical and surgical management of sinonasal disorders. Sections reviewing sinonasal malignancy, trauma, and cosmetic rhinoplasty can be found in the volumes dedicated to these disorders. Advanced surgical techniques are discussed in detail, including indications, techniques, and outcomes. We have also included thought-provoking chapters on the history and future of rhinology, current models of rhinology training, and practical aspects of practice management.

We are fortunate to have a dynamic and storied list of authors, each with an exceptional level of expertise and wisdom. Their individual contributions to this volume have helped to create a seminal reference for the field of rhinology.

Marvin P Fried MD FACS
Abtin Tabaee MD FARS FACS

Acknowledgments

The editors would like to thank Joseph Rusko, Marco Ulloa, Carol Rogers Field, Bridget Meyer, Thomas Gibbons and the rest of the Jaypee Brothers team. Without their perseverance and hard work, this volume would not have been possible. Special thanks are offered to the authors, who have shared their expertise and experience in order to improve the care of rhinology/allergy and immunology patients.

We would also like to thank Mr Jitendar P Vij (Group Chairman), Mr Ankit Vij (Group President), Ms Chetna Malhotra Vohra (Associate Director), Mr Umar Rashid (Development Editor) and Production team of Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India.

Contents

SECTION 1

History of Rhinology

CHAPTER

The History of Rhinology—From Ancient Times to the 21st Century

1

Patrick Colley, Marvin P Fried, Abtin Tabaee

Medicine is defined by a continuous stream of innovation and evolution. As such, change, often for better, at times for worse, is a fundamental feature of its history. In reviewing our collective understanding of the nose and paranasal sinuses from ancient times to the present, several general themes emerge. Advances throughout history have often reflected the cultural and disease-related needs of the civilization at that time. For example, detailed descriptions of treatment for syphilis-related ozena are prominent throughout the preantibiotic history of medicine. An additional theme is the propagation of concepts that are ultimately disproven by divergent thinkers including seminal concepts in physiology and anatomy. Further, the major diagnostic and treatment advances in medicine have had successful application to nasal and paranasal sinus disorders. This includes microscopy, anesthesia, radiography, and antimicrobial therapy. Finally, technology has been a major force in the development of rhinologic surgeries, especially over the past century. The adage that in order to know where you are going, you must first know where you came from has truth in the field of rhinology whose history is colored with innovation, misdirection, and evolution.

ANCIENT HISTORY

Interest in the nose and the diseases that affect it has puzzled human civilizations throughout history. Ancient Persian writings note that male noses with a "hawk type" appearance resembling that of King Cyrus were admired. The Huns during the age of Attila routinely used bandages to flatten the noses of their infants. The Old Testament comments on prejudices against "flat-nosed people."[1] Conditions such as nasal polyps, ozena, and epistaxis have plagued people of all civilizations since the first medical documents were written. Our knowledge about the anatomy and pathology of the nose has progressed over the centuries resulting in the current field of modern rhinology.

The ancient Egyptians were the first to demonstrate an understanding of the nasal anatomy and its surrounding structures. Egyptian papyri from 3500 BC shows that specially trained priests in charge of the embalming process were the first to access the brain through a transnasal technique; the brains of the deceased were removed through the nasal cavity using specially designed instruments. This precursor to the transnasal approach to the intracranial cavity shows the detailed anatomic knowledge of the ancient Egyptians. This civilization also provides information on the earliest historical figure who performed the role of a physician in approximately 3500 BC. Engraving on the pharaoh Sahura's tomb states that an attendant named Sekhet' enanch "healed the King's nostils."[2-4]

While the Egyptians were using the nose as a means of accessing the brain, the Hindus were also investigating the function and physiology of the nose. The Hindu document *Sushruta Samhita* provides the first detailed description of a nasal exam. It was written before the sixth century BC and notes a nasal speculum made of bamboo tree.[3,5] The Hindus developed multiple treatments for diseases of the head and neck and noted their findings in a document known as the *Sanskrit Atharvaveda*. In this document, they describe surgeries to remove nasal polyps and reconstructive techniques for nasal injury and

amputation, a common form of punishment at the time. Surgeons used local flaps from the cheek and forehead to reconstruct these defects and in doing so were the first to describe several important aspects of rhinoplasty and reconstruction still in use today.[3,4]

The ancient Chinese civilizations were using traditional eastern medical practices such as acupuncture to treat many nasal conditions. The Chinese also used their pharmacologic knowledge to provide relief to individuals with nasal congestion with a small shrub endemic to their area known as ma huang. This herb was documented to be an effective stimulant and nasal decongestant during the Han Dynasty in the second century AD.[1,6] It was not until the 19th century that the active chemical in ma huang, ephedrine, was discovered and produced commercially.

Nasal ailments are even described in religious texts including the Bible. In 2 Kings 4:35, the phenomenon of sneezing is described. Treatment of epistaxis using hemlock or other plant remedies is also detailed. "Lord God formed man of the dust of the ground and breathed into his nostrils the breath of life" (Genesis 2:7) represents one of the first documented references to the respiratory function of the nose.[7]

ANCIENT GREECE AND ROME

The "Father of Medicine," Hippocrates, wrote extensively about nasal disorders in the 5th century BC including management of nasal fractures, polyps, and epistaxis. Nasal trauma was commonplace during the time of Hippocrates in both Greek athletes and soldiers. For mildly displaced fractures, Hippocrates recommended lifting the fragments of bone and cartilage back into place within the first 24–36 hours after injury and using bandages and internal stents made of leather to keep the reduced fragments in the proper position. He detailed the use of a large external splint made of olive tree branches or a leather thong that would be tied around the head and kept in place using glue in order to reduce severely displaced nasal fractures. Hippocrates also wrote detailed descriptions of his methods of removing nasal polyps. This technique consisted of tying several sponges along a string, placing them deep into the nose or nasopharynx and slowly pulling them out in the hopes of removing the polyps along with the sponges. He was also the first to describe polyp removal using a snare.[4,8] These techniques were revolutionary for their time and were practiced well into the 19th century.

The Romans played a large role in advancing medical knowledge and the study of rhinology. A Roman nobleman by the name of Aulus Cornelius Celsus is believed to have documented the extent of Roman medical knowledge during the first century AD in his eight volume encyclopedia, *De Medicina*. These eight volumes are all that survived from a much larger collection. They were discovered in the papal library in the early 15th century AD and published in 1478. His work details information regarding diet, pharmacology, and surgery practiced in the Roman Empire. Celsus is the first to note the four cardinal signs of inflammation: dolor, calor, rubor, and tumor. He translated the work of his Greek predecessor Hippocrates and became the first person to use the Latin term *cancer* to refer to a malignant lesion.[4] It is unclear whether he was a practicing physician himself, but he documented medical treatments and often provided his opinion on the subject. In his works, he described the, "two nasal passages separated by an intermediate bone." Like many other physicians or anatomists of the time, Celsus believed that, "these passages break up into two branches, one for respiration and one leading to the brain through which we get our sense of smell." His treatment for nasal polyposis involved both the use of caustic material and surgical removal. Using specially designed instruments including a spatula shaped rod and a sickle knife or hook, he located and severed the stalk of the polyp prior to removal. Celsus also made the first note of a unified airway when he discussed lung infections possibly originating from the contents of the nasal cavities.[9]

Approximately two centuries after Celsus, another Roman played a large role in the advancement of medicine and rhinology. Claudius Galenus was a physician in the 2nd century AD who advanced medical knowledge and anatomy in such a major way that many of his theories were taught in medical schools until the 18th century (Fig. 1.1). His dissections of pigs and monkeys provided detailed information regarding many areas in anatomy, in particular the upper respiratory tract. He provided anatomic descriptions of the external and internal portions of the nose and continued the theory of the nose acting as the beginning of the respiratory tract. Galen divided nasal disease into two general categories: polyps and ozena. He noted the proximity of the nose and sinuses to the brain and believed that the sinuses contained fluid and mucus produced by the brain and pituitary gland. These fluids were thought to be waste products excreted by the brain. The work of these Greek and Roman physicians provided the basis for the study of medicine and rhinology for the next 1000 years.[4,10]

Fig. 1.1: Second century AD physician, Claudius Galenus, played a large role in advancing the medical and anatomic knowledge of the nose and paranasal sinuses.
Courtesy: National Library of Medicine.

THE ITALIAN RENAISSANCE

Progress in the study of rhinology, and in medicine in general, slowed during the early Middle Ages. During this period, most physicians believed that the function of the paranasal sinuses was to store oils used to lubricate the eyes or to function as drainage space for malignant spirits. As late as the 16th century, names such as "la cloaca del cerebro" were given to the sinuses demonstrating the continuation of this belief. Although not discovered until 1901, Leonardo da Vinci drew the nasal conchae and paranasal sinuses in detail in 1489.[1] Andreas Vesalius described the anatomy of the nasal bones, nasal cartilage, choanae and maxillary, sphenoid, and frontal sinuses in his landmark publication *De humani corporis fabrica* in 1543.[11] He also notes that these sinuses are air filled and not full of humor or spirits. Bartholomeus Eustachius, another anatomist of the time, played a large role in advancing rhinology and otolaryngology by describing most of the structures within the middle ear. In his 1562 treatise *Epistola de auditus organis (Examination of the Organ of Hearing)*, he described a tube that "originates at the anterior portion of the base of the skull, and takes an anterior course towards the pterygoid process of the sphenoid bone."[12] Although the function of the Eustachian tube was not completely understood at the time, the renewed emphasis on the study of medicine and the human body during the Renaissance laid the groundwork for advancements that would take place in medicine in the years to come.

Gaspare Tagliacozzi (1545–1599) made an impact during this time period through the publication of his book *Treaty on Rhinoplasty*. In it, he detailed the "Italian method" of rhinoplasty that differed from the "Indian method" that was detailed in *Sushruta Samhita* years earlier. Tagliacozzi developed pedicled flaps from the upper extremities and shaped them to cover the nasal defects. The upper extremity was then bandaged in an elevated position for approximately 20 days before the pedicle was transected and the transferred skin was trimmed to its final shape (Fig. 1.2).[13]

Other important European anatomists and physicians of the time also played a role in advancing the treatment of diseases affecting the nose. Gabriel Fallopius wrote in detail regarding his use of a wire snare to remove nasal polyps.[14] Petrus Forestus, known as the "Hollandic Hippocrates" claims in his 1591 text *Observationum et Curationum Medicinalium Libri* to have cured a girl of ozena by copious nasal douching "with perfumed white wine in which were dissolved cypress, roses and myrrh." In this same text, Forestus also treats ozena with silver nitrate and alum rubbed up with honey and applied with a probe. He was one of the first physicians to detail the findings in patients with nasal syphilis and notes that they should be treated differently than lesions of other etiologies.[15] Another European physician practicing at the same time as Forestus was Hieronymus Fabricius. He described treatment of intranasal ulcers secondary to ozena using cautery by a "glowing hot instrument." The cautery was to be continued until the area "was thoroughly cleansed of crusts."[1]

EUROPE 17TH–19TH CENTURIES

During the 17th century, physicians and anatomists made major strides in describing the function of the nose and

Fig. 1.2: Italian surgeon Gaspare Tagliacozzi designed pedicled flaps from the upper extremities for use in reconstruction of the nose.
Courtesy: National Library of Medicine.

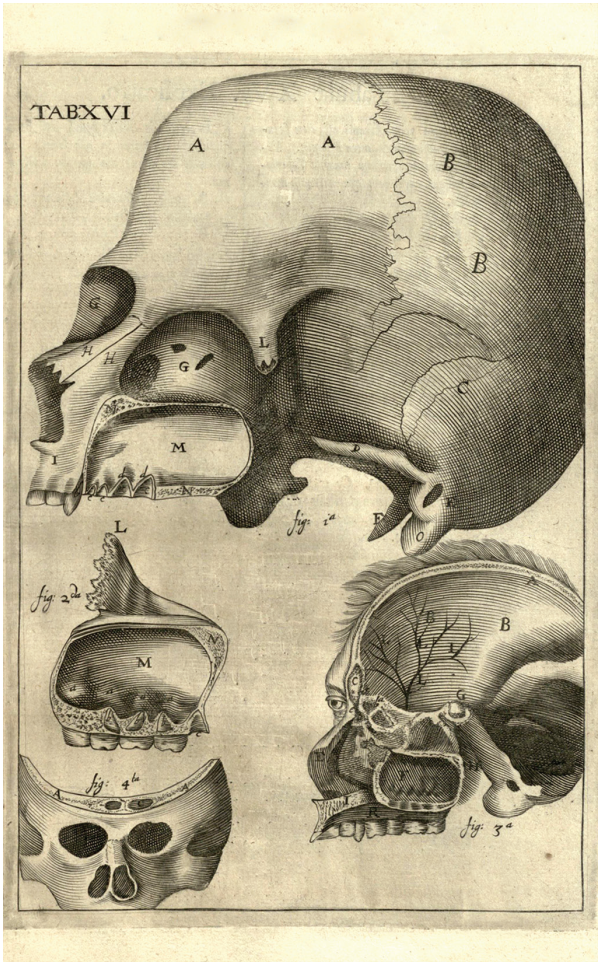

Fig. 1.3: An engraving from the British surgeon and anatomist Nathaniel Highmore's treatise *Corporis Humani Disquisitio Anatomica* detailing the anatomy of the maxillary sinus and antrum.
Courtesy: New York Academy of Medicine.

paranasal sinuses. Until this time, the belief that nasal mucus and secretions were actually "purgings of the brain" dominated most medical teachings. These secretions were believed to percolate through the bony foramina of the anterior skull base to enter the nasal cavity. Conditions such as halitosis or facial acne were associated with the nose and paranasal sinuses. The recommended treatment of such conditions was total or partial middle turbinectomy.[4]

In 1651, the British surgeon and anatomist Nathaniel Highmore published his treatise *Corporis Humani Disquisitio Anatomica* in which he described and illustrated the antrum of the maxillary sinus, a structure that later became known as Highmore's antrum (Fig. 1.3). Highmore also became the first person to use the term *ostomy* to refer to an opening made to permanently drain an organ.[16] Ten years after Highmore published his work, a German physician named Conrad Victor Schneider made the assertion that nasal secretions did not come from the cranial cavity. In his published treatise on the membranes of the nose, *De Catarrhis*, Schneider stated that nasal secretions actually originated from the mucous membranes of the nose and sinuses.[17] This change of belief would have important implications for future rhinologists.

In 1707, two English physicians named James Drake and William Cowper published a medical treatise *Antropologica Nova* in which they described multiple cases of halitosis caused by suppuration of the maxillary sinus. This suppuration was relieved by removal of maxillary teeth creating an oral antral fistula that allowed drainage of the sinus through the alveolus.[18] In 1768, French surgeon Louis Lamorier described a similar method of

draining the maxillary sinuses. After its description, Lamorier's transalveolar technique remained the procedure of choice for the treatment of maxillary sinus suppuration for nearly a century.[19] An 1889 paper by Dr. Joseph H Bryam, one of the four founding physicians of the Episcopal Eye, Ear and Throat Hospital of Washington DC, notes that the best surgical method to drain an abscess of the maxillary sinus is to remove a molar tooth and perforate into the antrum through the alveolus.[20]

A new technique of accessing the maxillary sinus was developed by Charles Joseph Heath of London in 1889 and William Robertson of Newcastle–on-Tyne in 1892. It involved trephination of the anterior maxillary wall and removal of all sinus contents.[21] In 1893, George Walter Caldwell, a physician in New York, published his method of opening the maxillary sinus using trephination of the anterior maxillary wall. However, Caldwell also created an inferior antrostomy through the lateral nasal wall.[22] At roughly the same time as Caldwell described his technique, the French physician Luc independently reported his technique for opening the maxillary sinus using a nearly identical technique to Caldwell's.[23] This surgical technique became known as the Caldwell–Luc operation and remains in practice to this day.[24,25]

In addition to surgical developments in rhinology, the 19th century also heralded vast leaps in our understanding of the histology, physiology, and anatomy of the nose and sinuses. The development of the microscope in the 1830s allowed individuals like Rudolph Virchow and Friedrich Henle of Germany along with J.F.L Deschamps of France to study the epithelia of the nose and sinuses. Henle provided detailed descriptions of the different types of epithelia. He also first noted the function of the ciliated epithelium found throughout the upper respiratory tract.[4,26] In 1870, Emil Zuckerkandl of Austria published an extremely detailed anatomic and pathologic descriptions of the paranasal sinuses. Other anatomists such as L. Grunwald of Munich, M. Hajek of Austria, Adolf Onodi of Hungary, and Harris Mosher of Boston also contributed to the rapidly growing fund on rhinology knowledge.[4]

Technology was also developing rapidly during this era. The rhinologic exam became much more informative and accurate following German physician Phillip Bozzini's creation of endoscopy in 1806 (Fig. 1.4).[27] In addition to developing laryngoscopy, Czech physician Johann Czermak further improved the nasal exam by promoting the use of the nasal speculum, head mirror with reflected light, and endoscope in 1879.[28] Following the discovery of the analgesic properties of cocaine by Carl Koller of Austria in 1884, these tools contributed greatly to the surgical and anatomic teachings of physicians.[4]

Fig. 1.4: The endoscopic light source developed by German physician Philip Bozzini involved candle light reflected by a mirror into the endoscope.
Courtesy: National Library of Medicine.

With these new tools in hand, surgeons began to develop new treatments for old ailments. In 1893, Charles Henry Burnett of Philadelphia detailed a number of conditions that he believed were due to hypertrophy of the inferior turbinates and recommended inferior turbinectomy as an effective treatment. These conditions all related to "nasal stenosis" and consisted of habitual mouth breathing, rhinorrhea, excessive nasal mucous, serous otitis media, obstruction of the lacrimal duct, nasopharyngitis, laryngeal hyperemia, laryngitis, and secondary lung disease.[29] Others such as D. Braden Kyle[30] and Chevalier Jackson[31] of Philadelphia along with William Jarvis of New York supported this procedure and its benefits. As a result of the popularity of inferior turbinectomies, investigators in the United States and Europe evaluated nasal

airflow patterns and developed anterior and posterior rhinomanometric methods still in use today.[32-36]

The understanding and treatment of nasal polyps improved during the 19th century as well. As far back as the times of Galen (200 AD), nasal polyps were believed to be "a constitutional disease due to the state of the humors of the body." They were treated with knotted thread, caustic agents, and snare ligation.[37-39] Deschamps was one of the first people to describe nasal polyps as a local disease of the nasal and sinus mucosa. He developed a classification system for nasal polyps consisting of "fungous and vascular, mucous and lymphatic, scirrhous, and sarcomatous."[26] The Austrian surgeon Theodore Billroth later described nasal polyps as adenomatous in nature while Virchow called them myxomata. Treatment of these lesions improved due to the use of the endoscope, nasal speculum, and topical anesthetics such as cocaine. Due to its effectiveness, the primary method of polyp removal remained the wire snare. While the design of this instrument improved during the 19th century, it still relied on principles present for hundreds of years.[4]

In 1881, Dr. Francke Bosworth of New York City published one of the first otolaryngology textbooks, *A Textbook of Diseases of the Nose and Throat*. In it, he details a multitude of pathologies affecting the nose and discusses how these can affect the entire body. He provides descriptions of thorough nasal exams and demonstrates an impressive understanding of nasal and sinus anatomy. Dr. Bosworth is often referred to as the "Father of Rhinology" in North America due to his extensive work on the subject.[40,41]

Besides Dr. Bosworth, many other American physicians of the 19th century advanced the field of rhinology. Drs. Morris Asch,[41] Fletcher Ingals,[42] Robert Weir[44], and John Rowe[43] played large roles in the development of new nasal surgery techniques. These "early rhinologists" were all part of the American Laryngological Association, a group formed in 1878 to promote knowledge "in all that pertains to the diseases of the upper air passages." This interest in rhinology as well as laryngology and otology grew to such an extent that specialty eye and ear hospitals opened in New York (1820) followed by hospitals in Philadelphia and Boston.[4]

THE 20TH CENTURY

The beginning of the 20th century continued the rapid progression of rhinology seen in the previous century. This progression was largely due to advancements in surgical techniques that allowed for more effective treatment of nasal ailments. Drs. Otto "Tiger" Freer and Gustav Kilian built on septal surgery techniques taught by Ephraim Ingals of Chicago 20 years earlier and developed the submucous resection of the nasal septum.[45] To aid in this procedure, Freer produced new surgical instruments including new nasal speculae, rasps, scissors, knives, forceps and elevators. He published extensively on this procedure and described the areas of the septum that can be safely resected, proper postoperative follow up, the proper use of cocaine, and post-operative packing. It is noteworthy that Freer's surgical teachings and instruments remain in use today.[46-48] At the same time that Freer was publishing his works in Chicago, Killian of Germany developed a similar method of submucous septal resection that yielded comparable results. Freer and Kilian's work quickly turned septal surgery into a popular procedure performed by rhinologists throughout North America and Europe.[49-51] This popularity lead others to further refine the technique, develop new instruments and decrease the operative time. During this time, most nasal surgeries were performed under local anesthesia using cocaine or epinephrine that did not allow for long procedures. Freer claimed to require 45 minutes to complete his procedure.[52] William Ballenger's invention of the swivel knife and John Mackenty's technique for application of local anesthetic reduced to average operative time for a submucous nasal septal resection to 20-30 minutes by 1908.[53]

Septal surgery was not the only rhinologic procedure that took leaps forward during this century. Surgery on the ethmoid and sphenoid sinuses was developed in the early 20th century by Albert Jansen. His transantral route to the ethmoid and sphenoid sinuses relied on the widely taught Caldwell-Luc procedure to provide access to the lateral nasal wall. Mosher, a prominent anatomist and physician in Boston, noted that this route was effective in treating "combined empyema of the antrum, ethmoid region and the sphenoid."[54] However, Jansen's procedure required removal of the majority of the lateral nasal wall including the middle and inferior turbinates that likely resulted in significant atrophic rhinitis. This led to the procedure falling out of favor among many rhinologists.[55,56]

In 1912, Mosher published one of the first descriptions of an intranasal method of performing an ethmoidectomy. The procedure required wide exenteration of the labyrinth and complete removal of the middle turbinate. This wide dissection performed through a small nasal cavity lead

others to question the safety of this method of ethmoidectomy.[57] Mosher eventually became disenchanted with this procedure and in 1929 noted that "it has proved to be one of the easiest operations with which to kill a patient."[58] In response to the poor success rate of intranasal and transantral access to the ethmoid sinuses, Robert Lynch of New Orleans[59] and W. Howarth of London[60] described external approaches to these sinuses that did not leave unsightly scars or bony deformities. The Lynch frontoethmoidectomy provided a safe and relatively effective method of opening and treating the anterior ethmoid and frontal sinuses. Mucosal flaps and stents were also developed in the hopes of improving the patency of the frontoethmoid recess but none of them were used with any success.[61]

In order to treat patients who did not receive relief from their frontal sinus disease after a Lynch procedure, rhinologists of the time developed external approaches to this sinus. Originally, these procedures led to defects in the anterior table and left unsightly scars. However, a new technique developed by Howard Lothrop of Boston in 1917 allowed for treatment of frontal sinus disease with minimal aesthetic impact. Lothrop developed a method to bypass the nonfunctional frontal sinus by removing the inter-sinus septum and frontal floor to allow sinus contents to drain through the opposite side.[62,63] In 1964, Robert Goodale and William Montgomery of Boston combined the osteoplastic flap with fat obliteration of the frontal sinuses to treat chronic frontal sinus disease.[64] This technique became the treatment of choice for chronic frontal sinus disease for many years afterwards.

Another common surgical technique that developed in the early 20th century was the inferior meatus antrostomy. This procedure was promoted by Jan Mikulicz-Radecki of Austria and Lothrop for the treatment of chronic maxillary sinusitis.[65] Critics of the time did not like that it did not remove the diseased mucosa of the sinus. However, poorly controlled rabbit model studies conducted by A. C. Hilding suggested that the natural ostium of the maxillary sinus should not be surgically altered.[66] This misinformation influenced the rhinology community for over 40 years until it was finally disproven by Messerklinger.[67-70]

In addition to surgical advancements, the 20th century let to technologic advancements that benefitted the field of rhinology. The first of these was radiography. Cornelius Coakley of New York City was the first otolaryngologist to report using this new equipment. He described how he was able to diagnose frontal sinus disease using a posterior-anterior view with an exposure time of 3.5 minutes.[71] The Waters, Caldwell, and lateral views were all in use by 1915 and played a major role in the diagnosis of sinus disease before computed tomography was developed.[72,73] According to Stammberger, the lack of detail found in these early radiographs likely delayed the understanding of the complex surgical sinus anatomy.[4]

In addition to radiology, advancements in nasal endoscopy were coming about during the mid-20th century. Although the first endoscope had been invented in 1801 by Bozzini, it was not frequently used by physicians due to poor visualization and illumination. Endoscopic examinations were limited to the peritoneum and bladder. In 1853, French physician Antonin D'Esormeux demonstrated an alcohol illuminated urethroscope. Following the development of electricity, distal illumination improved significantly that led Max Nitze of Germany and Joseph Leiter of Austria to develop the Nitze–Leiter cystoscope. Using a modified version of this instrument, E. Zaufal examined the Eustachian tube orifice during the 1880s. Twenty years later, Alfred Hirschmann of Germany described the first nasal endoscopy using a special 4.0 mm diameter endoscope. He examined the middle meatus and maxillary sinus ostia through the nose as well as via the molar tooth socket. Roughly at this same time, M Reichert, also of Germany, described minor manipulation of sinus tissue using endoscopy. However, Hirschmann's and Reichert's advancements and their possible applications to the field of rhinology were ignored for the next six decades. Harold Hopkins of England designed the modern endoscope 1948. He drew influence from the work of John Baird earlier in the century who patented the transmission of images through glass fibers. Over the next two decades, Hopkins and German manufacturers improved endoscope technology to provide a precise, detailed picture. Using Hopkin's new technology, surgeons of the day slowly began performing more endoscopic examinations and eventually surgical procedures.[74-77]

Important figures in rhinology were plentiful early in the century. Arthur Proetz, an otolaryngology professor at Washington University, wrote his thesis entitled "The Displacement Method of Sinus Diagnosis and Treatment." In this thesis Proetz describes using sophisticated equipment and head positions to diagnose and treat an array of sinus conditions. For his work, Proetz was awarded the Castlebury Prize from the American Laryngological Association in 1931.[78-81] Ten years later, Professor Van Alyea of Chicago authored a legendary textbook entitled "Nasal Sinuses." In the book, he details information about nasal anatomy

Fig. 1.5: Maurice Cottle was a founding member and the first president of the American Rhinologic Society. His teaching and leadership in the field of rhinology spurred its growth that led to his nickname "the father of rhinology."

and physiology as well as the role that allergy may play in sinus disease. The book discusses newer concepts such as the mucociliary blanket, mucosal information and the role of new medications known as antibiotics in the treatment of sinusitis.[82]

Maurice Cottle of Chicago is often referred to as the "rhinologist of the century" for his work in this field and his dedication to its advancement (Fig. 1.5). He is considered to have restored rhinology to the same prominence as laryngology and otology. Dr. Cottle is known as a great educator who taught his functional approach to nasal and sinus surgery at his lecture series beginning in 1944. The series became known as "Cottle courses" and soon attracted specialists from around the country.[4] It was at one of these courses at Johns Hopkins Hospital in 1954 that the American Rhinologic Society (ARS) was formed and Dr. Cottle was elected the first president of the group. His leadership and mentoring helped the ARS flourish and grow from a somewhat small group of practitioners to a robust academic society with a strong presence in the otolaryngology community. Although the interests of the ARS originally concerned the structure and function of the nose, the advent of nasal endoscopy and surgery shifted its focus towards disease of the paranasal sinuses and skull base. The development of the ARS spurred the academic study of diseases affecting the paranasal sinuses and aided in the dissemination of effective endoscopic surgical techniques for the treatment of these conditions.[83]

In the latter half of the 20th century, pioneers such as Walter Messerklinger of Austria entered the field of rhinology and embraced the new technology and concepts introduced earlier in the century. Endoscopes developed by Hopkins were refined by German manufactures and provided significantly better visualization of the nasal cavity and sinuses than previous versions. Messerklinger was the first person to use these endoscopes to examine and treat sinus disorders.[84] He provided detailed endoscopic anatomy using this new technology and opened the gates for other pioneers to follow. David Kennedy from Johns Hopkins,[85] Heinz Stammberger of Austria,[70] and Wolfgang Draf of Germany[4] built on these concepts and further developed modern endoscopic sinus surgery. Their work showed the importance of mucociliary function and detailed the need for proper antrostomies in the treatment of chronic rhinosinusitis.

The rapid evolution of endoscopic sinus surgery also required development of new surgical instruments and other supportive technologies. The removal of only diseased mucosa and sparring of normal tissue required through cutting and power instrumentation. These instruments allowed for precise cutting of mucosal edges in order to avoid stripping mucosa and exposing the underlying bone.[86] Computed tomography, developed by Geoffrey Hounsfield in 1969 allowed for improved preoperative visualization of complex sinus anatomy and aided in the diagnosis and treatment of sinusitis. Improvements in computed tomography lead to the development of intraoperative image guidance navigation. These systems were developed to satisfy a clinical need for better intraoperative orientation and localization. Modern navigation technologies are based on stereotactic systems developed for neurosurgery.[87]

As endoscopic surgery progressed, rhinologists began pushing the boundaries of indications and pathologies for transnasal surgery. Endoscopic septoplasty and endoscopic ligation of the sphenopalatine artery for refractory epistaxis became commonly performed procedures. Transnasal endoscopic orbital procedures such as endoscopic dacryocystorhinostomy and orbital decompressions for optic neuropathy and Graves' disease were developed. Based on the work of Draf and others, frontal sinus surgery evolved from primarily an open procedure

into one with multiple methods of endoscopic treatment.[4] The increase in endoscopic sinonasal surgery naturally lead some rhinologists and neurosurgeons to begin to explore the application of this new technology to the field of neurosurgery. Gerard Guiot of France with Karl Bushe and E. Halves of Germany reported the first use of a transnasal endoscope to access a pituitary lesion in 1970.[88] Over two decades later, Hae-Dong Jho and Ricardo Carrau from Pittsburgh published their first series using strictly endonasal transsphenoidal approach to resect pituitary tumors.[89] Their success led others to develop methods of accessing and treating anterior skull base, clival, and infratemporal fossa lesions.

Mirroring the paradigm shifts that have occurred throughout the history of rhinology, the past quarter of a century has refined our understanding of the pathophysiology of sinusitis. The disease began to be viewed not just as an infectious process but also the result of an inflammatory process within the mucosa itself. Mediators of inflammation such as cytokines and interleukins became targets of research and potential intervention.[90-92] The role of eosinophils in chronic sinusitis and the destructive inflammatory contents that they release became better understood.[93] Bent et al. detailed the pathogenesis of allergic fungal sinusitis.[94] Multiple research groups described the bacteriostatic role nitrous oxide plays within the paranasal sinuses.[95] Others showed that this substance that is naturally found in high concentrations within the sinuses also has antiviral properties and upregulates mucociliary activity.

The end of the 20th century and the beginning of the 21st century saw many changes in the medical management of sinusitis due to the improved understanding of its pathophysiology. Evidence supporting a polymicrobial etiology of chronic rhinosinusitis became more prevalent and the role of bacterial biofilms began to be investigated.[96] Antimicrobial therapy remained the mainstay of treatment for both acute and chronic sinus disease. However, treatment methods directed at inflammation took on a larger role in the management of chronic sinusitis.[97]

In addition to improved basic science research into the pathophysiology of chronic sinusitis, the 21st century also witnessed an emphasis on patient-centered quality of life measures in defining treatment outcomes in rhinosinusitis. Using psychometrically validated questionnaires and large patient databases, a more robust measure of treatment intervention and impact of comorbidities has become available.[98,99] As patient databases grow and researchers abilities to analyze information improve, rhinologists are sure to refine their treatments methods even further to the benefit of the millions of patients with sinus disease.

The history of rhinology can be traced back to the earliest cultures on earth. Our understanding of the anatomy and pathologies in this field has advanced steadily over the past 3 millennia leading to the fevered pace of study that has taken place in the last four decades. As more information is discovered, more questions arise. Research directed at the pathophysiology and treatment of sinus disease, collaborative dissemination of information, and technological advances will continue to advance the field of rhinology.

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SECTION 2

Embryology, Anatomy and Physiology

CHAPTER

Evolution of the Human Nasal Respiratory Tract: Nose and Paranasal Sinuses

2

Samuel Márquez, Anthony S Pagano, William Lawson, Jeffrey T Laitman

INTRODUCTION

From our humble beginnings as lobe-finned fish to our current role as the dominant species on planet Earth, the nasal cavity has been at the forefront of our evolutionary story. It is not a single unit but rather a composite structure with several developmental and evolutionary origins. These have each undergone considerable change, especially among the early mammals and during the rise of the primates. The modern human nasal cavity is thus the product of many millions of years of adaptation and preadaptation to novel functional demands. It is through the study of this evolutionary past that one may gain a deeper understanding of disease etiology and malformations of the nasal cavity and related structures. This chapter will focus on nasal evolution among humans and the nonhuman primates from the primitive mammalian condition to our extremely specialized anatomy.

In conceptualizing the human nasal cavity, one must understand its composite origins. That is, the external nasal vestibule, nasal cavity floor, lower and upper conchae, cribriform plate, and choanae all arose at separate times and in relation to varied functional demands. Indeed, this complicated evolutionary history is reflected in the various functions performed by the modern human nasal complex, which acts directly in the transport and conditioning of respiratory airflow, olfaction, the perception of flavor in food, production of nitric oxide gas (in the paranasal sinuses), and regulation of brain temperature via the pterygoid plexus of veins. It also serves several passive functions as the nasal cavity floor both braces against masticatory stresses and allows proper suckling by infants (achieved through complete separation of the nasal and oral cavities) while the cartilaginous Eustachian tube and soft palate attach to its posterior wall and floor, respectively.

SEGMENTATION AND THE BEGINNINGS OF THE PREOTIC HEAD

A discussion of the evolutionary origins of the various components comprising the nasal complex may best begin with head segmentation. Among the earliest to consider head segmentation was Goethe in a series of unpublished letters. His argument was later elaborated in several formally published works.[49,51,93] Early authors held that the entirety of the axial skeleton and its soft tissues, including the head, grows from iterative segments. The skull was believed to have formed from modified vertebra and, as described by Owen,[94] was derived from as many as four separate cranial vertebrae. Huxley[62] later challenged this paradigm, citing that only the anterior two thirds of the skull grow from the notochord (which is the main embryologic progenitor of the vertebral column) and that several basicranial cartilages remain unsegmented and continuous throughout vertebrate growth (reviewed by Northcutt[91]).

By the time of Goodrich,[52] discussion of head segmentation no longer centered on cranial vertebrae, but rather on series of somites and pharyngeal arches. He argued that the three anterior-most somites contribute to the preotic skull (mostly the facial skeleton) while the posterior four are successively associated with developing branchial

arches and cranial nerves. This paper is important in contributing to the modern concept of skull segmentation over gastrulation and distinguishing between the preotic and periotic divisions. These roughly correspond to the division observable in the nasopharyngeal wall between the anterior and posterior portions, which are distinct in anatomy, histology, and development.

Gans and Northcutt[48] later proposed separate evolutionary origins for the pre- and postotic portions of the vertebrate skull. The former was derived from a series of sensory adaptations for active predation, developing exclusively from neural crest cells while ectodermal placodes contribute to the development of the sensory organs and some nerves. The vertebrate skull was thus an ectodermal addition to the basic protochordate body plan (with the notochord progressing only as anterior as the basicranial fenestra). The distinct origins of the elements composing the anterior and posterior nasopharyngeal walls may thus be as old as the appearance of the first vertebrates.

The developmental evidence cited by Gans and Northcutt[48] were corroborated by Couly et al.[27] who mapped the fates of neural crest, somitic, and mesodermal cells in the cranial development of the chicken. Tissue grafts were taken from quail embryos and implanted into chicken embryos between E8 and E12 (the 8th and 12th days of embryological growth, respectively). It was determined that the splanchnocranium, mandible, frontal bone, and parietal bones were all derived from neural crest cells. The sphenoid was divided into an anterior neural crest-derived half and a posterior mesoderm-derived half. The otic capsule was shown to contain elements from all three sources. These results favor the "new head" hypothesis of Gans and Northcutt[48] by confirming the neural crest origin of the prechordal skeleton and by describing the separate developmental trajectories of areas corresponding to the anterior and posterior nasopharyngeal walls.

Further evolutionary depth is given to the division of the pre- and postotic head in a synthesis by Baker and Bronner-Fraser.[4] They argue that the homologs of vertebrate neural crest cells and ectodermal placodes may be present in nonvertebrate chordates such as the cephalochordates, which are classified in the subphylum Chordata and are defined by the presence of a notochord that persists throughout the life of the organism (e.g. lancelets). These possible homologs are ectodermally derived and tend to migrate over development. It is also argued that homologs for the neural crest and placodes may be found in the neural cords of enterpneust worms, which are considered good models for the condition of the last common ancestor of all chordates.

BEGINNINGS OF THE NASAL CAVITY PROPER: IMPORTANCE OF THE CHOANAE

Fossil evidence suggests that the presence of choanae may have been among the earliest occurring synapomorphies (i.e. a shared derived trait) characterizing the tetrapods.[63] Panchen and Smithson[97] gave the first formal anatomical definition of ancestral tetrapodomorph choanae (i.e. four-limbed tetrapods) as being constrained laterally by the premaxilla and/or maxilla and medially by the vomer. The osteolepiformes, a group of fossil lobe-finned fish likely related to stem tetrapods, share synapomorphic choanal morphology with tetrapods but predated the earliest known terrestrial vertebrates by approximately 30 million years.[63] This condition is distinct from most fishes, which possess a pair of anterior and posterior nostrils on the external snout.

von Bischoff[8] first described the presence of choanae in the lungfishes and grouped them with amphibians. They were considered excellent models for the respiratory morphology of early tetrapods as they appeared intermediate in morphology between the amphibians and fishes. Lungfishes exhibit choanal morphology similar to that seen in the primitive tetrapod condition, as spaces that communicate between the nasal sac and oral cavity (Fig. 2.1). However, a nasopharynx *sensu stricto* may not be found in lungfish or ancestral tetrapods including lobe-finned fishes as no distinct airway is present. The communicative channel between the anterior and posterior nares remains, as in most fishes, an olfactory pathway lined with specialized epithelia (*see* the description by Derivot[37]). These are used specifically for olfaction in aquatic environments and are closed off during air swallowing by specialized valves.[37] As can be inferred from modern lungfish, air breathing animals that lack a means of nasal respiration may engage in an activity known as air swallowing (*see* description and review by Smith[124]) in which air is passed to the lungs through the mouth. Given the antiquity of the choanae and their function in lungfish, it appears that these apertures may not have evolved as respiratory pathways. Indeed, choanae are absent among the African lungfish (*Polypterus*), which instead exhibits a primitive nasopalatal duct.[2]

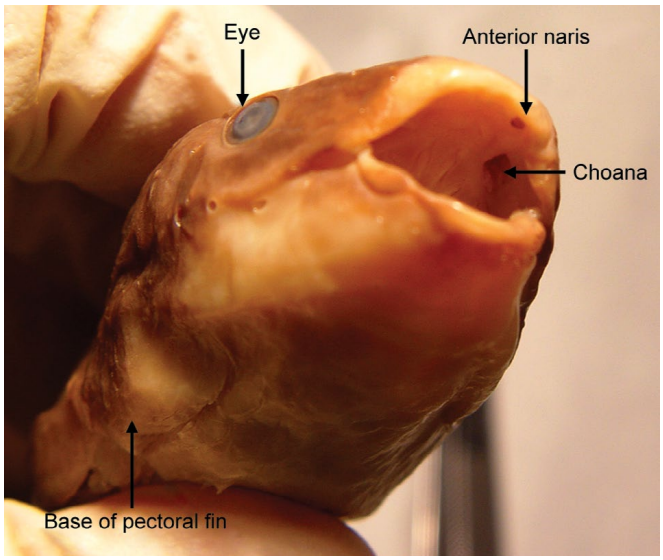


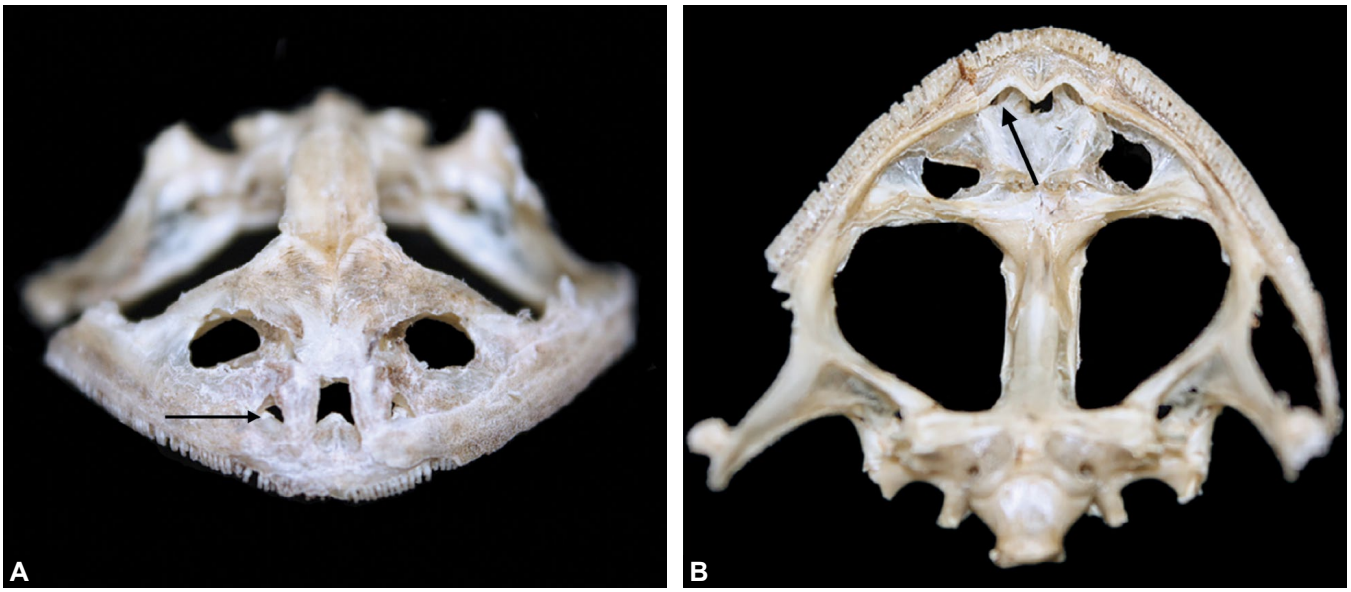
Fig. 2.1: Above is an Australian lungfish (*Neoceratodus forsteri*) exposing its oral cavity. Note that the choanae open ventrally into the hard palate. This is not a respiratory airway as the lungfish passes inspiratory air directly through its oral cavity. Rather, the nasal cavity houses specialized olfactory epithelia that function in aquatic environments. Photograph of specimen catalog # 55451, Group 7, from the Division of Ichthyology at the American Museum of Natural History, Collection of Fishes.
Courtesy: Anthony S. Pagano, Icahn School of Medicine at Mount Sinai, NY, USA.

The phylogenetic polarity of the lungfish choanae has long been debated.[142] The choanata was erected by Save-Soderbergh[112] as a taxonomic group including all tetrapods, lungfishes, and lobe-finned fishes that possessed choanae or choana-like apertures, which communicate with the palate. Similarly, Romer[108] proposed the inclusion of all choanate fishes into the taxon Choanichthyes. Rosen et al.[109] were some of the most recent authors to suggest that lungfish choanae are homologous to those of tetrapods. Yet, despite the presence of gross similarities, evidence from both the fossil record and cladistic analysis suggest that the ancestors of the modern lungfish may have homoplastically (i.e. independently) evolved choanae. Chang[22] first described *Diabolepis*, an extinct lungfish that exhibits the primitive piscine morphology of both an anterior and posterior set of nostrils that did not communicate with the oral cavity. In addition, a primitive piscine configuration of the maxillary nerve occurs in which it runs medial to the posterior nasal aperture among extant and extinct representatives of the lungfish. It has been displaced even further medially from its ancestral position by the migration of the posterior nostril into the oral cavity over lungfish evolution.[63]

Zhu and Ahlberg[142] were the first to describe a genus (*Kenichthys*) that exhibited a morphology intermediate between that of fishes and tetrapods, in which the choanae were present at the junction of the maxilla and premaxilla. It evolved as a displaced posterior external nostril, which was redirected ventrally from its primitive position on the snout to the lateral edge of the maxilla. These choanae are more laterally located than those of early tetrapods but clearly differ from the primitive piscine morphology. In addition, the maxillary nerve is located lateral to the choanae, a synapomorphy with tetrapods and their osteolepiform relatives.[63] The evidence suggests that the anatomical configuration of the tetrapod choanae (arguably the earliest aspect of the nasopharyngeal boundaries to evolve) may have resembled *Kenichthys*, first evolving from the standard posterior nostril bounding the piscine nasal sac and later migrating to a position on the palate. The palatine choanae of early tetrapods also appears similar to the condition seen during human embryologic growth, potentially serving as a resume of evolutionary history (as per Crelin[28]).

Amphibians

The earliest land tetrapods were probably amphibians.[25,77] Modern amphibians are extremely specialized relative to the first land tetrapods, which possessed dermal plates overlying the skull and lacked occipital condyles, among other primitive traits expressed in common with their piscine ancestors.[25] Nonetheless, they maintained choanae that communicate between the nasal cavity and oral cavity, which allowed them to pass air through the external nares and nasal cavity into the oral cavity via the inferiorly oriented choanae (Figs. 2.2A and B). Once air reached the oral cavity, they may have used a bucchal pump system similar to modern anurans (frogs) in which the inspired air is pumped downward toward a nearly intraoral glottis by specialized pharyngeal muscles. There is thus no nasopharyngeal airway among amphibians as they lack clear postnasal separation between the airway and alimentary tract. The nasal cavity itself is an anteroposteriorly closed sac bounded by the external nares superiorly and the choanae inferiorly in most amphibians.[99] Anurans possess the most intricate of amphibian nasal cavities; they are multichambered with at least one nasal concha and separate areas for respiratory air conditioning, olfaction, and the potential homolog of the vomeronasal organ.[92,99] The only known terrestrial tetrapod to possess completely



Figs. 2.2A and B: (A) Frontal view of a bullfrog (*Rana catesbeiana*) with the right anterior naris indicated by a black arrow. (B) Basal view of the same specimen with the right choana indicated by a black arrow. Note that the choanae exit into the oral cavity.
Courtesy: Joy S. Reidenberg, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

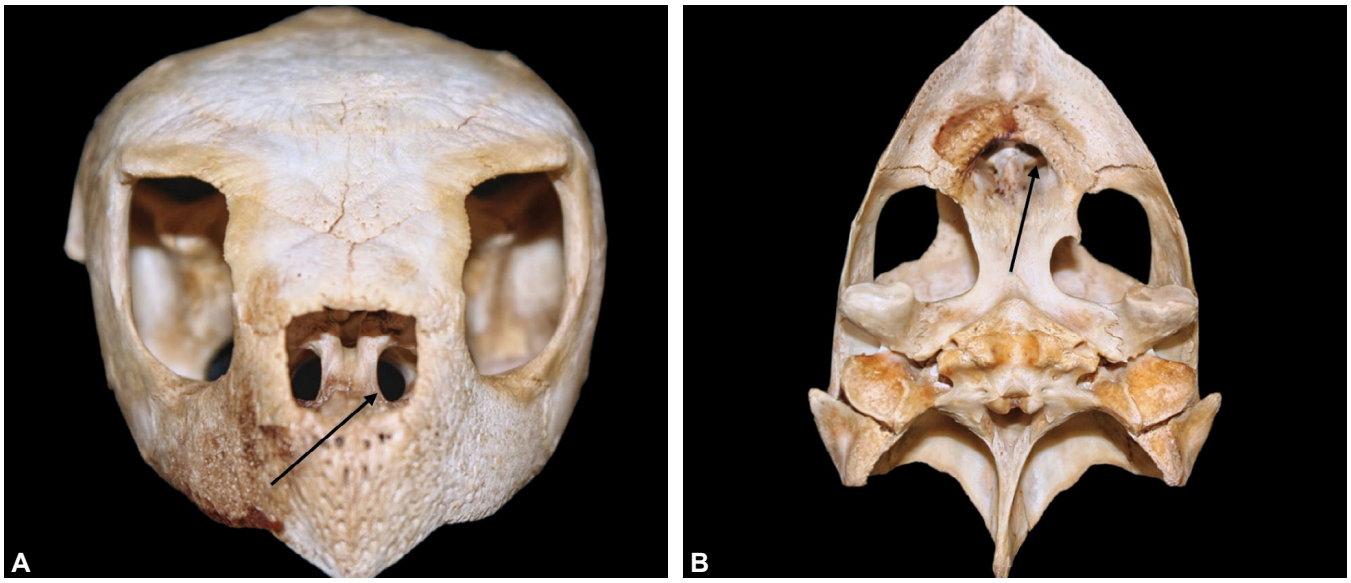
occluded choanae as part of its adult morphology is *Atretochoana eiselti*, a large lungless salamander from the cold, mountain habitats of the Andean highlands.[136] It conducts respiration solely through specialized epithelia over its skin, much like other members of the Plethodontidae (i.e. the family of lungless salamanders).

JUMPING FORWARD IN TIME: EVOLUTION OF THE SECONDARY PALATE

Among most reptiles, as in the amphibians, there is no nasopharyngeal space sensu stricto. Rather, the choanae end in the oral cavity, opening between the parasphenoid wings and epipterygoid bone at the roof of the alimentary tract.[59] The pterygoid plates are ventrally oriented and located far from the choanae, which lay anteriorly at the junction of the primary and secondary palate derivatives between the premaxilla and maxilla (Figs. 2.3A and B). As per Fuchs'[47] classic description of reptilian nasal embryology, the nasopharyngal duct is defined as the posterior ending of a space overlying a well-developed secondary palate as seen in the Crocodilia and mammals but not in most extant reptiles, which lack this structure. Parsons,[98] however, used the term more broadly to describe the area of the cavum nasi leading into the choanae in all reptiles.

The mammalian nasal cavity can arguably be identified as having arisen with the appearance of the secondary palate present among the earliest cynodonts (early mammal-like reptiles). It has been argued that a transversal ligament spanning between the tubercles of the vomer and the vomerine processes of the maxillae on either side ventrally covered the choanae to create a ligamentous precursor of the secondary palate.[5,13,15,30,79,127] Barghusen[5] and Maier et al.[79] argue that the development of this palatal precursor within the common ancestors of therocephalians and cynodonts (early, mammal-like reptiles) was tied to the development of bony choanal crests to anchor fleshy choanal folds capable of separating the nasal cavity from the oral cavity. These choanal crests were believed to be the precursor of the osseous portion of the secondary palate.[5] Maier et al.[79] suggest that this was an adaptation to carnivory, which allowed for the continued patency of the airway during deglutition of large meat boluses, which could not be reduced via mastication as no shearing or occluding postcanine dentition had yet evolved among early therocephalians and cynodonts.

In addition to alimentation, other functional demands may have influenced the evolution of the mammalian secondary palate. Our highly specialized morphology may be defined by the presence of an elongated, composite (primary and secondary) hard palate, and velum along with well-defined pharyngeal constrictor musculature.



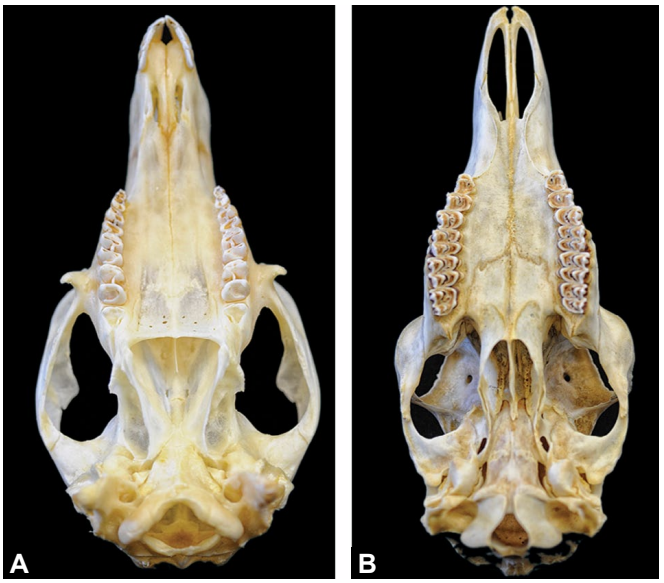
Figs. 2.3A and B: (A) Frontal view of a sea turtle (Lepidochelys sp.) with the enlarged choanal opening visible through the anterior naris (arrow on left choanal communication). (B) A basal view of the same specimen illustrating the position of the choanae opening into the oral cavity (black arrow indicating the position of the left choana).
Courtesy: Joy S. Reidenberg, Icahn School of Medicine at Mount Sinai, New York, NY, USA. Photograph by Samuel Marquez and Anthony S. Pagano.

The former trait likely evolved alongside a differentiated nasal cavity containing an olfactory recess (a probable adaptation for heightened olfactory acuity) separated from a nasopharyngeal duct inferiorly by a transverse ethmoidal lamina. In addition, this specialized morphology may have evolved to allow more efficient suckling among neonates.[79] Proper suckling is mediated by the induction of negative pressure in the oral cavity, which must be completely separated from the nasal cavity. Such separation is normally achieved via the passive action of the hard palate and active contraction of the velar and pharyngeal constrictor muscles, which can separate the nasopharynx from communication with the alimentary tract. The functional importance of this mechanism is demonstrated in cases of cleft palate infants who exhibit insufficient separation of the oral and nasal cavities, thus rendering normal suckling difficult.[24,107]

Despite the presence of choanal crests and a secondary palate among therodonts (a group of early mammals), the choanae are ventrally oriented and the pterygoid plates do not appear to border the choanae laterally. It is not until the Triassic period among early anomodont mammals such as the dicynodonts that truly posteriorly oriented choanae are observable. In *Kombuisia*, the choanae take on an elongated, funnel-shaped appearance with the pterygoid element at the caudal end of a long process of the palatine bone (see figures within Frobisch[46]). The choanae among early anomodonts are primarily bounded by the palatine bones as in the therodonts, although the position of the pterygoid element in the former group may signify a transition to the choanal morphology of extant mammals (Figs. 2.4A and B).

Distinguishing Primates—Microsmatic Versus Macrosmatic

Among mammals, primates are a decidedly derived (i.e. departing from the primitive mammalian condition) order in many aspects of cranial and postcranial anatomy. This may be reflected in the century-old debate on their proper classification and the traits that distinguish them from other archontons such as *Tupaia* (the tree shrew). However, within the order Primates, strepsirhines (i.e. lemurs and lorises) exhibit primitive morphology in aspects of the face and upper respiratory tract related to olfactory acuity, a condition called macrosmia. A major feature distinguishing macrosmatic mammalian species is the percentage of the nasal airway that is covered by olfactory epithelium (OE). In rodents, OE covers a relatively large area of the nasal cavity and confers greater olfactory acuity than among monkeys and humans, who possess



Figs. 2.4A and B: Basal views of a red kangaroo (Macropus rufus) (A) and whitetail deer (Odocoileus virgineanus) (B). Note the location of the choanae is posterior and superior to the hard palate, even among distantly related mammals. This creates a separation of oral and nasal cavities not present among reptiles. *Courtesy*: Joy S. Reidenberg, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

OE only on the superior-most reaches of the nasal cavity walls.[55] In a histological examination of the nasal region of F344 rats (i.e. Fischer laboratory rodents that exhibit good reproductive performance, big litters, and low level of aggression toward their handlers) Gross et al.[54] found OE covering about 50% of their nasal cavity. In contrast, Sorokin[125] found that neuropeithelium covered 500 mm^2 in the human nasal cavity, comprising only 3% of its total surface area. Primates, such as the haplorhines (tarsiers, monkeys, apes, and humans), lack these specializations and are thus considered microsmatic. This division has long been discussed in relation to morphological variation in the primate nose.[18,19,20,120,132] Although there is currently no reliable histological criterion for distinguishing macrosmatic primates from microsmatic ones,[119,121] certain soft tissue and skeletal features of the nasal cavity tend to distinguish these two groups.

Morphologically, macrosmats often possess a rhinarium (i.e. wet nose), a patent nasopalatine duct serving as the entrance to the vomeronasal organ, greater cover of the lateral nasal wall by OE, and a greater number of ethmoturbinals that are vertically arrayed and separated from respiratory air flow by a posterior transverse lamina or lamina transversalis posterior,[20,120] otherwise known as the "schlussplatte" of Zuckerkandl.[143] At the end of this recess lies the vertically oriented cribriform plate. A "nasopharyngeal duct"[123] is created in the space between the posterior transverse lamina and the hard palate, which ends in a vertically reduced (compared with haplorhines) choanal opening. The medial pterygoid plates usually take on an elongated, funnel-shaped appearance as in other nonprimate mammals, which may be a structural consequence of a long, narrow rostrum, and nasopharyngeal duct. These features are shared among most placental mammals and suggest that the earliest representatives of the order Primates exhibited skeletal traits related to the enhancement of olfactory acuity, which are absent among most haplorrhines. However, some haplorhines have been shown to exhibit a high degree of olfactory acuity, necessitating caution when inferring sensorial abilities from gross anatomy.[18,120]

Relative to most generally macrosmatic strepsirhines, microsmatic haplorhines are characterized by a dry external nose covered in skin, an anteroposteriorly shorter hard palate and nasal cavity, a reduced lamina transversalis posterior, a weakly defined or absent olfactory recess, fewer ethmoturbinals (usually two), reduction of the nasoturbinal (the agger nasi of humans), and choanal apertures not bounded anteriorly by a nasopharyngeal duct.[120] Accompanying relative foreshortening of the rostrum and nasal cavity, the medial pterygoid plates reach laterally at a relatively obtuse angle with the posterior hard palate. The choanae take on a tall, narrow appearance and are variably angled anteroinferiorly.

Accompanying these traits is orbital convergence, frontation, and retraction of the nasal cavity under the forebrain, which characterizes anthropoids relative to other primates (discounting the highly specialized orbital morphology of *Tarsius*). Ross and Ravosa[110] argue that orbital convergence among haplorhines renders facial, nasal, orbital, and anterior cerebral morphology part of a single functional unit so that, when any of these structures undergoes morphologic change, it influences basicranial flexion to a greater degree than among the strepsirhines. They measured internal basicranial flexion (angle made at the intersection of the lines connecting the planum sphenoideum with the occipital clivus) from lateral plain-film radiographs of a diverse sample of nonhuman haplorhine and strepsirhine primate crania. It was found that, among haplorhines, basicranial flexion was positively and significantly ($p < 0.05$) correlated with angle of

facial kyphosis (the angle made between the intersection of the lines connecting the palatal plane and the occipital clivus) and orbital axis orientation (angle made at the intersection of lines passing through the midpoint of the orbital cavity and the occipital clivus). It was also shown to be negatively correlated with encephalization (the cube root of endocranial volume scaled over the length of the basicranial axis). Thus, a pattern emerges in which the anthropoids exhibit a reduction of conchal complexity and the recessus olfactorius alongside changes in brain size, orbital orientation, basicranial flexion, and facial orientation from their more primitive ancestors. The nasal cavity may also be seen as one of several cranial functional units, which may exhibit integration with other such units.

Differences Among Anthropoids

The skeletally microsmic haplorhines are conventionally divided into platyrrhines (New World monkeys) and catarrhines (Old World monkeys, apes, and humans) based, in part, on nasal morphology. The former group may be characterized by widely separated, anteriorly facing nares, whereas the latter possess closely approximated, inferiorly directed nares. The fetal growth of the external nose has been studied by Maier[78] who traces this difference to morphology of the cupulae nasi, or the cartilage-lined, anterior-most extent of the nasal capsule. Platyrrhines express primitively broad nasal cupulae during fetal growth, which result in the widely separated, anteriorly oriented nares observable in postnatal life. Catarrhines, however, exhibit narrow nasal cupulae as fetuses, eventually resulting in narrow, inferiorly facing nares.[78]

Differences between the platyrrhines and catarrhines may also be found in the internal nasal cavity. The former have a more strongly expressed olfactory recess and a better expressed (albeit reduced from the strepsirhine condition) vomeronasal organ.[61,80,122] They also retain primitively (relative to catarrhines) well-expressed marginoturbinals and atrioturbinals. As among the more primitive insectivores, the marginoturbinal of strepsirhines begins at the nasal roof and communicates between the piriform aperture margin and maxilloturbinal via the atrioturbinal. These were described by Maier[78] as anchoring a muscle that attaches it to a posterior (cartilaginous) alar process, ultimately dividing inspiratory airflow at the nasal cavity entrance between a superior olfactory area and an inferior, strictly respiratory area. Among Old World monkeys, the marginoturbinal is not in contact with the maxilloturbinal but rather appears as a separate turbinal bone. Hominoids (i.e. apes and humans) appear to exhibit a remnant of a marginoturbinal during fetal life, which may persist as a weakly expressed protrusion into adulthood. Maier[80] argues that the possession of well-expressed atrioturbinals and marginoturbinals during fetal life followed by loss or reduction in adulthood is a defining trait of catarrhines.

Hominoids (apes and humans) are distinct from most Old World monkeys in the orientation of the ethmoturbinals, which are horizontally arrayed rather than the vertical orientation characterizing most other primates.[80] This may be related to reduction in prognathism and a trend in shifting the facial skeleton farther under the forebrain. Indeed, the superior-most extent of the pre-maxillary-maxillary suture is located at the distal-most boundary of the nasal bone or at the piriform aperture rim among hominoids, whereas Old World monkeys exhibit a contact point more superiorly by the frontal bone articulation or midway on the lateral edge of the nasal bone.[102] The hominoid configuration suggests a reduction in the premaxilla and overall facial length, which is observable even among the earliest fossil apes who still exhibited primitive, monkey-like postcranial skeletal traits.[102] Horizontal orientation of the ethmoturbinals may thus accompany a large-scale change in nasal cavity architecture and airflow dynamics.

Unlike most other anthropoid taxa, nearly all Old World monkeys lack any true paranasal sinuses, instead exhibiting recesses that have not undergone secondary pneumatization by nasal epithelia (sensu[19,80]). The one exception is the genus *Macaca*, which has been argued to have independently evolved the expression of maxillary sinuses.[103] Most hominoids (humans and apes) and platyrrhines do exhibit true paranasal sinuses with at least a maxillary sinus.[19,21,89,111] However, Rossie[111] argues that some platyrrhines exhibit sinuses that, based on apomorphic (unique to that species) developmental patterns, are not homologous (that is, not inherited from a common ancestor).

Although the processes and patterns of hominoid skull pneumatization are not fully understood, the presence and extent to which these air-containing spaces invade the bony elements of the cranium has been an important consideration of hominoid phylogenetic analysis. As is well known, modern humans exhibit all four paranasal sinuses: the maxillary, frontal, sphenoid, and ethmoid (Figs. 2.5 and 2.6). It should be noted that the human ethmoid sinus system is composed of 2 to 12 distinct air

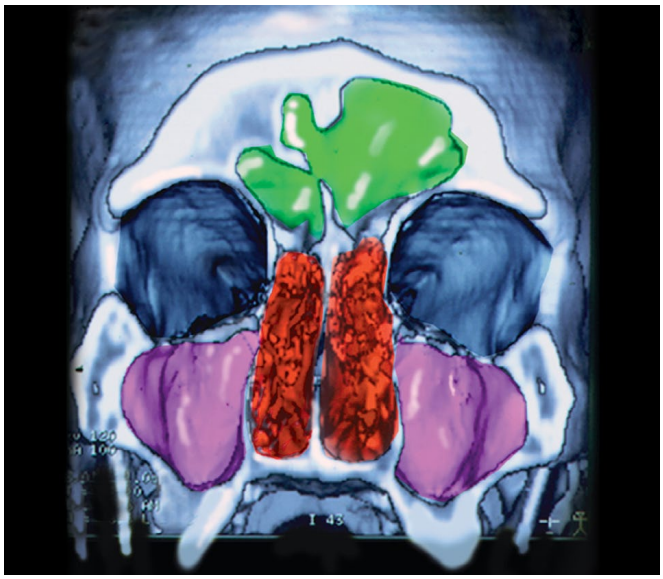


Fig. 2.5: Frontal view of a 3-D computed tomography reconstruction of an adult male human (author SM) showing the topographical relationship between frontal sinus (seen in green) and maxillary sinus (seen in purple) to the nasal cavity proper (seen in red); note the characteristic asymmetry in frontal sinus morphology. The maxillary sinus is the largest of the four paranasal sinuses exhibited by humans and dominates the midfacial architectural space. Sphenoid sinuses are not visible in this coronal plane.

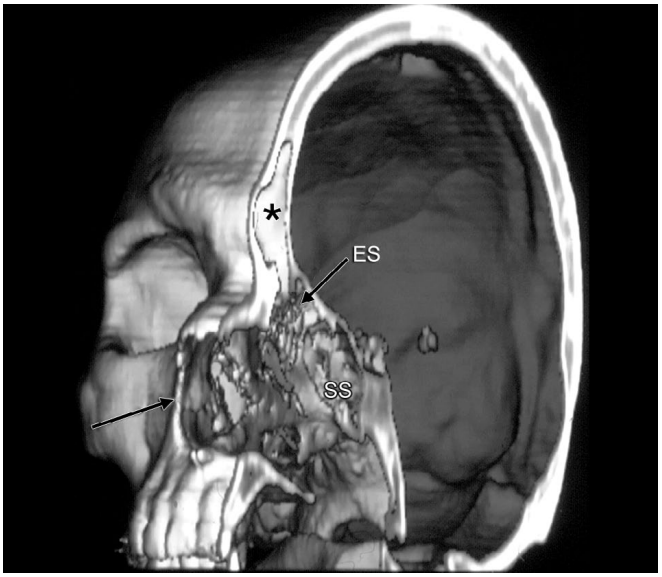


Fig. 2.6: A 3-D computed tomography reconstruction of the same individual in Figure 2.5 shown in oblique parasagittal view where ethmoid (ES) and sphenoid air sinuses (SS) can be viewed. The black asterisk indicates the frontal sinus and the black arrow is pointing to the piriform aperture rim where, just posterior to it, is the site of attachment of the inferior turbinate.

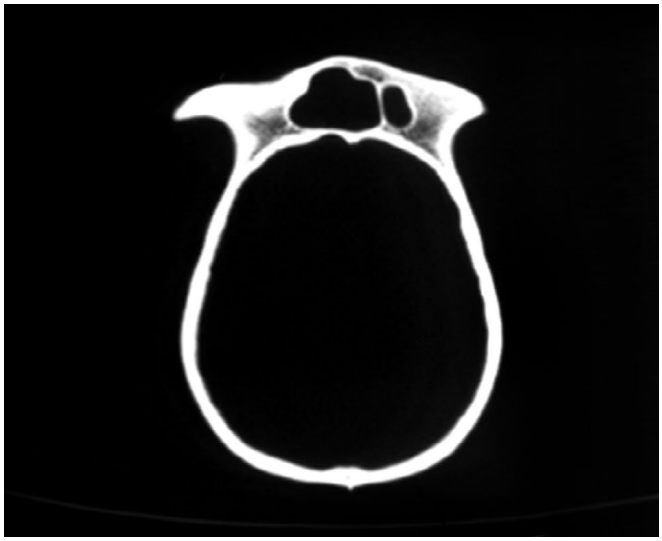


Fig. 2.7: An axial computed tomography scan showing the asymmetric frontal sinuses of the chimpanzee. This individual exhibits an enlarged right frontal sinus.

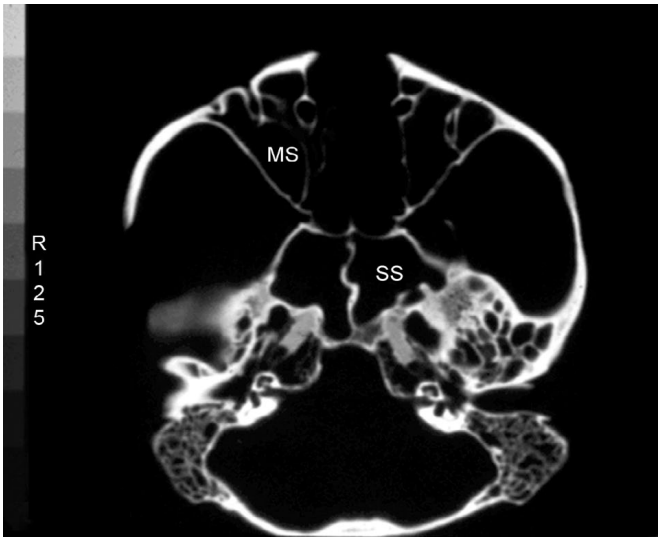


Fig. 2.8: An axial computed tomography scan of a chimpanzee cranium demonstrating distinct maxillary sinuses (MS) and sphenoid sinuses (SS).

cells on each side, making it somewhat distinct from the other paranasal sinuses.[82,83,86] A CT examination of living ape skulls selected from the Division of Anthropology of the American Museum of Natural History found a maxillary sinus present in all three genera of chimp, gorilla, and orangutan (*see* Figs. 2.7 to 2.10). These findings corroborate previous reports on ape sinonasal anatomy.[21,68] The ethmoid sinus system is well developed among

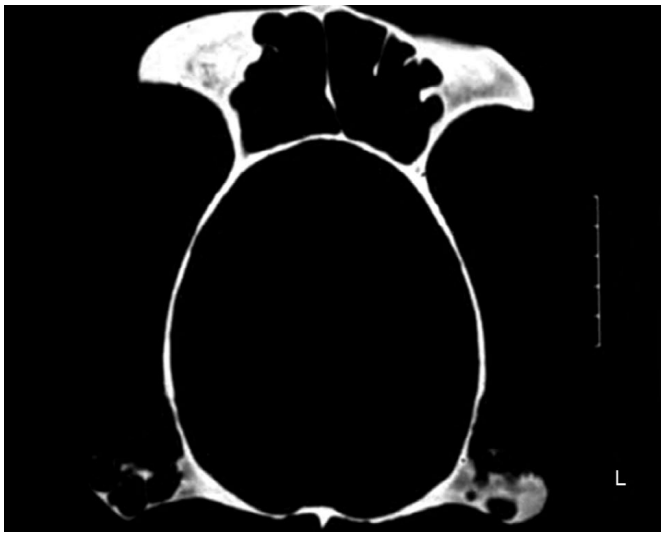


Fig. 2.9: An axial computed tomography scan through a gorilla cranium revealing enlarged, septated frontal sinuses.

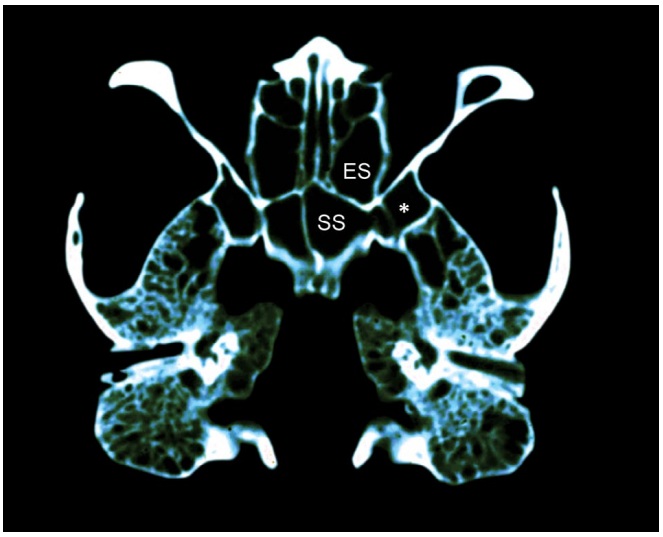


Fig. 2.10: An axial computed tomography scan of a gorilla cranium. Note the distinct, two-celled ethmoid sinus (ES) and the extensive sphenoid sinus (SS), which may be seen invading the greater wing of the sphenoid (asterisk).

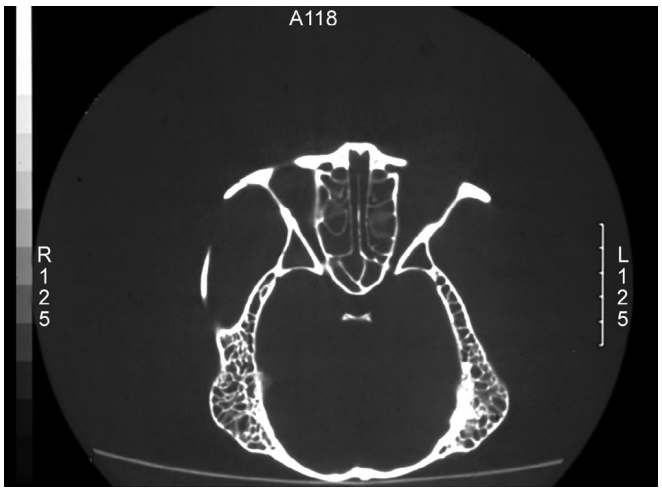


Fig. 2.11: An axial computed tomography scan of a chimpanzee cranium. Note the extensive system of ethmoid air cells. This anatomic pattern is similar to the human condition.

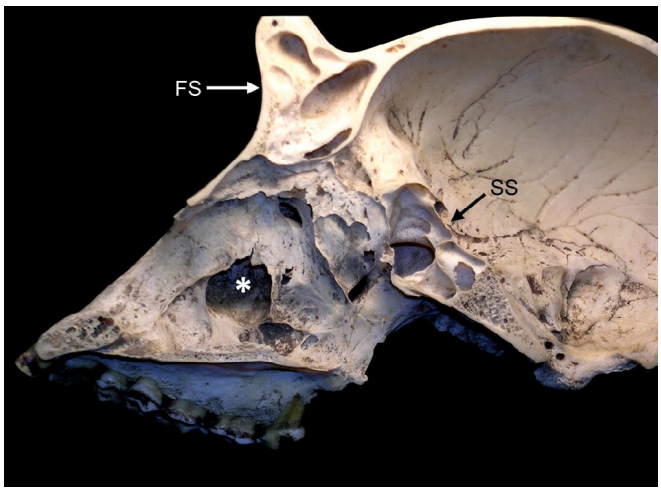
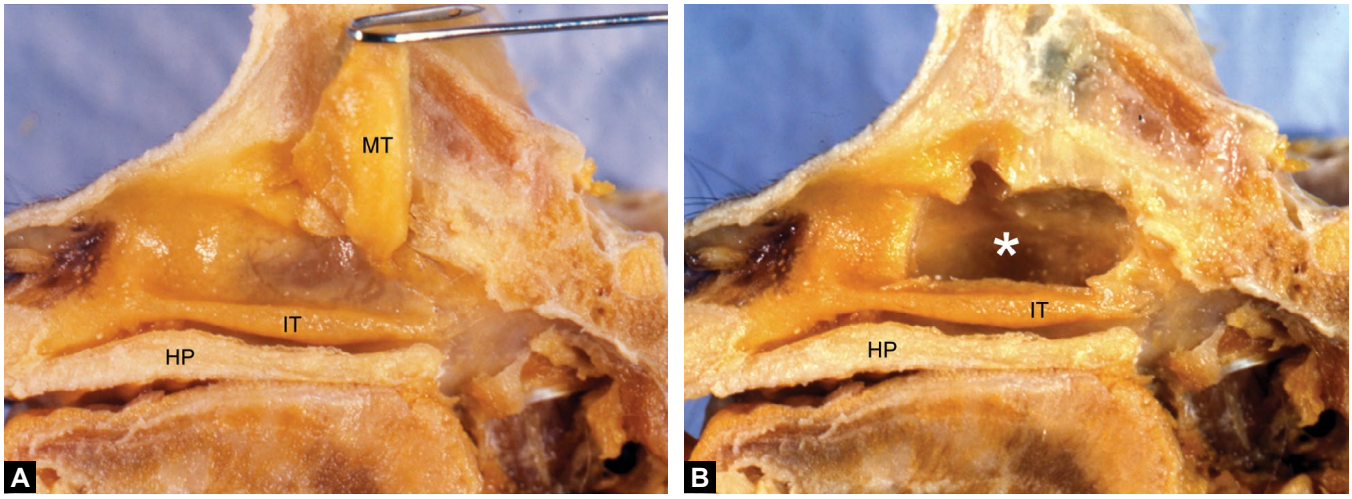


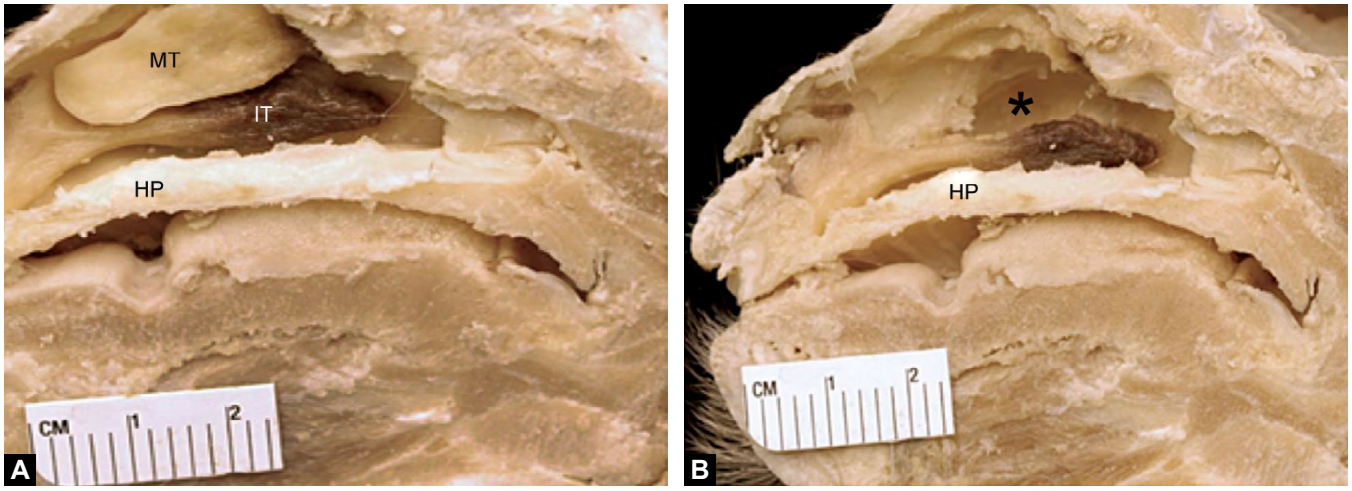
Fig. 2.12: A midsagittally sectioned gorilla cranium. Note the extensive pneumatization of the maxillary sinus (asterisk), frontal sinus (FS), and sphenoid sinus (SS).

both gorillas and chimpanzees, with 1–2 and 4–5 air cells in adults, respectively (Fig. 2.11). Frontal and sphenoid sinuses are confirmed to be restricted to the living African great apes (Fig. 2.12). Sphenoidal development is particularly extensive within the gorilla, involving the pterygoid plates and even the greater wing of the sphenoid (*see* Fig. 2.10).

Given the presence of only a maxillary sinus in *Macaca* (the one genus representative of the Old World Monkeys), it appears that development of any other sinus cavity is a derived character state among catarrhines – the group that includes humans, apes, and monkeys (Figs. 2.13 to 2.15). Orangutans are conservative morphologically but exhibit a dominantly enlarged MS that can expand to other cranial bony elements. The diverticula of the maxillary sinus (i.e. the mucosal evaginations, which are the developmental precursors of the paranasal sinuses) can greatly invade the frontal and/or sphenoid bones to create the appearance of frontal and sphenoid sinuses.[114] However, due to the origins of these spaces as extensions of the maxillary sinus,



Figs. 2.13A and B: (A) Right lateral view of nasal cavity wall of adult male *Macaca fascicularis* showing hard palate (HP), inferior turbinate (IT), and middle turbinate (MT). (B) The middle turbinate has been removed revealing the internal morphology of the maxillary sinus (white asterisk is within the sinus). Note the margin of the sinus cavity has been cut away.



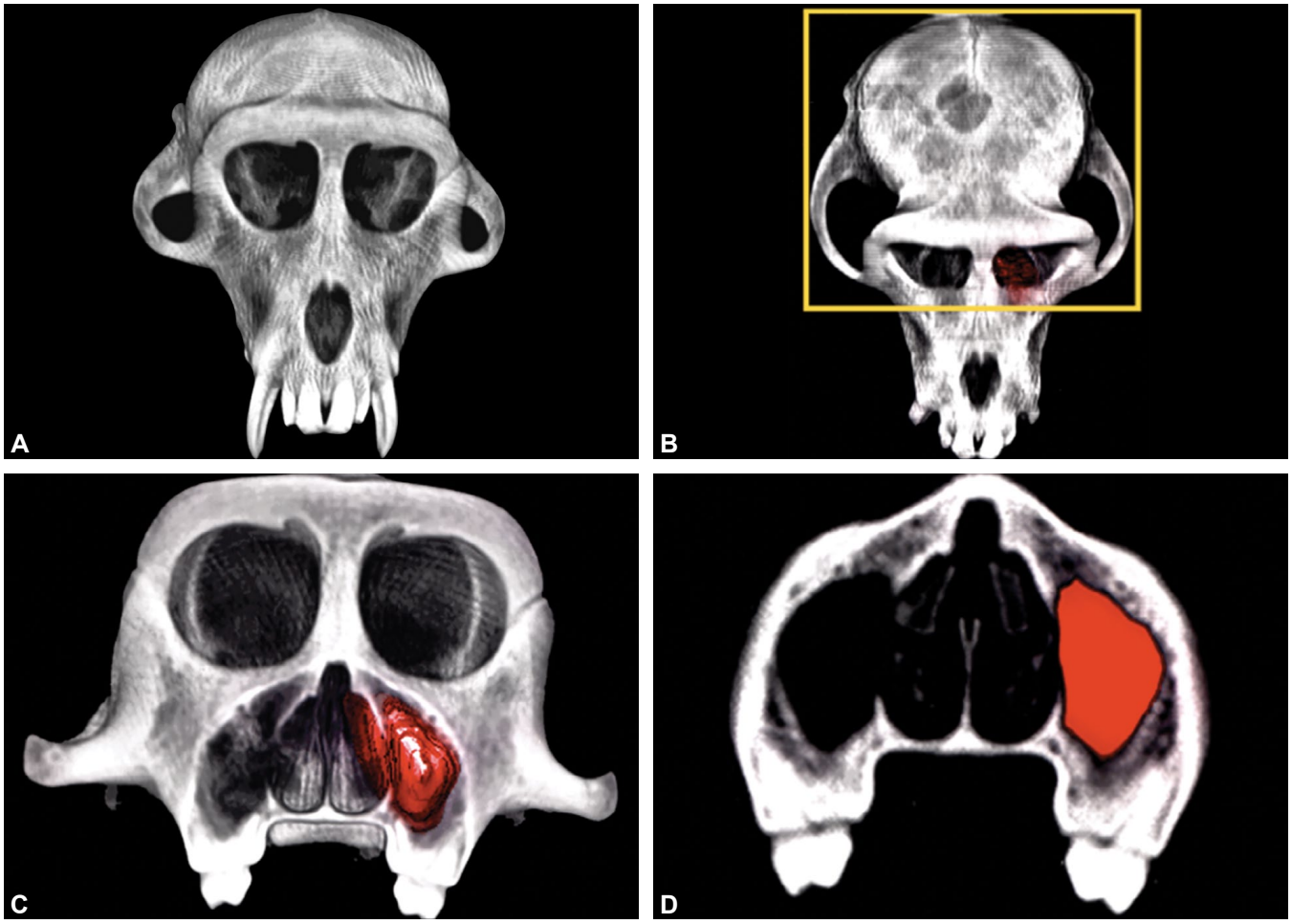
Figs. 2.14A and B: (A) Right lateral view of nasal cavity wall of adult male *Macaca mulatta* showing hard palate (HP), inferior turbinate (IT), and middle turbinate (MT). (B) The maxillary sinus (black asterisk) appears smaller than in *M. fascicularis*.

they may not be identified as distinct sinuses according to Cave's[19] definition (Figs. 2.16 and 2.17).

Among the African apes, distinctions may be made between the nasal morphology of chimpanzees and gorillas, there being a number of derived (i.e. evolutionarily novel) traits among the former. The nasal conchal configurations and larger number of ethmoid air cells of chimpanzees appear more human-like (Figs. 2.18A and B). These may constitute synapomorphies (shared derived traits) of the chimpanzee-human lineage, corroborating the close genetic relationship found between these groups. Furthermore, the presence of these synapomorphies allows for the reconstruction of nasal morphology within the most recent common ancestor of humans and chimpanzees, a valuable tool for assessing the evolutionary importance of traits observed among fossil humans.

EVOLUTION OF NASAL COMPLEX FROM EARLY HUMAN ANCESTORS TO *HOMO ERECTUS*

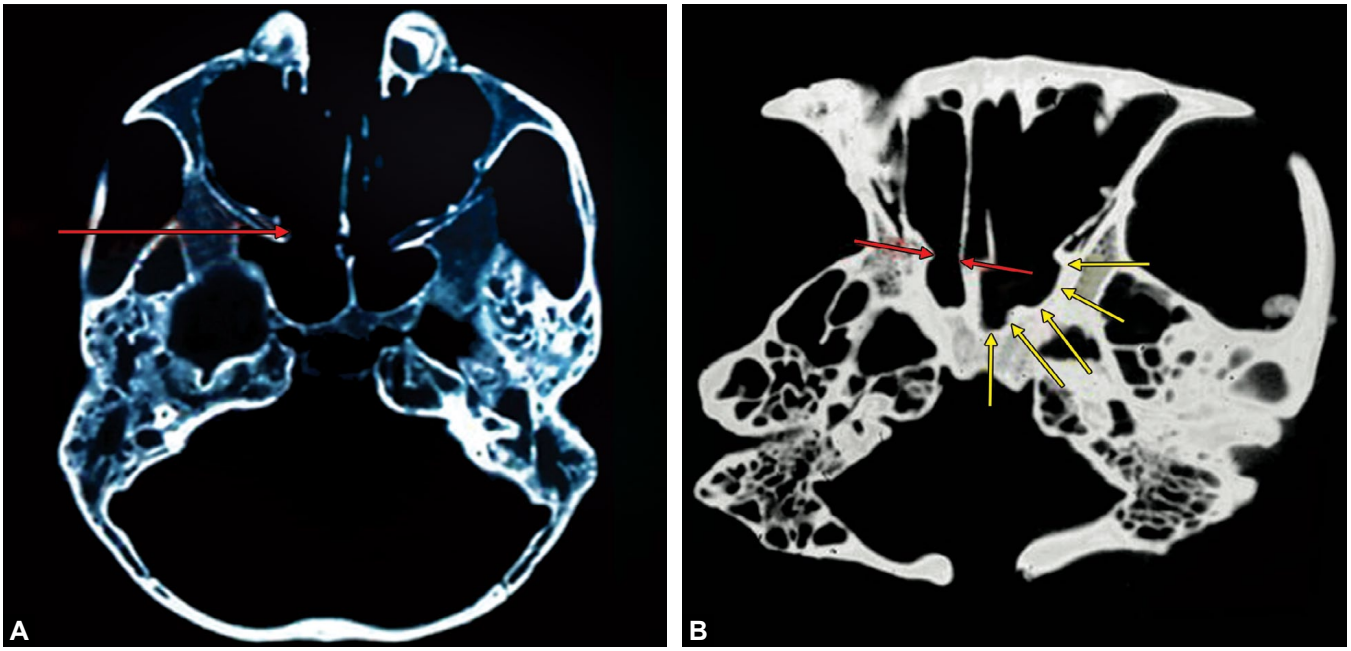
The osseous boundaries of the nasal cavity have an extremely long evolutionary history. However, aspects of the piriform aperture, external nose, and nasal vestibule have



Figs. 2.15A to D: A composite plate showing: (A) a 3-D computed tomography reconstructed skull of an adult male *Macaca fascicularis* viewed anteriorly and (B) a reference coronal slice transection line (seen in yellow) viewed superiorly. The coronal slice can be reconstructed 3-D or presented in 2-D (D). Such reconstructions allow quantitative and qualitative sinus assessments.

undergone relatively recent evolutionary changes so that the anterior nasal complex of humans differs markedly from that of the great apes as well as early fossil humans. For example, otolaryngologists would routinely see an anterior nasal spine in their human patients but such a structure is absent within the apes. Indeed, many aspects of the human skeleton can be reliably traced to between 2.5 and 1.8 million years before present (m.a.), whereas our most recent common ancestor with the chimpanzee, our closest living relative, likely existed over 6 m.a. with some potential interbreeding still occurring after this initial speciation event.[100] As can be seen from aspects of the postcranial skeleton, our ancestors appeared to have locomoted equally among terrestrial and arboreal substrates (*see* the classic study of *Australopithecus afarensis* by Stern and Susman[126]) until the appearance of the oldest member of our genus, *Homo habilis*, approximately 2.6 m.a.,[117] when the earliest stone tools were produced for butchering animal carcasses and (at least in some locations) utilizing more open environments.[38,76,101]

The facial skeleton also remained ape-like during this nearly four million year interval with only moderate reduction in hard palate length and canine dentition. The piriform aperture and surrounding nasal skeleton also retained primitive characteristics. Rather than exhibiting an anterior nasal spine, a nasoalveolar clivus was instead present so that the nasal floor sloped into the alveolar process of the premaxilla. When considered alongside flat nasal bones, location of the internasal suture in the same coronal plane as the nasomaxillary suture, and coronal orientation of the lateral piriform aperture margin, these early "australopith-grade" human relatives may not have



Figs. 2.16A and B: An axial scan of a subadult orangutan (A) showing what appears to be a sphenoid sinus but is actually the maxillary sinus invading the sphenoid bone. An adult orangutan (B) exhibiting clearly patent communication between the left maxillary sinus and the evacuated sphenoid bone (in yellow arrows); red arrows illustrating the path of the right maxillary sinus in its intrasphenoidal encroachment.

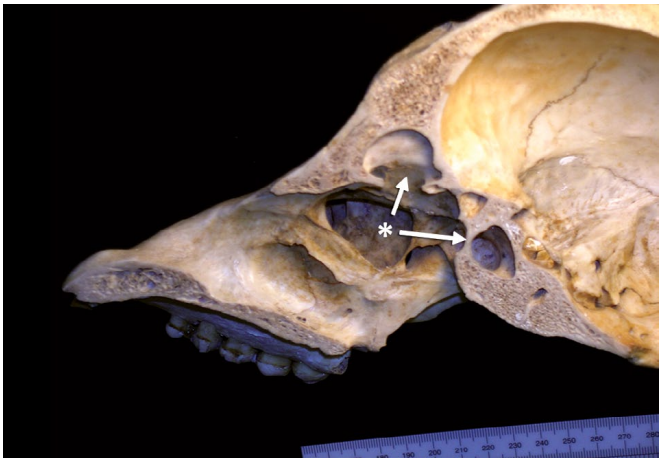
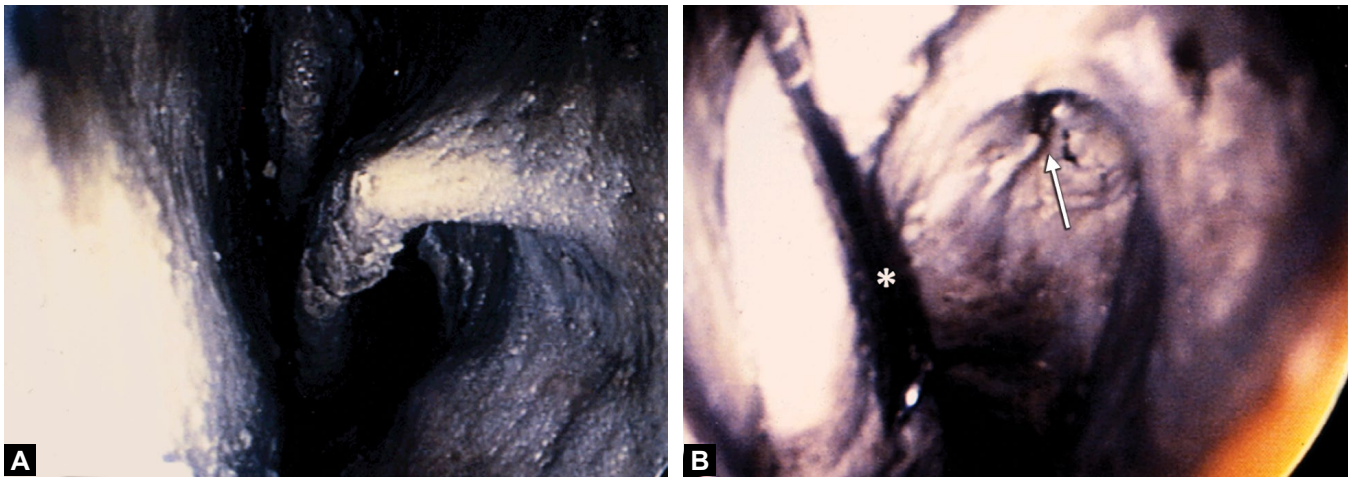


Fig. 2.17: A midsagittally sectioned orangutan cranium. Note that the maxillary sinus (asterisk) is in communication with both the frontal and sphenoid bones (illustrated by arrows) to create the appearance of separate frontal and sphenoid sinuses thus nullifying their status as "true" paranasal sinuses.
Courtesy: Anthony S. Pagano.

had external noses as modern humans but rather the appearance of the great apes, who lack a nasal vestibule.[45] Many also exhibit an apelike piriform aperture outline,[31] which is short and broad relative to the modern human condition.[113]

Arguably, the first fully committed biped in our evolutionary history was *Homo erectus*. This species exhibited a human-like postcranial skeleton and was the first to leave Africa and eventually colonize Asia. Its fossils may be found in locations as varied as South Africa, Kenya, Israel, Georgia, China, and Indonesia. *Homo erectus* likely operated in conditions far more arid than its predecessors, requiring more human-like patterns of nasal projection. These include elevation of the internasal suture above the plane of the nasomaxillary sutures, eversion of the lateral piriform aperture margins, and a more acute nasoalveolar angle despite the absence of an anterior nasal spine.[45]

Relatively few studies have focused on cranial pneumatization among *Homo erectus*. Márquez et al.[87] described an Asian *Homo erectus* calvaria from Indonesia's Sambungmacan region (designated Sm 3; Fig. 2.19), dated around 1.0 m.a.[87] Unfortunately, the ethmoid, sphenoid, and maxillary bones were missing due to poor preservation. However, the frontal bone remained intact and was assessed for pneumatization. This analysis was inconclusive at the time of its publication as the frontal sinus was filled with rock matrix, obfuscating its boundaries. It was not until the return of Sm 3 to Indonesia that the mineral infill was removed. What remained was



Figs. 2.18A and B: Endoscopic imaging of a chimpanzee nasal cavity. (A) The inferior turbinate is visible in situ. (B) When it is protracted away from the nasal wall (white asterisk on the Freer elevator instrument), the ostium of the nasolacrimal duct becomes visible (black arrow).

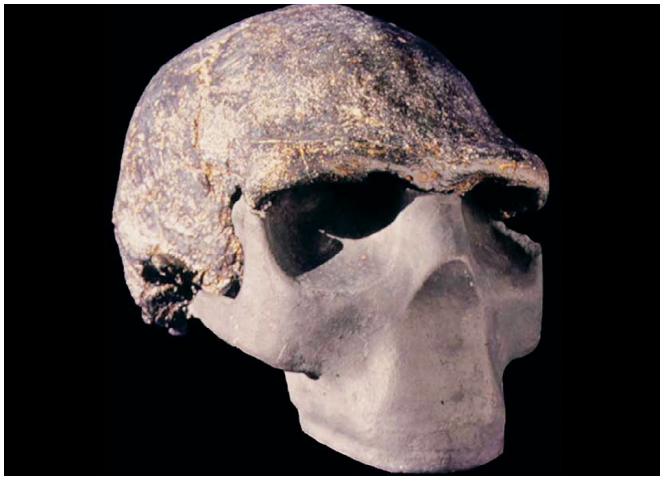


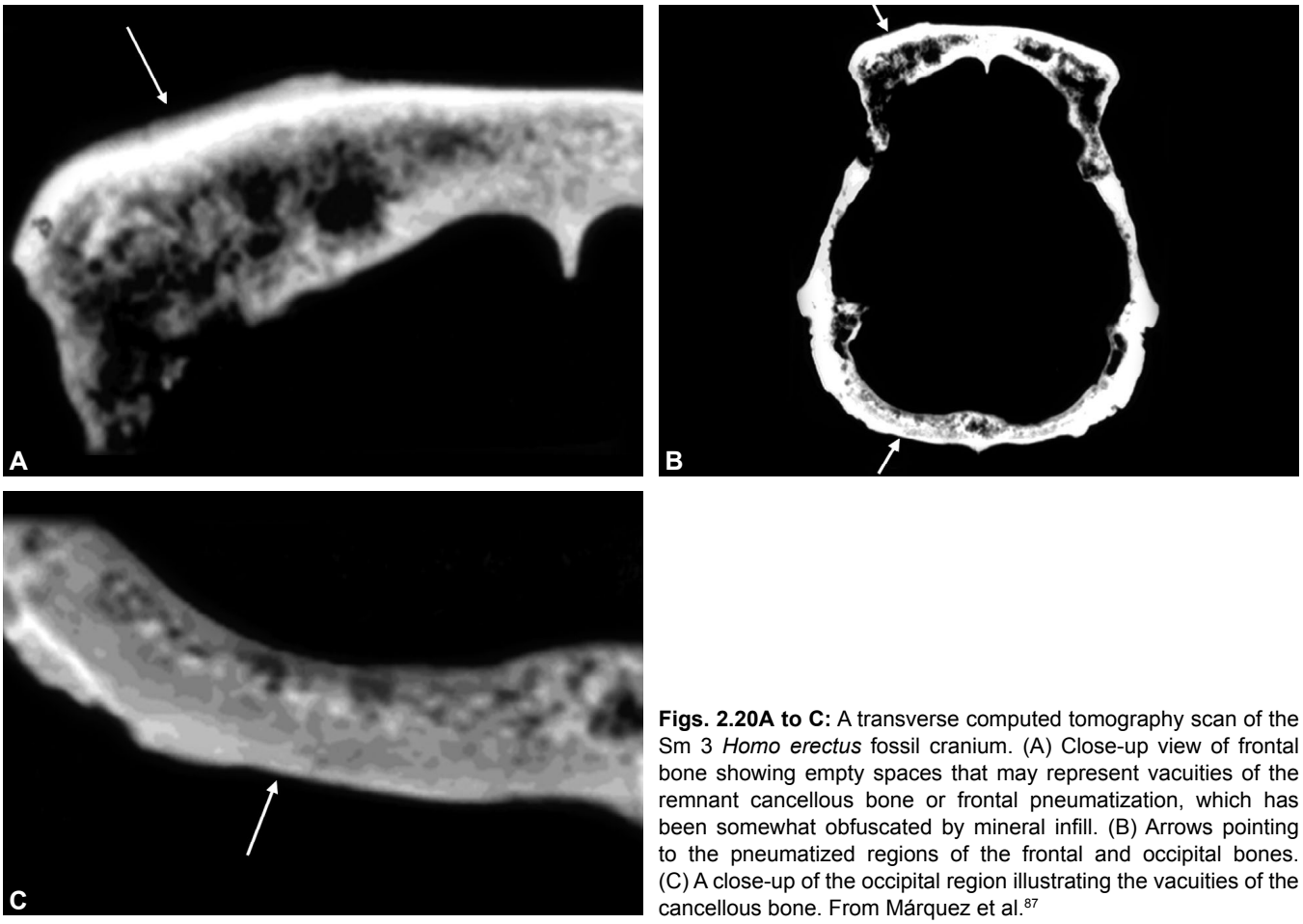
Fig. 2.19: A one-third frontal view of the Sm 3 *Homo erectus* calvarium from Sanbungmacan, Indonesia. Note that the bar-like supraorbital torus (brow ridge) is well developed and protrudes far anteriorly to the short, sloping frontal bone.
Courtesy: Samuel Márquez, SUNY Downstate Medical Center, Brooklyn, NY, USA.

a marked cavitation area indicating the frontal sinus. Despite exhibiting massive supraorbital tori (bony brow ridges), these structures were not invaded by the frontal sinus, which was smaller than expected (Figs. 2.20A to C).

The Evolutionary Relationship between the Nasal Complex and Climate

When anatomically modern humans migrated out of Africa approximately 50,000 years ago, they were able to populate arctic climates despite having evolved in tropical African ecogeographic conditions. Today, humans are able to shift from one extreme environment to another over relatively short periods of time without injuring the upper or lower respiratory systems. Such a useful ability is afforded by the nasal cavity, which equilibrates inspired air with interior body conditions with remarkable efficiency to protect the internal *milieu* of the lung. The nasal cavity apparatus can air condition inspiratory airflow by fully saturating it into water vapor and modify its temperature close to core body temperature, ideal conditions for gas exchange in the alveolae of the lungs. These dual processes are performed in the mucosal and submucosal layers of the nasal cavity walls, respectively.

Humidification of inspiratory air occurs largely via the action of goblet cells in producing mucin, a substance that also protects the epithelia from desiccation and traps particulate matter from inspiratory air flow. Heating of air takes place at the submucosal layer where corpora cavernosa carry venous blood and drain into the pterygoid veinous plexus. The warmth of the venous blood is transmitted through the mucosal layer to the inspiratory airflow. Thus, cool, dry ambient air requires greater contact with nasal epithelia to warm and humidify. Population differences in human nasal morphology have long been studied as adaptations to climatic stresses, in which groups from cold, dry regions exhibit features promoting increased contact between inspiratory air and nasal mucosa. These include increases in nasal surface area and reorientation of the external nasal vestibule to promote greater turbidity as inspiratory airflow is redirected to contact the nasal walls.



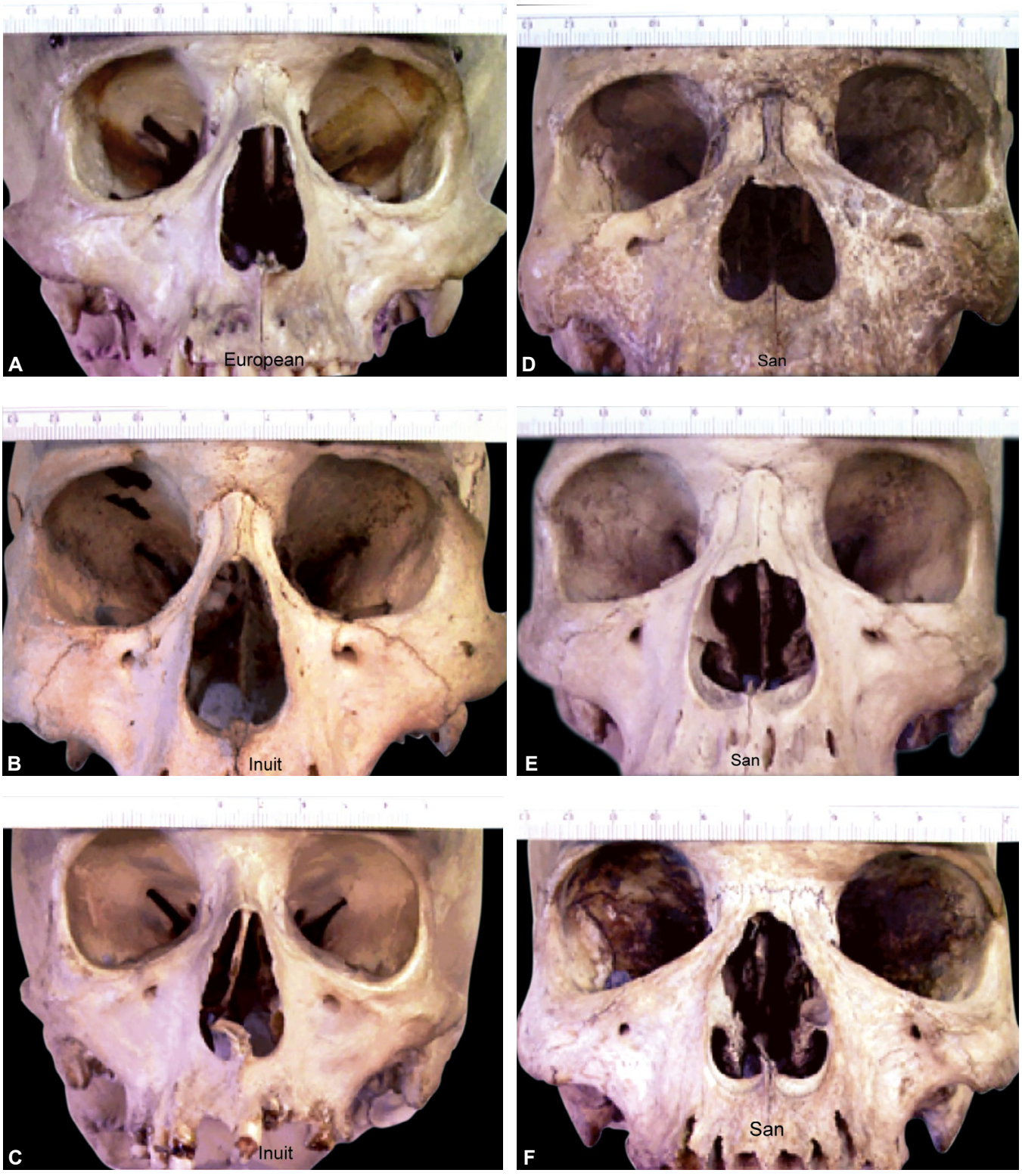
Figs. 2.20A to C: A transverse computed tomography scan of the Sm 3 *Homo erectus* fossil cranium. (A) Close-up view of frontal bone showing empty spaces that may represent vacuities of the remnant cancellous bone or frontal pneumatization, which has been somewhat obfuscated by mineral infill. (B) Arrows pointing to the pneumatized regions of the frontal and occipital bones. (C) A close-up of the occipital region illustrating the vacuities of the cancellous bone. From Márquez et al.[87]

Variation in piriform aperture dimensions has been the most extensively studied aspect of human upper respiratory tract variation. As early as the 18th century, data had been collected on the piriform aperture dimensions of a wide range of human populations. These were often monographs (e.g.[14,130]) that offered descriptions of varied biological phenomena without offering deeper analyses of specific hypotheses or their physiologic/evolutionary implications. Specifically, nasal index (defined as [maximum nasal breadth/nasal height] × 100) has been widely used in anthropology for distinguishing human "races" since the 18th century (e.g.[14,12,131]).

It was not until the study of Hrdlicka's[60] on the cranial morphology of the Inuit that a relationship was considered between piriform aperture shape and climate. In his publication on the craniology of the Eskimo, he suggested that the narrow nasal aperture of this population was directly related to the effects of the Arctic cold.[60] Although Hrdlicka did not discuss the functional significance of this narrowing, a comparison between a group of Eskimo and West Africans clearly illustrates piriform breadth differences (Figs. 2.21A to F).

Osteological changes of the nasal region as seen in Figure 2.5 may reflect an adaptation that serves as a protective mechanism for the respiratory mucosa. Many later studies focused on the functional relationship between nasal morphology and climate (e.g.[34,128,135,137]). For example, Endler[40] cited the action of natural selection, as there exists an association between the variation in a single trait, or set of traits, and specific environments. Thomson and Buxton[128] were among the earliest workers to specifically study the relationship between the nasal index and climatic factors among geographically diverse populations.

Weiner[135] suggested that the critical variable determining nasal shape (i.e. the nasal index) was not temperature/relative humidity but rather absolute humidity. According to Weiner,[135] correlations among the nasal index



Figs. 2.21A to F: Composite of nasal breadth profiles illustrating the narrow breadths clustering around cold weather populations (*see* A through C), whereas wide nasal breadths were associated with warm weather populations (*see* D through F). (A) European (Cat. No. VL/1466), (B) Inuit (Cat. No. 99/6690), (C) Inuit (Cat. No. 193), (D) San (Cat. No. 99/8449), (E) San (Cat. No. 99/9976), (F) San (Cat. No. 9978). Specimens courtesy of Division of Anthropology, American Museum of Natural History.

and temperature and relative humidity were not as high as the correlation between the nasal index and absolute humidity. From this finding, he concluded that absolute humidity was the critical operative factor in determining nose form. Later studies[6,29,44] concluded that differences among populations from cold, dry and warm, wet climates in the nasal index (nasal width/height ×100) were related to an increased area of nasal mucosa for warming and moisturizing airflow. However, Wolpoff[137] questioned the use of piriform aperture height as it did not correspond to internal nasal cavity height. He instead argued that external nasal width was a better indicator of climatic adaptation as it bears a closer relationship with nasal cavity width among Inuits and Aboriginal Australians, estimated by hard palate width. Carey and Steegman[17] later proposed that nasal projection is related to humidity using data from Woo and Morant.[138]

Many investigators hold to the premise that environmental factors, which affect craniofacial dimensions would also affect the primary entry portal of the upper respiratory system, the piriform aperture. Examples of related craniofacial adaptations include masticatory apparatus adjustments due to differences in diet and foreshortening of the splanchnocranium caused by brain expansion.[75] Bergland[7] noted that the size and shape of the nasopharyngeal cavity is largely determined by the bony nasopharynx. However, little attention has been paid to the internal nares (choanae), even though the nasal cavity communicates with the nasopharynx via this portal. Its potential importance as a functional determinant warrants investigation of this region.

Glanville[50] has suggested that there is a direct relationship between nasal shape, prognathism, and the shape of the maxillary dental arch. He found a strong correlation between nasal height and the length of the cranial base and also between nasal breadth and the distance that separates the upper canines. Such relationships can lead to inferences about functional relationships as Laitman and others.[70,71,72,73,74] have suggested in regard to cranial base flexure and positional descent of the larynx. If both the nasal shape and maxillary dental arch-prognathism complex are subject to direct selection by environmental stress, then, comparing these results with nasal complex dimensions could potentially uncover functional relationships between the accessory cavities of the nose and climate.

Most recently, Noback et al.[90] applied geometric morphometrics to the study of nasal morphology. They used 21 externally accessible landmarks to estimate the boundaries of the nasal cavity. Specifically, the ethmoid foramina were used as a proxy for the nasal cavity roof and the piriform aperture and choanal margins were, respectively, considered two areas in which steep dimensional changes could promote greater turbidity in inspiratory air. They also collected landmark coordinate data on the basicranium to model the nasopharyngeal boundaries, which they consider a part of the nasal cavity given its predominantly respiratory function.[129] A geographically diverse group of pooled sex crania representing populations from cold and wet, cold and dry, warm and wet, and warm and dry environments of known temperature and vapor pressure (i.e. humidity) was used. They found that, when expressed as a function of temperature, the nasal cavity grows longer at the piriform aperture and narrower between the left and right ethmoid foramina. Anterior displacement at the anterior ethmoid foramina suggests that elongation occurs at the middle of the nasal cavity roof as well. They also express a heightened and elongated nasopharynx, paradoxically suggesting a smoother transition from cavum nasi with less postnasal turbidity. However, when expressed as a function of vapor pressure, the nasal cavity appears vertically lower with posteriorly located ethmoid foramina to create a stronger "tapering" from posterior to anterior. There is also a more abrupt difference between choanal height and posterior nasal cavum height measured at the posterior ethmoid foramen. These results suggest that the overall nasal cavity dimensions may be more closely related to temperature while nasopharyngeal dimensions are influenced more by vapor pressure.

Few studies have directly examined aspects of the internal nasal cavity as potential sites for climatic adaptation. Charles[23] analyzed internal nasal morphology among a group of African and European American crania and found that the latter group exhibited a longer nasal cavity, but there was little difference in the height or width of the internal nasal fossa. However, Franciscus[42] collected many of the same measures on a diverse group of Old World crania spanning from Northern Europe to Sub-Saharan Africa and concluded that nasal fossa breadth, especially at its superior-most extent, was narrower among Supra-Saharan populations of both modern human and archaic *Homo*. Yokley and Franciscus[141] later combined measures from both of these studies to perform a principal components analysis. On both the first and second principal components vectors, the data indicated a separation of Supra- and Sub-Saharan groups (including African and European Americans) where the former is characterized

by a taller and longer nasal cavity while the latter exhibits greater nasal cavity breadth. It was not until Yokley[139,140] that the actual surface area of the internal nasal cavity was analyzed for a relationship with climate. He used a sample of European (n = 40) and African American (n = 9) live subjects who underwent computed tomography (CT) imaging of the head. Measurement of cross-sectional surface area revealed that the European American sample had a greater endonasal surface area, likely an adaptation for colder, drier climate.

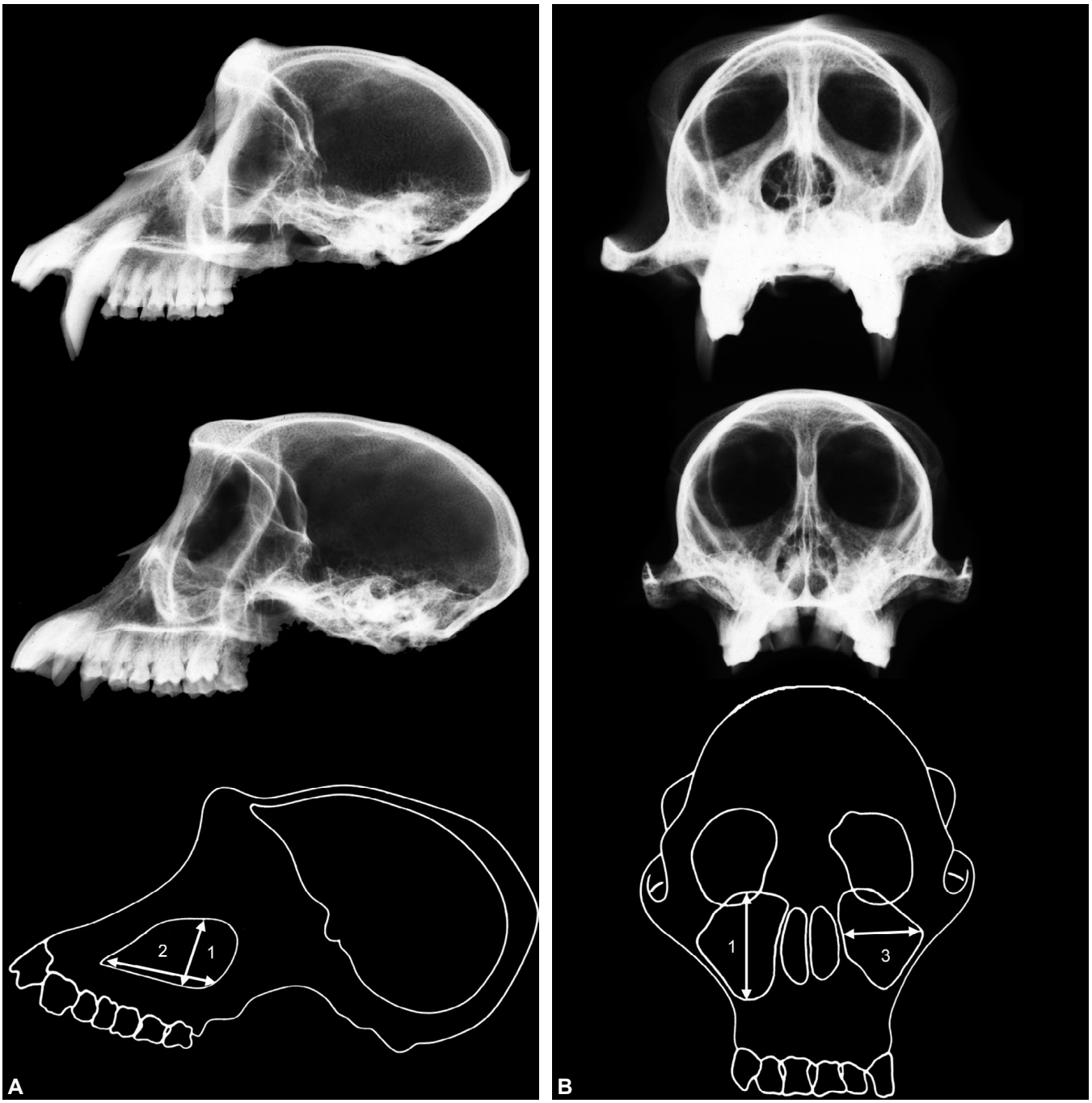
Considerably fewer studies have centered on the relationship between climate and paranasal sinus size. Koertvelyessy[67] and Shea[118] both used Inuit samples from varying latitudes and discovered that those farther north, in colder, drier conditions exhibited smaller paranasal sinuses. Rae et al.[104] reproduced this study design on *Macaca fuscata* (the Japanese snow monkey) from different latitudes within the Japanese archipelago and showed that samples from colder, drier habitats exhibited smaller maxillary sinuses (the only paranasal sinus present among *Macaca*). However, in another study of *Macaca*, Márquez et al.[85] and Márquez and Laitman[84] revealed a more complicated dynamic in which *M. mulatta* (the rhesus monkey) from colder climates and higher altitudes exhibited patterns of functional integration of the maxillary sinus different from those in *M. fascicularis* (the cynomologous monkey) from the warmer lowlands (Figs. 2.22 and 2.23). Their results suggest that cold, dry and warm, wet habitats exert different stresses on the paranasal sinuses and that they function as a part of the larger nasal complex.

Butaric et al.[16] found that absolute maxillary sinus volume was not significantly correlated with any other cranial metric (including nasal cavity volume) nor with climatic variables among a sample of CT scanned crania representing geographically diverse populations (n = 39). However, different results were reached by Holton et al.[58] who utilized the sample of Yokley[139], Yokley,[140] and Holton[56] to examine the relationship between relative volumes of the maxillary sinus and nasal cavity. These spaces were scaled over the centroid size of seven landmark locations on the external face, so as to directly compare relative size (this method has also been used by Pagano et al.,[95] Pagano et al.[96]). A sample of European Americans (n = 20) and a combined group of African Americans and Native South Africans (n = 20) were used to model populations from cold and warm climates, respectively. Interestingly, the South Africans did not differ significantly (p < 0.05) from the African American population despite the former representing a temperate location and the latter descended from equatorial populations. It was found that relative nasal cavity volume was significantly (p < 0.04) larger in this African-derived sample and that relative maxillary sinus volume was significantly (p < 0.001) greater in the European-derived group. Their results also indicated that, in the pooled sample, maxillary sinus and nasal cavity volume exhibited a lower correlation (r = 0.338, p < 0.033) than existed within either the individual European-derived (r = 0.76, p < 0.001) or African-derived groups (r = 0.515, p < 0.021). Holton et al.[58] concluded that, contrary to previous studies (e.g.[104,118]) maxillary sinus volume increases with nasal cavity volume, but that nasal cavity breadth is negatively correlated with maxillary sinus volume. Thus, the more voluminous maxillary sinuses of the European-derived group may be related to their narrower nasal cavities, a potential climatic adaptation. These results corroborate an earlier study by Fernandes[41] in which the absolute dimensions of the maxillary sinuses of European-derived crania (n = 26) were significantly (p < 0.05) larger than those of South African Zulu crania (n = 27).

Neanderthals

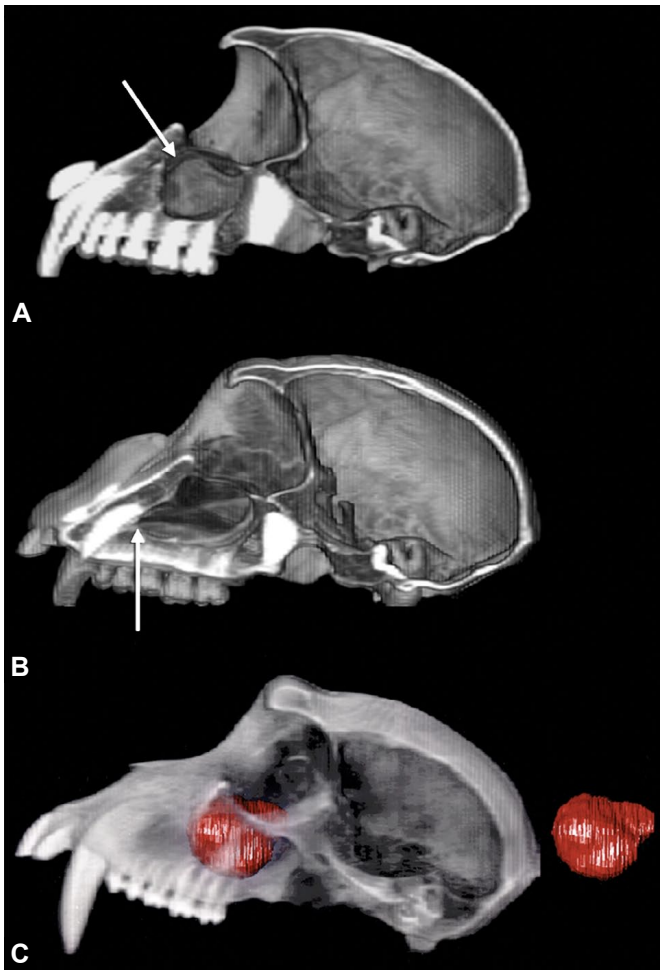
Neanderthals may be characterized by their possession of tall, broad piriform apertures as well as marked midfacial projection and large paranasal sinuses. Many explanations have been posited for this unique suite of features, which does not reflect the upper respiratory tract morphology of modern human populations from cold, dry climates but instead resembles those from tropical populations. Biomechanical models have been proposed in which the sagittally oriented zygoma and broad piriform aperture were functionally related to the stresses of anterior dental loading.[36,106]

Among the earliest models of climatic adaptation in Neanderthal nasal morphology was that of Coon[26] who argued that their increased midfacial prognathism functioned to augment the distance between the nasal apparatus and arteries supplying the brain. This would extend the nasal cavity and allow for greater air conditioning to protect the brain from cold stresses. However, as cited by Yokley,[139] nasal air conditioning impacts lung function more directly than it does thermoregulation of the brain,[133] which is more likely to undergo heat stress than hypothermia.[35,39] Dean[35] proposed that the relatively



Figs. 2.22A and B: Lateral and frontal plain film radiographs of *Macaca fascicularis*. (A) and (B) show an adult male (above) and adult female (below). Schematic drawing represents the lateral and frontal view of X-ray used to derive sinus volumes. Note from schematic drawing from lateral view how measures of height (1) and length (2) of the maxillary sinus are derived. Schematic drawing from frontal view shows how to obtain the two dimensions of height (1) and width (3) of the maxillary sinus.

large nasal cavities of Neanderthals may have provided greater surface area for nasal mucosa to offset increases in core body temperature during bouts of intense physical activity. He suggested that the relatively large Neanderthal brain would have been at increased risk of hyperthermia, especially when combined with the effects of other potential sources of insulation such as body fat or clothing.



Figs. 2.23A to C: (A) Parasagittal computed tomography (CT) section through a *Macaca mulatta* cranium with the right maxillary sinus superior boundary (white arrow) indicated. Note the anterior boundary of the left maxillary sinus is not in contact with the canine root. (B) A parasagittal CT section through the same specimen showing the boundaries of the right maxillary sinus. Note that, on the right side, it is in contact with canine root. There may be asymmetry in maxillary sinus pneumatization as it occurs via opportunistic mucosal evagination of surrounding bone. (C) Its relative size and morphology can be visualized digitally.

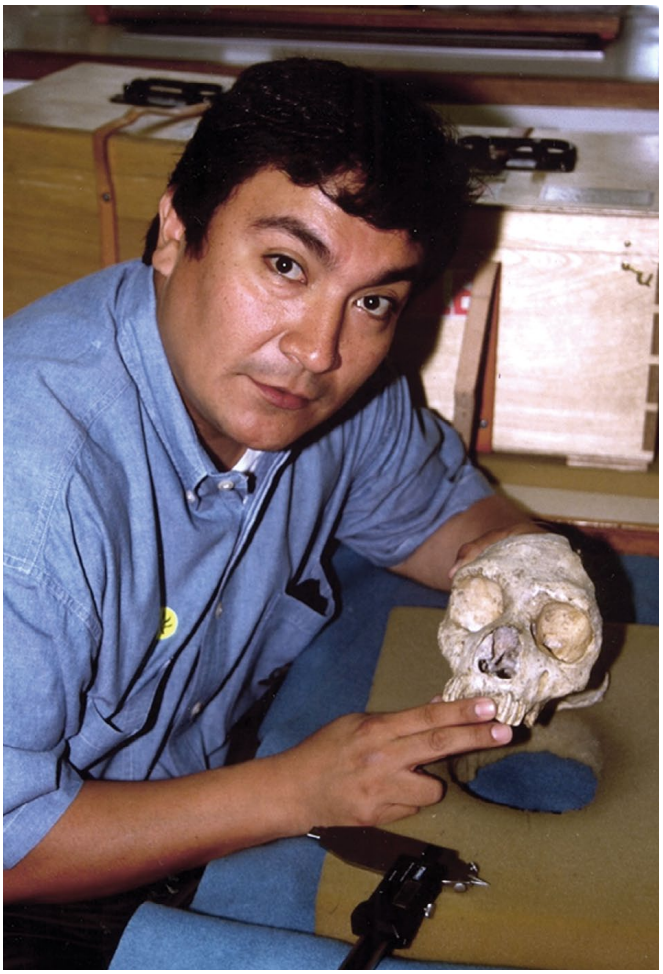


Fig. 2.24: The first author (SM) with the Forbes' Quarry Gibraltar 1 cranium at the British Museum on Natural History, London in 1997. This specimen is among the earliest discovered Neanderthal fossils in 1848.

Schwartz and Tattersall[115] identified a suite of features among Neanderthals (i.e. Forbes' Quarry Gibraltar 1 cranium), which includes a vertically oriented, continuous crest running along the lateral edge of the piriform aperture and a medial projection from this crest (Figs. 2.24 and 2.25). These traits were suggested to increase the amount of surface area available for the air conditioning function of nasal mucosa, serving as an adaptation to cold climate. The authors consider such a condition to be autapomorphic relative to other hominin groups and unlike any nasal morphology exhibited among other mammals. Nonetheless, they acknowledged that the seldom preserved internal conchal morphology of Neanderthals would be needed to fully assess the adaptive benefit of this suite of features.

Arsuaga et al.[3] argued that the medial projection and lateral crest observed by Schwartz and Tattersall[115] is a superior swelling continuous with the confluence of the maxillary conchal crest and the nasal spine. They described this "spinoturbinal crest" on the Monte Circeo 1 specimen and several of the Sima de los Huesos fossils, stating that it can take on a variety of appearances among modern humans.[69] Its appearance in one of the most complete fossil skulls found in Sima de los Huesos (i.e. SH 5) is similar to that of the Neanderthals and is used as evidence that the population represented at Sima de los Huesos is ancestral to them. In addition, Franciscus[43] contended that the

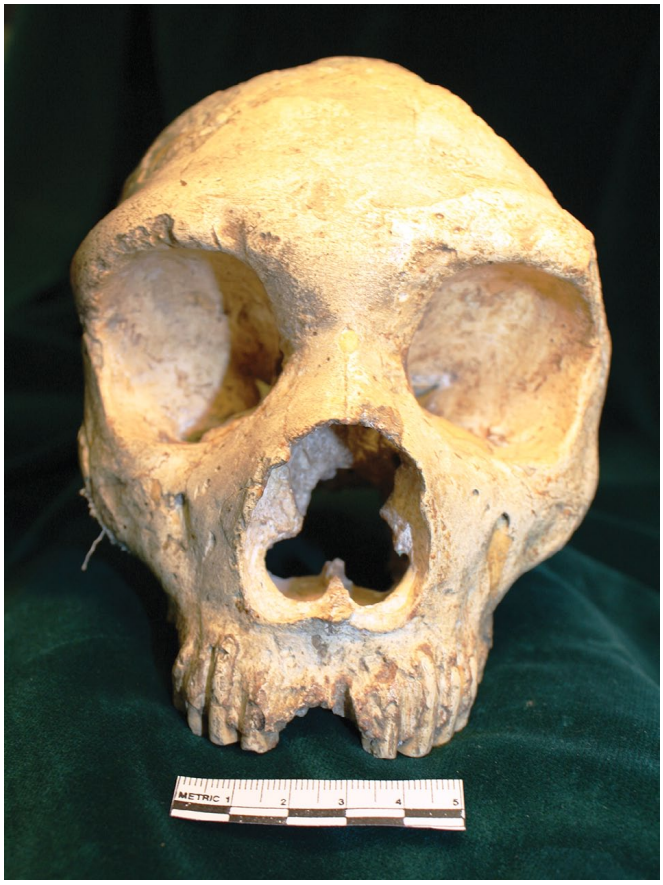
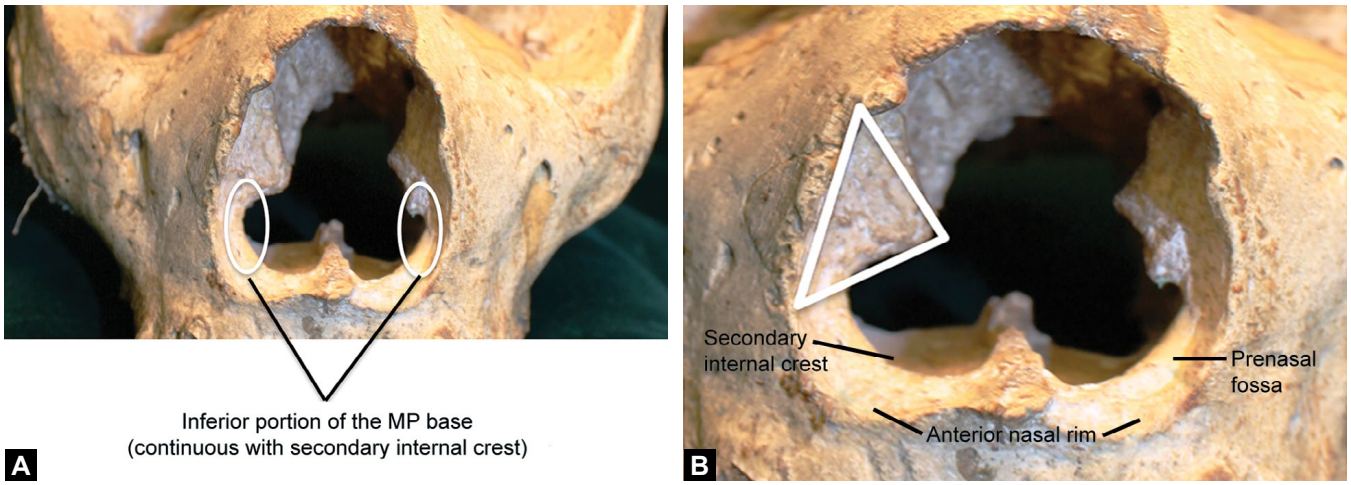


Fig. 2.25: A frontal view of the Forbes' Quarry Gibraltar 1 cranium. Note the extremely tall and wide piriform aperture, a condition not found among any modern human population.

pronounced, continuous crest lining the lateral piriform aperture rim of Neanderthals is a morphologic pattern present among modern humans, which was previously described by Gower[53] in his Stage 5 of a set of six anatomic stages/configurations observed among modern humans. This morphologic pattern includes a fusion of the crista lateralis (from the lateral piriform margin), crista spinalis (from the nasal spine), and crista turbinalis (from the maxilloturbinal). Franciscus[43] also argued that the medial projection observed by Schwartz and Tattersall[115] is actually a maxillary conchal crest, not an autapomorphic feature.

Márquez[81] later reassessed the application of Gower's stages to Neanderthal nasal morphology. He specified that, according to Gower's[53] definition, the crista turbinalis does not vertically exceed the superior boundary of the maxilloturbinal (as was described in Monte Circeo 1 and specimens from Sima de los Huesos by Arsuaga et al.[3]). Also, both Marquez[81] and McCown and Keith[88] noted that the continuous crest of bone visible in the Forbes Quarry Gibraltar 1 cranium creates a prenasal fossa, which Gower[53] precludes from the Stage 5 morphology (Figs. 2.26A and B). The medial projection rooted from this crest projects far medially relative to the modern human conchal crest. Márquez[81] noted that its presence among Neanderthals does not necessarily produce a narrower internal nasal cavity breadth as argued by Franciscus.[43] Indeed, a medially projecting crest may provide extra surface area to an otherwise broad nasal cavity.



Figs. 2.26A and B: (A) A close-up view of the Forbes' Quarry Gibraltar 1 nasal region showing the inferior border of the medial projection (MP) base continuous with the secondary internal crest. This character alone negates inclusion of Gibraltar 1 into Gower's Stage 5 category as argued by Franciscus.[43] Furthermore, this picture points out that the superior base of the MP extends superiorly beyond the demarcation of the inferior orbital rim. (B) Visible from the second image is the pyramidal shape of the MP (outlined in white) with its apex projecting medially. Also, the prenasal fossa and secondary internal nasal crest are clearly visible. Notice that the medial projection and prenasal fossa in Gibraltar 1 are expressed bilaterally.

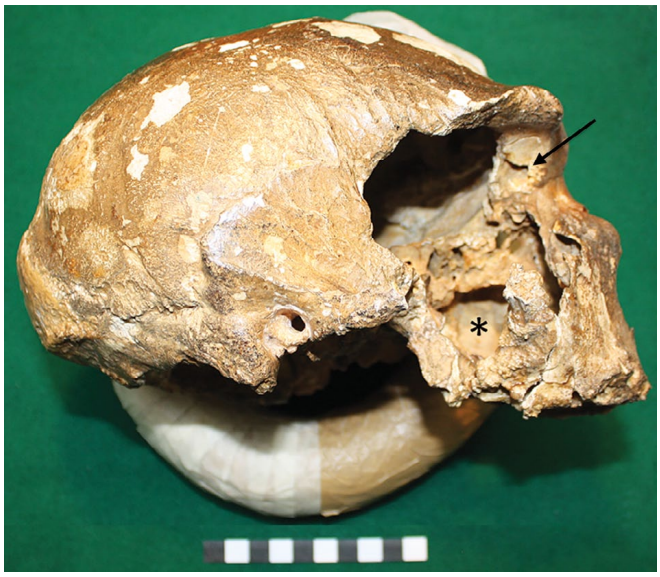


Fig. 2.27: A right lateral view of the Monte Circeo 1 Neanderthal cranium. This specimen exhibits damage to much of the facial skeleton, revealing extensive pneumatization at the left maxillary sinus (asterisk) and frontal sinus (arrow), which continues to the inferior edge of the frontal bone.
Courtesy: Anthony S. Pagano.

Fig. 2.28: A left lateral view of the Steinheim 1 fossil cranium (*Homo heidelbergensis*). This specimen exhibits extensive damage to the left side of the facial skeleton by which an enlarged frontal sinus is exposed (arrow). This space appears enlarged as in Monte Circeo 1, both of which possess greater amounts of frontal bone pneumatization than the Sm 3 *Homo erectus* cranium from Indonesia.
Courtesy: Anthony S. Pagano.

Schwartz et al.[116] refined the description of the lateral nasal morphology of Neanderthals and expanded their discussion to a larger sample of fossil hominins. A taxonomically and temporally broad range of fossils were cited as lacking a clearly defined anterior maxillary conchal crest or any kind of lateral nasal swelling (e.g. fossil skulls included OH 24, KNM-ER 1470, KNM-ER 3733, SK 847, Jinniushan, Arago), whereas some modern humans and other fossil hominins (from Sima de los Huesos, Kabwe, Petralona, and Nariokotome) exhibit a horizontally oriented conchal swelling anteriorly in the nasal cavity. Neanderthals and Steinheim 1, unlike all other hominins sampled, show some form of a vertically oriented strut or swelling on the lateral nasal wall near the piriform aperture located partially or completely superior to the location of the maxilloturbinal. This condition was interpreted as an autapomorphy.

Recently, some[57,105] have proposed that the Neanderthals lacked cold adaptation in their facial skeletons and nasal cavities. They cite their large paranasal sinuses, marked midfacial prognathism, and tall, broad piriform aperture dimensions as a functional consequence of retaining ancestral facial morphology. The Neanderthals and their ancestors are thus considered a tropical primate species inhabiting a glacial climate. Weaver et al.[134] argued that genetic drift was a more likely means by which the Neanderthals acquired aspects of their nasal and overall cranial morphology that may be considered derived relative to other members of *Homo* (Figs. 2.27 to 2.29).

FINAL THOUGHTS

The goal of this chapter on the origin of the nose and paranasal sinuses is to add evolutionary depth to disease etiology and treatment. Growing numbers of otolaryngologists are seeking the assistance of evolutionists, physical and cultural anthropologists in an effort to better understand the clinical issues and modify aspects of diagnostic and therapeutic management of disease processes in the head and neck. For example, Charles Bluestone—a world-recognized researcher and pediatric otolaryngologist—has devoted his life's work to treating children with ear, nose, and throat ailments. Recently, he turned to evolutionary theory in an effort to explain his life-long observations on the patterns of disease processes of the head and neck, particularly the impact of evolution on Eustacian tube physiology.[10] The extremely high frequency of otitis media within the pediatric patient population led Daniel et al.[32] to seek out interdisciplinary experts in an effort to influence the diagnosis and treatment of otitis media:

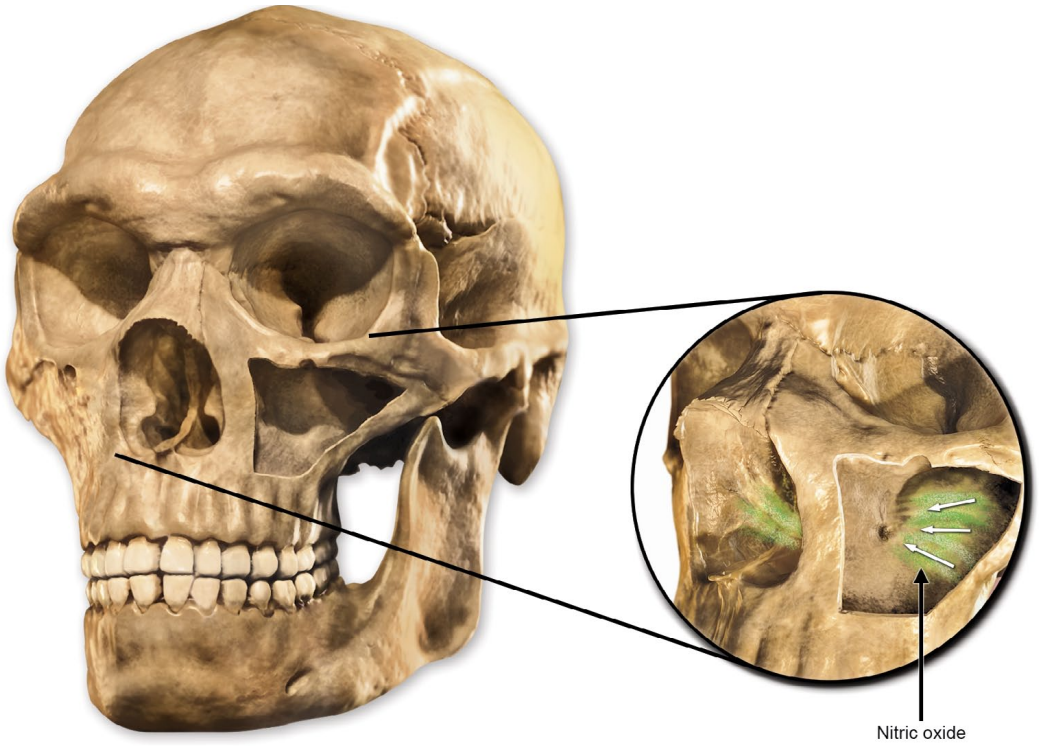


Fig. 2.29: A hypothetical 3-D reconstruction of the Neanderthal nasal complex showing the highly specialized upper respiratory apparatus, which may have been an adaptation to the challenging climatic conditions during the cold intervals of Europe. Note that the bony medial projection in the nasal cavity is strategically positioned to confront incoming plumes of cold air, thus preparing the air for warming before it is infused with nitric oxide (NO) gas. This structure may have also increased airflow turbulence during expiration for greater heat and moisture reclamation. NO gas reverses pulmonary hypoxia in the lower respiratory tract without affecting overall systemic circulation, facilitating the strenuous physical activity (e.g. close-quarters dispatching of large animal prey) that has been attributed to Neanderthals. (© Samuel Márquez, SUNY Downstate Medical Center, Brooklyn, NY, USA.)

"Our paper provides a review of specific aspects of OM [otitis media] that are necessary in any consideration of its etiology. We believe that interdisciplinary research may be the sort most likely to advance our understanding of the causes of this disease. Anthropologists, given their expertise in dealing with biocultural phenomena, can provide unique insights, and it is to this group of researchers that our review is addressed." ([32,p. 144])

Among the evolutionary changes studied by anthropologists, bipedalism has been linked to several clinical conditions. While freeing the hands allowed humans to change the landscape with their tool-making capabilities, this key adaptation came at a "clinical" cost. Early bipeds with ape-like brain size did not face a life-threatening prospect when passing neonates through a birth canal that was narrowed to accommodate bipedal gait. However, when brain size increased relatively recently in our evolutionary history (approximately 1.8 m.a.), it necessitated that infants be birthed at a relatively immature developmental stage relative to other primates, at 9 months' gestation. Thus, human infants are born 12 months too early with immature immune capabilities and Eustachian tube length and compliance.[9] Bluestone et al.[11] argued that rhinosinusitis is another direct consequence of the emergence of obligate bipedalism with concomitant changes in head posture impeding drainage of the maxillary sinus. Adaptations to speech in reorganization of velar musculature and descent of the hyolaryngeal complex have also been implicated in the etiologies of otitis media[10] and obstructive sleep apnea,[33] respectively.

Evolutionists focus on morphological patterns through time and space, whereas otolaryngologists study variations in growth and development of the head and neck to better understand pathophysiology of upper respiratory disease. French otoloaryngologist Roger Jankowski explored these two perspectives[64] and, in a recently published treatise, convincingly demonstrated that these two disciplines, so disparate on the surface, can remarkably complement

and enlighten each other.[65] When Jankowski observed that many diseases were concentrated within specific areas of the nose, such as nasal adenocarcinomas invariably developing in the olfactory cleft region among his pool of wood worker patients,[66] he turned to Evolutionary Developmental biology (Evo-Devo) for an explanation of this phenomenon. By delving into the phylogenetic history of the nose, he traced the origin of the human sinonasal complex back to primitive vertebrates and divided it into three areas with different physiologic functions. He further proposed that these separate derivations have also resulted in pathological processes arising selectively in these separate areas of the nasal cavity. Some examples include adenomastoid hamartomas of olfactory cleft origin and juvenile nasopharyngeal angiofibromas from the sphenopalatine recess. The latter may represent ectopic arrest of vascular tissue designated to form the cavernous portion of the inferior turbinate. While otolaryngologists grapple with the myriad of pathologies presenting from the nasal complex, there now appears a growing understanding that the structures of this complex region are not merely static entities, but instead the products of a vast and eventful evolutionary history. Knowledge of this history is essential if we are to master both etiology and treatment of the pathologies that occasionally emerge.

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CHAPTER

Embryology and Development of the Nose and Paranasal Sinuses

3

Martin Anderson, Jastin Antisdel, Raj Sindwani

INTRODUCTION

The embryologic development of the nasal cavity and the paranasal sinuses is a complex process. This chapter organizes sinonasal embryologic progression chronologically, according to developmental age. Details of development are examined, beginning with the early formation of the nose, lateral nasal wall, and middle meatal structures, and ending with the maturation of key prenatal structures that continue postnatally. A clinical perspective is offered that frames contemporary surgical approaches to endoscopic sinus surgery in a way that essentially mirrors the embryological development of key sinonasal structures. Gaining a nuanced understanding of sinonasal embryology can provide the practitioner with a unique perspective on the surgical management of diseases that affect this region.

EARLY DEVELOPMENT: THE NOSE AND FACE

Sinonasal development begins early in the sequence of embryologic progression. Between the 2nd and 3rd weeks of development, through the process of gastrulation, the human embryonic disk progresses from a bilaminar layer of cells to a trilaminar structure. The trilaminar embryonic disk is comprised of three cell layers: endoderm, ectoderm and mesoderm. From the ectoderm, along the neural groove, the neural crest cells will develop. The face and nasal structures are derived from three sources of embryonic tissue: ectoderm, mesoderm and neural crest. The majority of facial mesenchymal tissue comes from neural crest cells. The ectoderm provides a tissue cover and a pattern for the developing facial structures through its interactions with the underlying facial mesenchyme.[1]

As early as the 4th week of gestation, at about the same time the embryonic heart begins to beat, embryologic development of the human nasal cavities begins and primordial nasal cavities are evident.[2] At this early stage of development, five structures surround the stomodeum. The stomodeum is an early embryonic structure that will eventually develop into the mouth; the maxillary prominences and the frontonasal prominence will comprise much of the midface, including the palate and external nasal structures. As seen in Figure 3.1, the paired right and left maxillary prominences lie lateral to the medial frontonasal prominence to comprise the structures at the rostral aspect of the stomodeum. Paired right and left mandibular prominences lie inferolateral to the stomodeum. The frontonasal process grows over the developing forebrain and contributes to the formation of the nasal placodes, and by the end of the 4th week of gestation the nasal placodes are evident superolateral to the stomodeum. These structures will eventually become the nose and the nasal cavities.[1-3] Between the 4th and 6th weeks of gestation, separate nasal cavities form as the frontonasal process progresses posteriorly at the midline and fuses with extensions of mesoderm from the bilateral maxillary processes.[2] This fusion creates the midline septum, and thus two distinct nasal cavities. The posterior nasal septum continues to grow inferiorly from the nasofrontal prominence to meet the palatal shelf fusion of the secondary palate. The anterior nasal septum is contiguous with the primary palate, which originates from the nasomedial prominences.[1]

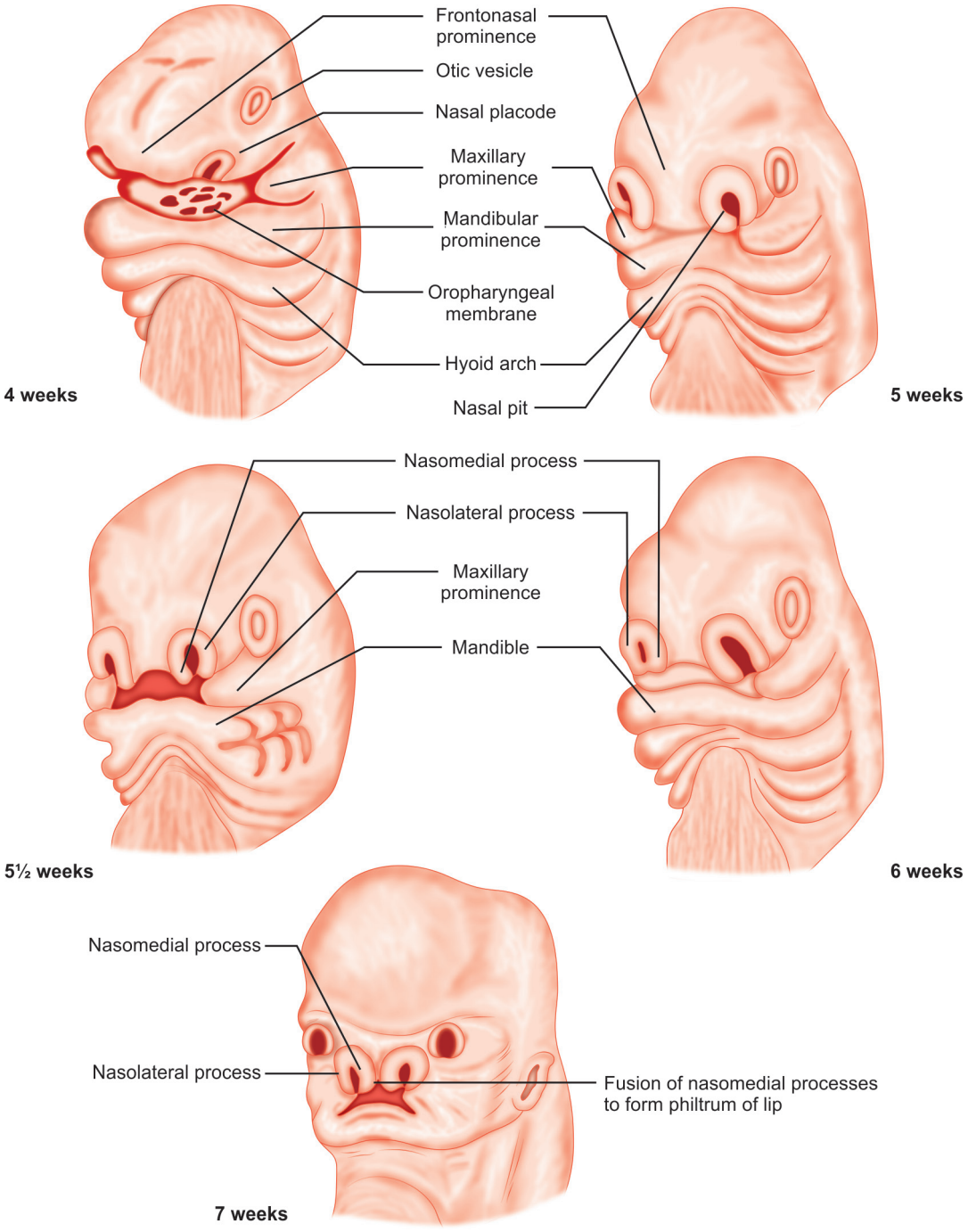

Fig. 3.1: Embryogenesis of the face. Weeks 4–6: The frontonasal process grows over the forebrain and forms the nasal placodes. Separate nasal cavities form as the frontonasal process progresses posteriorly and fuses with the bilateral maxillary processes. Weeks 5–6: Mesenchymal tissue surrounding the nasal placodes raises to form the nasomedial process and the nasolateral process, which will develop into the nares. The nasal pits deepen until only a small oronasal membrane separates the nasal and oral cavities. Weeks 6–8: The fusion of the nasolateral processes and the maxillary processes forms the ala nasi and the lateral border of the nostril bilaterally. Weeks 7–8: Fusion of the nasomedial process with the maxillary process forms the upper maxilla and the philtrum of the upper lip. The nasomedial processes fuse to each other, forming the intermaxillary segment, which will eventually become the primary palate, the tip and crest of the nose, and part of the anterior nasal septum.

As demonstrated in Figure 3.2, beginning at the 4th week of gestation and progressing through the eighth, the primary and secondary palatal shelves fuse in an axial plane to separate the nasal cavity and nasopharynx from the oral cavity and the oropharynx. This fusion of the primary and secondary palates occurs immediately behind the incisive foramen and extends both anteriorly and posteriorly in a zipper-like fashion.[2]

In the 5th week, mesenchymal tissue surrounding the nasal placodes raises in an inverted U-shape, as shown in Figure 3.1. The medial aspect of this "U" is termed the nasomedial process and the lateral aspect is termed the nasolateral process. These nasal prominences will eventually develop into the nares. The elevation of the nasolateral and nasomedial processes gives the appearance that the nasal placodes are depressed. Following this point in development, the nasal placodes are subsequently called the nasal pits. The nasal pits continue to deepen through the 6th week of gestation until only a small oronasal membrane separates the nasal and oral cavities. This membrane disintegrates posterior to the primary palate, creating a connection between the nasal and oral cavities.[1,2,4]

By the end of the 6th week of gestation, the nasolateral processes begin to fuse with the maxillary processes, and this fusion process continues through the 8th week of gestation. The fusion of the nasolateral processes and the maxillary processes form the ala nasi and the lateral border of the nostril bilaterally. Additionally, the fusion of these two structures forms the nasolacrimal groove. The ectoderm, which lies within the nasolacrimal groove, develops into cords of epithelium. These cords detach from the groove and canalize, forming the nasolacrimal ducts and lacrimal sacs. During the 7th and 8th weeks of gestation, the nasomedial processes fuse with the maxillary processes. Fusion of the nasomedial process with the maxillary process forms the upper maxilla and the philtrum of the upper lip. The nasomedial processes subsequently fuse to each other, forming the intermaxillary segment. The intermaxillary segment displaces the frontonasal prominence posteriorly and will eventually become the primary palate, the tip and crest of the nose, and part of the anterior nasal septum. Fusion failure of the nasomedial processes with the maxillary process results in cleft lip or palate deformity.[1,2,4] Piriform aperture stenosis is another anatomic abnormality caused by aberrations at this stage of development. Piriform aperture stenosis is caused by overgrowth of the nasal process of the maxilla during the fusion with the nasomedial processes.[1]

DEVELOPMENT OF THE VOMERONASAL ORGAN

Between the 5th and 7th weeks of gestation, the vomeronasal organ is first noted. It initially appears as bilateral epithelial thickenings of the anterior nasal septum termed the vomeronasal primordium. The vomeronasal primordium invaginates between the 5th and 6th weeks to form a blind pouch called the tubular vomeronasal organ, which separates from epithelium and remains spatially separate from the paraseptal cartilages. In other mammals, the vomeronasal organ has chemoreceptors with direct neural projections to the accessory olfactory bulb, and the accessory olfactory bulb connects to the amygdala and other limbic centers.[1,5,6]

THE LATERAL NASAL WALL: RIDGES AND FURROWS

By the end of the 6th week, the mesenchyme has formed a simple lateral nasal wall. All of the paranasal sinuses will eventually develop from the lateral nasal wall in some respect.[2,7] By the 8th gestational week, as the external architecture of the nose becomes more defined, the lateral nasal wall is also further anatomically developed. As seen in Figure 3.3, during the 7th and 8th weeks of gestation, the lateral nasal wall invaginates to form five to six complex mesenchymal ridges.[2,7-10] The surrounding mesenchymal cells further concentrate to form a cartilaginous nasal capsule that surrounds the nasal cavity. At this stage, the cartilaginous nasal capsule is contiguous with the nasal septal cartilage. In later development, numerous nasal structures will develop from the cartilaginous lateral nasal capsule. Although five to six ridges initially develop, through fusion or regression only three to four ridges ultimately persist. The early uncinate process is also identifiable as a soft tissue swelling on the superolateral aspect of the primordial inferior turbinate. At this stage, the uncinate appears as a double-beak as opposed to the adult hook shape.[1,7,8,11]

The most inferior ridge of the lateral nasal wall, referred to as the "maxilloturbinal," will develop into the inferior turbinate. The remaining ridges are referred to as "ethmoturbinals" and are numbered from inferior to superior. The inferior turbinate thus has a different embryological derivation than the other turbinates, which arise from ethmoturbinals. All ethmoturbinals are considered ethmoid in origin. The first ethmoturbinal is rudimentary and incomplete in the human. It is comprised of an ascending and

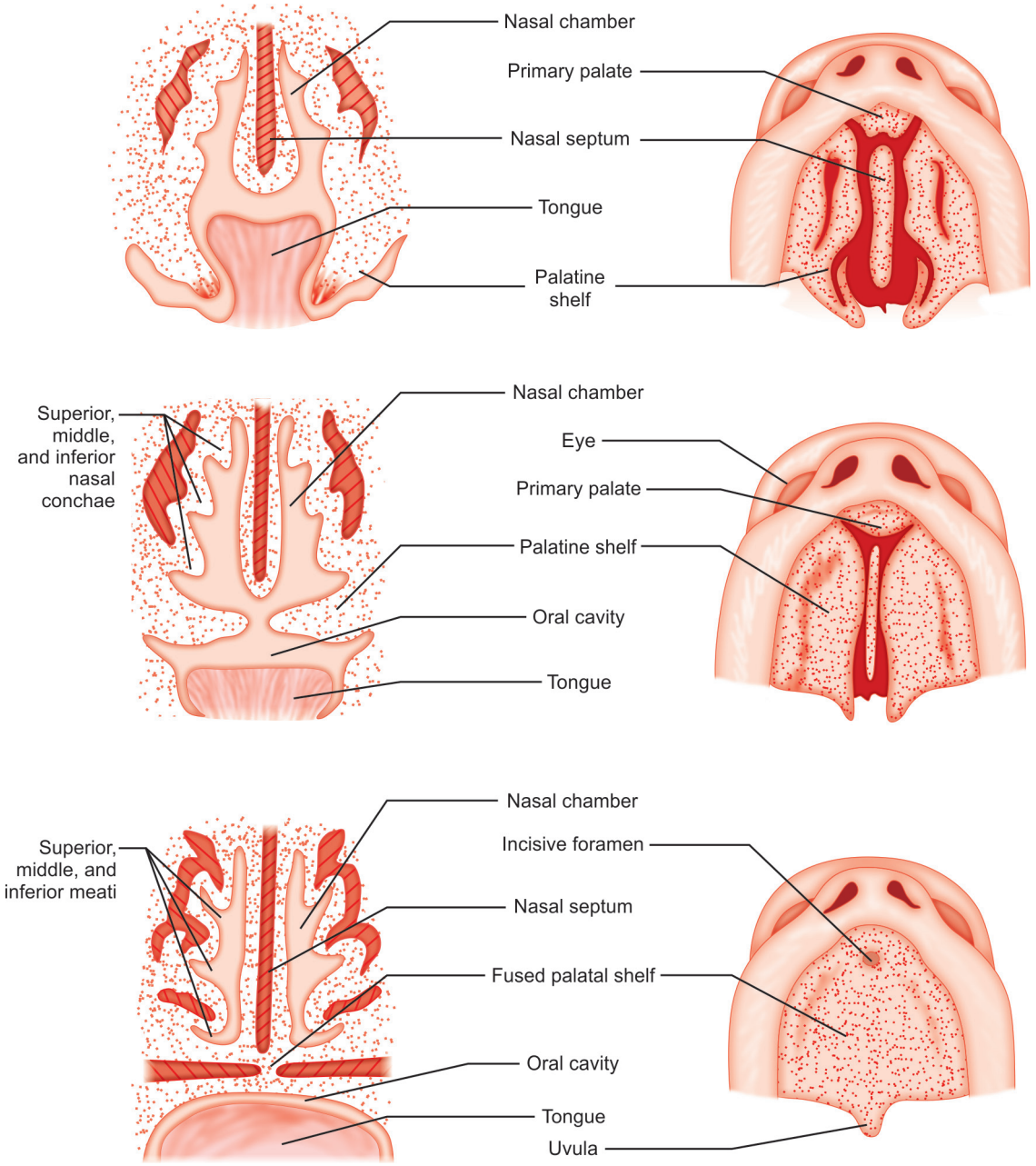

Fig. 3.2: Embryogenesis of the nasal cavity and palate. From weeks 4–8 of gestation, the primary and secondary palatal shelves fuse in an axial plane to separate the nasal cavity and nasopharynx from the oral cavity and the oropharynx. This fusion of the primary and secondary palates occurs immediately behind the incisive foramen and extends both anteriorly and posteriorly in a zipper-like fashion.

descending portion. The ascending portion develops into the agger nasi cell, while the descending portion will develop into the uncinate process. The second and third ethmoturbinals will eventually form the middle and superior turbinates, respectively. The fourth and fifth ethmoturbinals fuse to create the supreme turbinate.[7,8] The ethmoturbinals are also sometimes referred to as preturbinates.

Because of the ethmoturbinal theory, the uncinate process is named the first ground or first basal lamella,

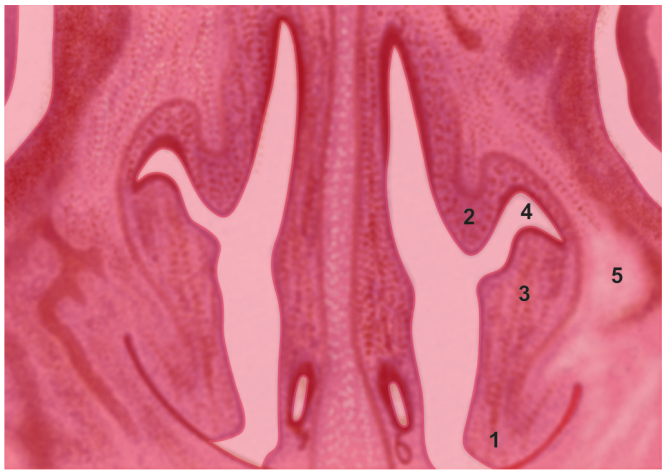

Fig. 3.3: Coronal section at 8 weeks. At 8 weeks, mesenchymal ridges on the lateral nasal wall have formed and the nasal cavity is surrounded by a cartilaginous nasal capsule. In this picture, consistent with histology at 8 weeks, the inferior turbinate (1), middle turbinate (2), primordial uncinate (3), rudimentary infundibulum (4) and the surrounding cartilaginous capsule (5) are evident.

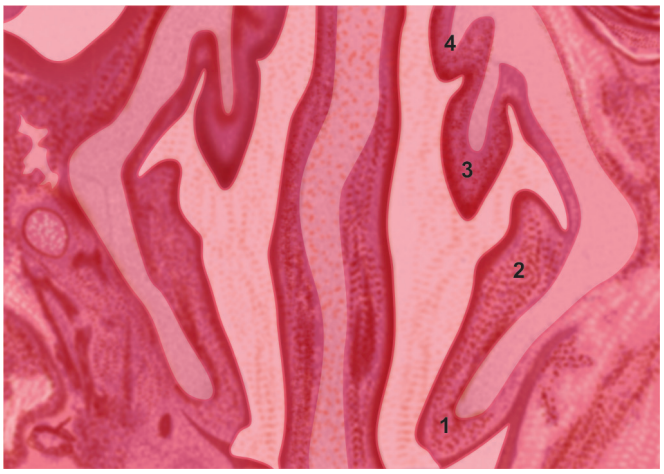

Fig. 3.4: Coronal section at 10 weeks. By 10 weeks, the cartilaginous capsule further extends into the mesenchymal ridges to define the structures of the nasal cavity. The inferior turbinate (1) is formed from the maxilloturbinal. The uncinate process (2), middle turbinate (3), and superior turbinate (4) form from the first, second, and third ethmoturbinals, respectively. The associated meatuses can be seen beneath each rudimentary turbinate.

as it is formed from the first ethmoturbinal. The ethmoid bulla is the second ground lamella, while the middle turbinate is the third ground lamella. Lastly, the attachment of the superior and supreme turbinates are the fourth and fifth ground lamellae, respectively.[7]

Between the ethmoturbinals lie furrows, which later develop into defined meati and recesses.[7,8,10,12,13] The first furrow, which arises between the first and second ethmoturbinals, forms the ethmoid infundibulum, hiatus semilunaris, and middle meatus. The first furrow has an ascending and descending portion. The descending portion contributes to the ethmoid infundibulum, while the ascending portion of the first furrow can also contribute to the frontal recess. The second and third furrows form the superior and supreme meati, respectively.[7,8,14,15] It is interesting to note that most intranasal structures including all of the turbinates (except the inferior turbinate) the uncinate process, ethmoid cells, and indeed even the crista galli are all ethmoidal in embryological derivation.

FORMATION OF MIDDLE MEATAL STRUCTURES

The transition from weeks 9 to 10 marks the progression from embryo to fetus. During weeks 9 and 10 of gestation, as seen in Figure 3.4, cartilaginous projections from the cartilaginous nasal capsule extend into the preturbinates, with the first of these projections noted within the inferior turbinate. An additional cartilaginous bud is also observed at the base of the primordial uncinate process as the uncinate process extends up at the entrance of the middle meatus.[1,7,8,10,13]

Initially, the nasal cavity is lined by a single layer of flattened cells, and then later by two to three layers of spherical cells intermixed with undifferentiated cells. However, at 9 weeks of development as the cartilaginous capsule invades the lateral nasal wall to define the anatomic structures, differentiation of the mucosa is also appreciated with pseudostratified ciliated columnar epithelium appearing within the nasal cavity. The lamina propria of the differentiated mucosa becomes increasingly vascularized during the 9th week of gestation. An invagination of this mucosa arises at the angle of attachment of the uncinate process and extends into the lateral nasal wall further defining the middle meatus. This invagination is the infundibulum and will eventually develop into the maxillary sinus as it extends further inferolaterally. The middle meatus extends further into the lateral nasal wall than the other meatuses, and is the site of initial development of the frontal and anterior ethmoid sinuses in addition to the maxillary sinus.[7,10,16] One to four secondary furrows will form within the ventral and caudal aspect of the primordial middle meatus above the uncinate. One of the small mucosal protrusions between the furrows will become the

bulla ethmoidalis, which will delineate the hiatus semilunaris. The early bulla ethmoidalis is the originating site of both the anterior and middle ethmoid cells. The secondary furrows on either side of the bulla ethmoidalis will develop into the suprabullar and retrobullar recesses. The origin of the frontal sinus is variable in the literature. It is postulated to either arise as an extension of the frontal recess or from an anterior–superior projection of the ethmoid infundibulum. The frontal recess is thus embryologically derived from the anterior ethmoid cells.[2,7,8,10,14]

At the 11th and 12th weeks, at about the same time that the fetal liver begins producing red blood cells, the primordial ethmoid infundibulum is clearly visible and begins to extend as a tract inferolaterally into the maxilla.[1] Week 12 also heralds a clearer distinction of the ethmoid bulla within the middle meatus, now with cartilage extending from the lateral nasal capsule to further define the previously noted mucosal bulge. Additionally, the pseudostratified ciliated epithelium noted during week 9 continues to differentiate until the 14th week of gestation. During weeks 11 and 12, the mucosa begins to exhibit glandular acini and goblet cells, which are first evident in the mucosa of the anterior septum. The mucosal development of the anterior nasal cavity precedes that of the lateral nasal wall and the adjacent paranasal sinuses.[7] Also between weeks 12 and 14 of gestation in the human, the vomeronasal organ loses any receptor cells and nerves it had developed and regresses to the same mucosa as adjacent tissues—pseudostratified ciliated epithelium. Thus, although all embryonic humans develop a vomeronasal organ, by the 14th week it has lost all functional components. Only a remnant of the vomeronasal organ remains through embryologic development and persists postnatally.[5]

ETHMOID AND SPHENOID SINUSES

The 13th and 14th weeks mark the beginning of the embryologic development of the ethmoid and sphenoid sinuses. The nasal mucosa invaginates into the posterior portion of the nasal cartilaginous capsule to form a cavity referred to as the cupolar recess of the nasal cavity. This cartilaginous complex ossifies in later fetal development and is referred to as the ossiculum of Bertini. It will later become the sphenoid sinus. Simultaneous with the primordial development of the sphenoid sinus, the anterior ethmoid cells are also seen arising from the superior middle meatus. The anterior ethmoid cells are visualized

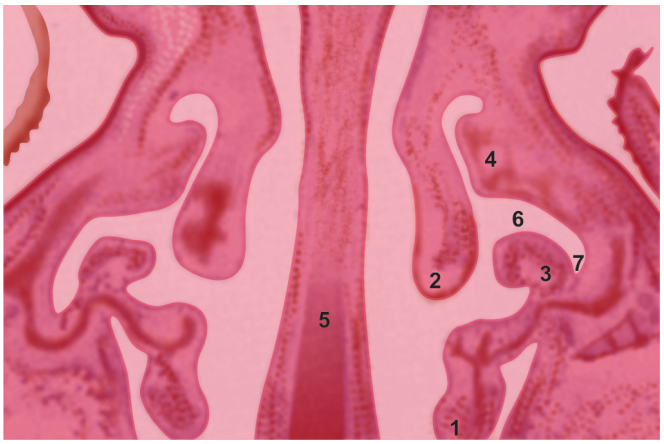

Fig. 3.5: Coronal section at 14 weeks. The ethmoid bulla (4) and uncinate process (3) are clearly visible; all three primordial turbinates, uncinate process, ethmoid bulla, and nasal septum (5) are supported by cartilage that extends from the nasal capsule; and the ethmoid infundibulum (6) extends inferolaterally into the maxillary bone precursor, forming a rudimentary maxillary sinus (7). Inferior turbinate (1) and middle turbinate (2).

as several blind epithelial invaginations, while the posterior ethmoid cells develop from the floor of superior meatus.[2,7,8,10,17] In fact, in histologic studies, it appears that the initial air cells of the anterior and middle ethmoid groups arise and differentiate from the primordial ethmoid bulla. The most ventrocephalic of the invaginations of the ethmoid bulla within the middle meatus will form the primordium for the frontal sinus. Therefore, by 14 weeks the nasal cavity begins to exhibit structures that are identifiable as those that exist in the adult. As seen in Figure 3.5, the ethmoid bulla and uncinate process are clearly visible; all three primordial turbinates, uncinate process, ethmoid bulla, and nasal septum are supported by cartilage that extends from the nasal capsule; and the ethmoid infundibulum extends inferolaterally into the maxillary bone precursor. A portion of the primitive ethmoid infundibulum also extends posteriorly. This extension will continue to grow and will eventually aid in the formation of the posterior ethmoid cells.[1,7,10,14]

OSSIFICATION OF SINONASAL STRUCTURES

By the 15th gestational week, ossification has begun with weeks 15 to 18 subsequently marked by further development of the maxillary sinus and bony maturation of the lateral nasal wall. At the 15th week, the maxillary sinus is surrounded by a sleeve of cartilage and has extended further into the apex of the maxilla. By the 16th week, the floor

of the primordial maxillary sinus is located lower than the inferior turbinate, approximating the orientation observed in the developed adult. During the 17th and 18th weeks, the cartilage capsule surrounding the maxillary sinus now begins to expand, extending further anteriorly, laterally, and inferiorly to increase the volume of the maxillary sinus. The infundibulum and the tract extending to the maxillary sinus run medial to the nasolacrimal duct origin at the eye. Ossification begins at the maxillary and palatine primordia, and from these sites of ossification, bony trabeculae will extend into the lateral nasal wall, first involving the inferior turbinate. Ossification extends up from the hard palate of the maxilla posteriorly to first replace the cartilaginous nasal capsule posterolaterally to form the bony lateral nasal wall.[1,10] Through weeks 17 and 18, the inferior turbinate begins to ossify at its attachment with the lateral nasal wall, with the medial free edge remaining cartilaginous. Ossification progresses laterally to medially from the lateral nasal wall for each of the turbinates. Over the following month of gestation, ossification will progress to involve the attachment of the middle turbinate at the lateral nasal wall as well as nearly the entire course of the nasolacrimal duct. Also over this same time period, the turbinates and uncinate enlarge in size, creating a narrow free airway. The middle and superior turbinates hang vertically, while the inferior turbinate assumes a more curved orientation.[1,7,10]

From the ossified ethmoid bulla, the anterior and middle ethmoid cells further develop. Previously seen as blind mucosal invaginations, the cells of the anterior and middle ethmoid groups are now more developed. In embryologic anatomic studies, during the 22nd week the first cell of the anterior ethmoid group was seen within the anterior–inferior portion of the ethmoid bulla, and during the 23rd week the first cell of the middle ethmoid group was seen within the superior aspect of the ethmoid bulla. As mentioned previously, ossification of the uncinate process and of the supreme turbinate also occurs during the 22nd and 23rd weeks of gestation.[7]

At 24 weeks of gestation, the primordial maxillary sinus has significantly invaginated into the bone of the maxilla. The maxillary sinus and infundibulum remain surrounded by cartilaginous capsule. The capsule is surrounded by woven trabecular bone of the maxilla. Laterally, a vertical plate of bone extends from maxilla to separate the inferior orbit from the lateral cartilaginous capsule. Medially, a second vertical plate of bone extends from the maxilla to separate the inferior turbinate from the lateral nasal cartilaginous capsule, forming the posteroinferior lateral wall of the nasal cavity. Therefore, by 24 weeks of gestation, the lateral nasal wall is nearly complete. The superior and middle turbinates have ossified from the ossification center of the ethmoid. The inferior turbinate, with its dual origins from the maxilla and lateral nasal cartilaginous capsule is also completely ossified. The superior aspect of the nasolacrimal duct is also completely encased in bone. Furthermore, at 24 weeks of gestation, the mucosa of the nasal cavity is a well-developed respiratory epithelium and the process of mucosal differentiation is complete.[1,7,10]

MIDDLE TURBINATE PNEUMATIZATION AND MATURATION OF PRENATAL STRUCTURES

In some subjects, the middle turbinate can undergo pneumatization and the formation of a concha bullosa or intralamellar cells. When it occurs, this "collateral pneumatization" of the middle turbinate proceeds as part of normal ethmoid development. By 32 weeks of gestation, an invagination in the superolateral portion of the middle turbinate is seen, which provides an ostium for the pneumatization of the middle turbinate. By birth, there are often two to three pneumatized cells within the middle turbinate. Also at this gestational age, the middle ethmoid cells are present and drain into the suprabullar furrow. The suprabullar furrow is a depression inferior to the insertion of the middle turbinate and superior to the ethmoid bulla formed from the secondary furrows of the middle meatus discussed earlier.[7]

The lateral nasal wall is well developed and the turbinates are at their adult proportions by 36 weeks of gestation. Although all structures are mature and the nasal capsule is ossified, the turbinates are not yet completely ossified at their distal aspects. A layer of bone surrounds the maxillary sinus and ossification of the nasolacrimal duct is complete down to the inferior meatus. The nasal airway is relatively narrow at this point, due to turbinate growth. Two weeks later, at 38 weeks, the anterior ethmoids can be identified draining into the ethmoid infundibulum.[2,7,10]

POSTNATAL PERIOD

Growth and maturation of sinonasal structures continue after birth. In the newborn, all paranasal sinuses are present to some degree, and all of the paranasal sinuses experience specific periods of significant postnatal growth. The ethmoid and maxillary sinuses are the only sinuses

readily identifiable at birth. The ethmoids are the most developed sinus group at birth and consist of the anterior and posterior ethmoid groups. The posterior ethmoid group is generally not well identified at birth. This group continues to pneumatize postnatally and will open into the superior meatus.[2,7,9,18] Embryologic development of the ethmoid sinuses is as convoluted as their postnatal anatomy. In 1951, Van Alyea stated, "The honeycomb-like appearance of the cells gives the impression of a melange, a hopeless entanglement, a jumble of cells thrown together with little design of reason, and considered en masse, as they usually are, they may well be regarded as a labyrinth."[7,19] There are two theories regarding ethmoid anatomy and drainage. The first posits that the ethmoid is divided into anterior and posterior groups, with the anterior group physiologically clearing into the middle meatus and the posterior group physiologically clearing into the superior meatus. Histologic studies of embryos demonstrate that in reality there are three ethmoid groups—the anterior, middle and posterior groups—with the anterior group physiologically clearing into the infundibulum, the middle group physiologically clearing into the suprabullar recess, and the posterior group physiologically clearing into the superior meatus. The maxillary sinus is the next most developed at birth. The maxillary sinus demonstrates a biphasic postnatal growth pattern, which coincides with periods of facial growth in early childhood and adolescence. The maxillary sinuses will expand and enlarge around 3 years of age and later between 7 years and 18 years of age. In sinusitis, the maxillary sinus is often the most commonly involved. This fact was recognized by Schaeffer in 1916 when he wrote, "the maxillary sinus is often a cesspool for infectious material from the sinus frontalis and certain of the anterior group of cellulae ethmoidales."[7,9,12,18] During the 2nd and 3rd year of life, the intervening cartilage between the sphenoid sinus and the sphenoid bone is slowly resorbed. This reabsorption allows for attachment of the ossiculum of Bertini to the body of the sphenoid. A period of significant sphenoid sinus pneumatization occurs at 6–7 years of age and is typically completed between 9 years and 12 years. Often, upon completion of sphenoid pneumatization at 12 years, the anterior clinoid processes and pterygoids can become collaterally pneumatized. At birth, the frontal sinus is the least developed and does not appear significantly until 5 or 6 years of age. The maturation of the frontal sinus is completed between 12 years and 20 years of age, and will have an adult volume of 4–7 mL.[8,9,17,18]

CLINICAL PERSPECTIVES

The evolution of endoscopic sinus surgery seems to have paralleled the embryologic development of the sinuses themselves. That is, conventional endoscopic sinus surgery has developed into a minimally invasive, minimally disruptive technique that focuses on addressing the lateral nasal wall and ethmoids. The Messerklinger technique supposes that paranasal disease is predominantly a consequence of impaired function of the lateral nasal wall and the anterior ethmoids, and thus addresses these sites primarily by removing anatomic obstructions and enlarging natural ostia and drainage pathways.[14,20] Therefore, much of conventional endoscopic sinus serves to address the embryologic ethmoid complex, as most of the sinuses are ethmoid in origin.

The uncinate process, hiatus semilunaris, ethmoid infundibulum, ethmoid bulla, anterior and posterior ethmoid sinuses, all the turbinates (except the inferior turbinate) and their associated meati are all ethmoid in origin as they arise from the ethmoturbinals. In fact, even the maxillary and frontal sinuses are ethmoid in origin, so it follows that focusing surgical interventions on the anatomic site from which they were derived would aid in the function of the paranasal sinuses. In the Messerklinger technique, the first step is to remove the uncinate process, which developed from the descending portion of the first ethmoturbinal.[15] Second, the ethmoid bulla is removed, which is the precursor of all of the anterior and middle ethmoid sinuses. The ethmoid bulla originally formed from secondary furrows with formed with the rudimentary middle meatus between the first and second ethmoturbinals.[2,7,10] Subsequent steps in conventional endoscopic sinus surgery, all focus on improving natural drainage pathways established through embryologic sinus development of the ethmoid tissues by removing obstructing anatomy or by opening stenotic ostia.

CONCLUSION

Human embryologic sinonasal development is equally as intricate as the anatomy itself. A thorough understanding of sinonasal embryology helps to provide the otolaryngologist with additional insight into the pertinent surgical anatomy. Knowledge of embryology provides an enhanced understanding of the pathophysiologic processes that affect the paranasal sinuses and provides a unique perspective on how these areas are approached surgically.

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CHAPTER

Anatomy of the Nose, Paranasal Sinuses, and Anterior Skull Base

4

Ameet Singh, Abtin Tabaee

INTRODUCTION

A mastery of normal and variant anatomy is the foundation of sinonasal and skull base surgery. This knowledge is applied throughout the course of the care of the patient, including understanding the impact of anatomy on the patterns of disease, correct interpretation of radiographic studies, and most notably the execution of successful and safe surgery. Germane to the field of rhinology is the need for an expertise in both endoscopic and open anatomy. As the field of rhinology has expanded to include both approaches to complex pathologies of the sinonasal and skull base cavities, our viewing lenses have changed. This chapter provides a description of sinonasal and skull base anatomy that will serve as a basis for the entire volume.

NASAL CAVITY

The nasal cavity and paranasal sinuses are paired airspaces within a bony and cartilaginous frame work. The mucosal lining is composed of ciliated, pseudostratified columnar epithelium with interspersed goblet cells, nonciliated columnar cells, and basal cells (Fig. 4.1). A ciliated layer of 50–200 cilia per cell lines the surface. In addition to respiratory epithelium, the terminal branches of the olfactory nerve are present in the nasal vault, the superior aspect of the nasal septum, and the superior and middle turbinates (Fig. 4.2). The nasal vestibule is the anteriormost portion of the nasal cavity, and is lined by squamous epithelium with numerous vibrissae. The mucosal membrane is demarcated from the cutaneous epithelium of the

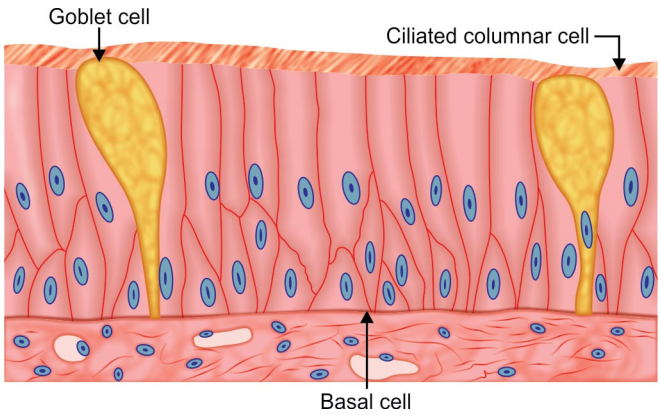


Fig. 4.1: The sinonasal mucosa is composed of ciliated, pseudostratified columnar cells (ciliated cells), with interspersed basal cells, goblet cells (mucous production), and nonciliated columnar cells.

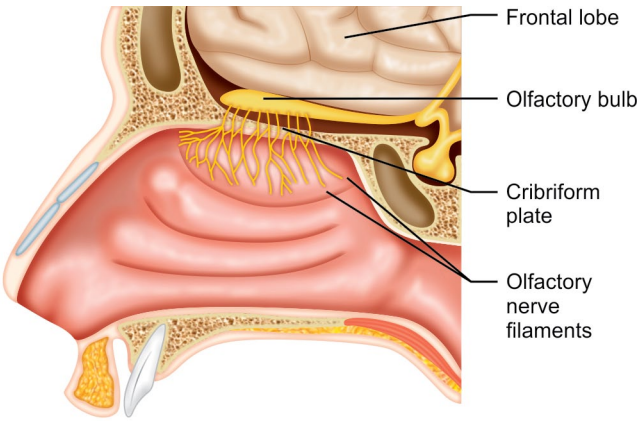


Fig. 4.2: Individual olfactory nerve fibers line the nasal vault, superior and middle turbinates, and the superior aspect of the nasal septum. The nerve fibers reach the olfactory bulb through multiple perforations in the cribriform plate.

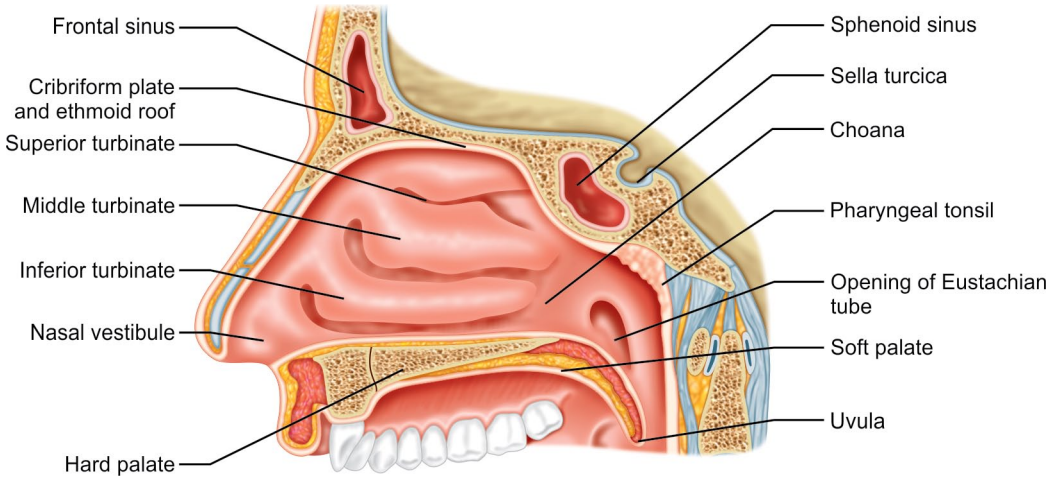


Fig. 4.3: The parasagittal nasal cavity is defined by the nasal turbinate projections from the lateral nasal wall and their representative meati. The anterior–posterior length spans from the nasal vestibule to the choana, respectively.

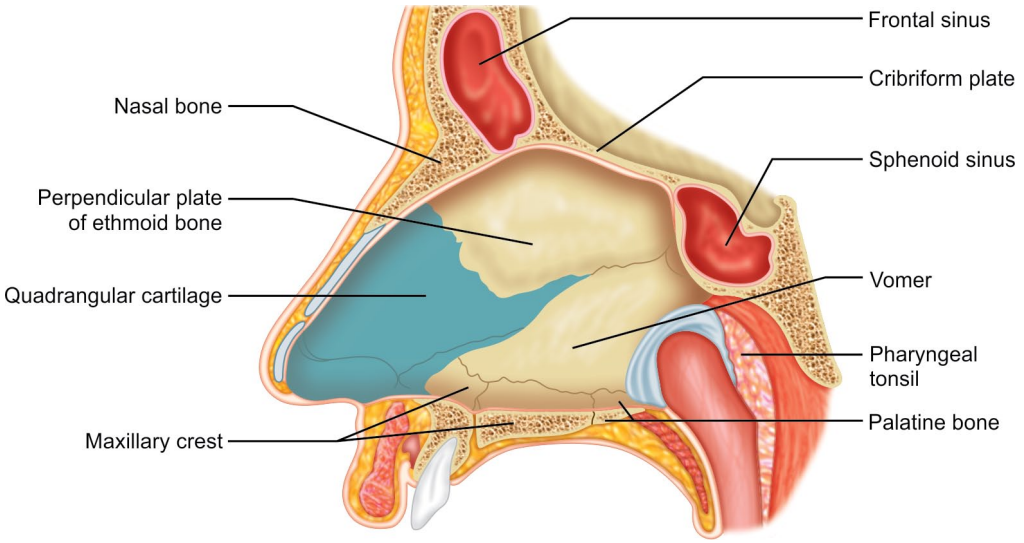
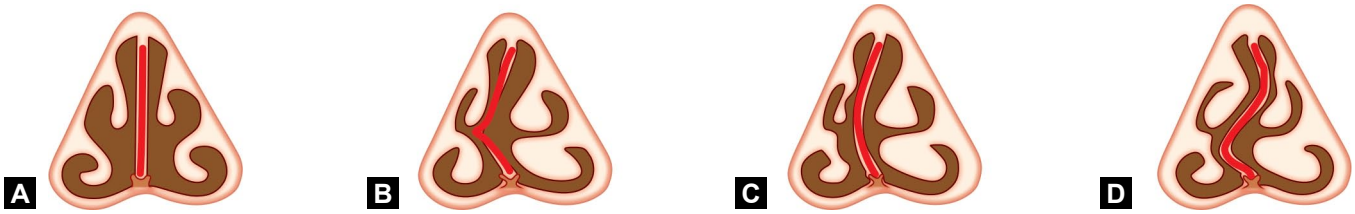


Fig. 4.4: Midsagittal representation of the different osseous and cartilaginous components of the nasal septum.

anterior nasal cavity by the limen nasi. The paired nasal apertures are defined by the floor of the nose, columella, and nasal ala. The posterior limit of the nasal cavity is marked by the choana. The nasal septum is the medial border and divides the left and right sides of the nasal cavity. The floor is composed of the nasal surface of the hard palate anteriorly and the soft palate posteriorly. The lateral nasal wall and the inferior turbinates define the lateral aspects along the majority of the length of the nasal cavity (Fig. 4.3). The medial pterygoid plates contribute to the osteology of the lateral aspects of the posterior nasal cavity in the region of the choana. The nasal vault is predominantly formed by the cribriform plate and ethmoidal roof.

Nasal Septum

The nasal septum separates the nasal cavity into two distinct corridors and provides nasal support. A combination of bone and hyaline cartilage lined by tightly adherent mucosal membranes constitutes the nasal septum. It is composed of the perpendicular plate of the ethmoid bone, the vomer, the crests of the maxillary and palatine bones, and the quadrangular cartilage (Fig. 4.4). Distinct fusion planes between these segments exist and can be identified surgically. The perpendicular plate of the ethmoid bone is the superior portion of the septum and is contiguous with the cribriform plate. As such, inadvertent trauma during



Figs. 4.5A to D: Schematic representation of common patterns of nasal septal deviation. (A) Midline nasal septum, (B) nasal septal spur, (C) C-shaped deformity of the nasal septum, (D) S-shaped deformity of the nasal septum.

surgery can result in skull base fracture and cerebrospinal fluid leak. The inferior junction of the perpendicular plate articulates with the vomer posteriorly and quadrangular cartilage anteriorly. The vomer, an independent bone, constitutes the posterior aspect of the septum. It articulates with the rostrum of the sphenoid bone posteriorly. The crests of the maxillary (anterior) and palatine (posterior) bones form the inferior aspects of the nasal septum. Buckling at the articulation plane between the maxillary crest and the quadrangular cartilage is a common source of nasal septal spurs. Deviation of the nasal septum is present in approximately 90% of the population based on examination by rhinoscopy, although only a small portion will present with clinically significant nasal obstruction. The incidence and structural patterns of the deviation vary by ethnicity.[1] Common deviation patterns are described in Figures 4.5A to D.

Nasal Cavity Vascular Supply, Innervation, and Lymphatics

The blood supply to the nasal septum and paranasal sinuses is extensive and comes from branches of both the internal and external carotid arteries. The terminal branches of these vessels run in the mucoperiosteal and mucoperichondrial layers. The anterior and posterior ethmoidal arteries arise from the ophthalmic branch of the internal carotid artery (ICA) and provide vascular supply to portions of the paranasal sinuses and superior aspect of the nasal septum. The anterior ethmoidal artery courses over the medial rectus, penetrates the lamina papyracea, traverses the ethmoid cavity, sends branches to the nasal septum, and penetrates the cribriform plate terminating as the anterior meningeal artery. Its position at the base of the frontal recess in proximity to the ethmoid bulla places it at risk of iatrogenic injury during endoscopic sinus surgery. Adding to this risk is the potential for the artery to be dehiscent in this area rather than flush with the bony

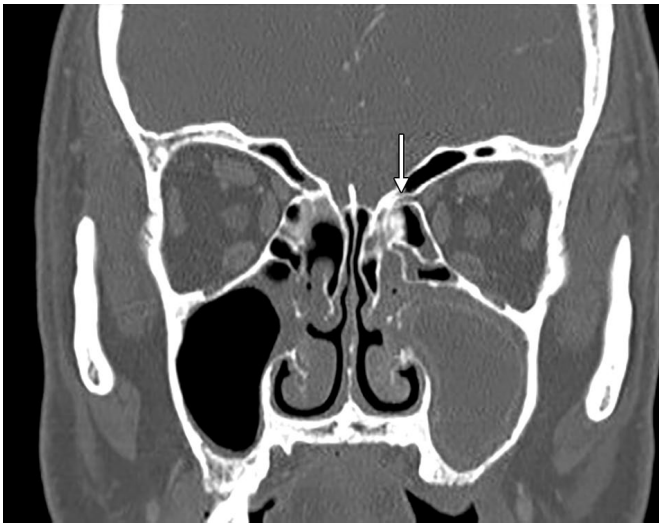


Fig. 4.6: Coronal computed tomography scan demonstrating the anterior ethmoidal artery (arrow) as it exits the orbit and traverses the ethmoid cavity. Dehiscence within the ethmoid cavity places it at risk of iatrogenic injury.

skull base (Fig. 4.6). The posterior ethmoidal artery courses over the medial rectus, penetrates the lamina papyracea, and traverses the posterior ethmoid sinuses near the anterior face of the sphenoid sinus, terminating in the middle turbinate, superior turbinate, and nasal septum. In a recent cadaveric study, a middle ethmoidal artery with an incidence of 31.8% has also been described.[2] The sphenopalatine artery (SPA) is a terminal branch of the internal maxillary artery (IMA) that itself is a branch of the external carotid artery. The SPA passes through the pterygopalatine fossa (PPF) and enters the nasal cavity through the sphenopalatine foramen. A variable degree of branching (typically two to four) occurs either proximal or distal to the area of the foramen. The posterior lateral nasal branch of the SPA divides to supply the inferior and middle turbinates, and variably, the superior turbinate. The posterior nasal septal branch of the SPA traverses posteriorly from the sphenopalatine foramen along the

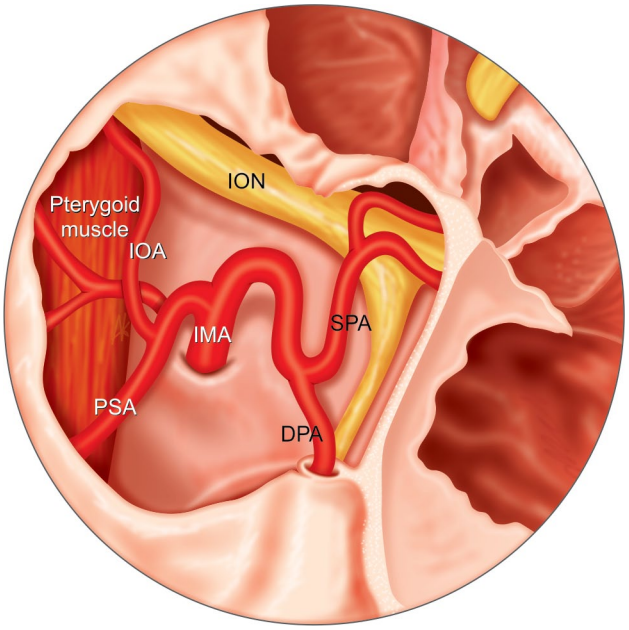


Fig. 4.7: Schematic representation of the vasculature of the right pterygopalatine fossa showing the terminal internal maxillary artery (IMA) including infraorbital artery (IOA), descending palatine artery (DPA), and posterior superior alveolar artery (PSA). The sphenopalatine artery (SPA) enters the nasal cavity through the sphenopalatine terminal and branches to form the posterior lateral nasal and posterior nasal septal branches.

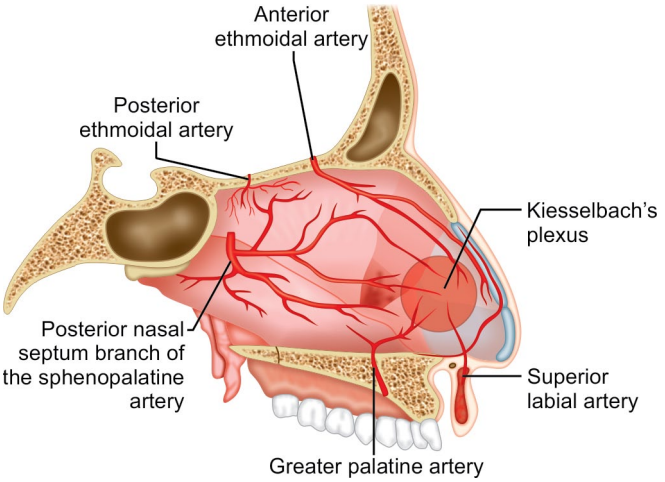


Fig. 4.8: Kiesselbach's plexus is located on the anterior nasal septum and is composed of terminal contributions from the external (sphenopalatine, greater palatine, superior labial) and internal (anterior ethmoidal) carotid artery systems.

lateral nasal wall, continues along the basisphenoid, inferior to the sphenoid sinus ostia, and supplies the posterior and inferior portions of the nasal septum[3] (Fig. 4.7). The anterior nasal septum is supplied by the septal branch of the superior labial branch of the facial artery, itself a branch of the external carotid artery. The greater palatine artery is a terminal branch of the descending palatine artery, a branch of the maxillary artery, which itself arises from the external carotid artery. The greater palatine artery travels through the incisive canal to supply the nasal septum. The anastomosis of the terminal branches of the anterior ethmoidal, sphenopalatine, greater palatine, and superior labial arteries in the anterior nasal septum is termed Kiesselbach's plexus (also known as Little's area) (Fig. 4.8).

The neural supply of the septum draws from both the autonomic and sensory systems. The sensory innervation is from the first two divisions of the trigeminal nerve: the ophthalmic (V1) and maxillary divisions (V2). The nasal septum is supplied by the nasopalatine nerve (branch from anterior and posterior ethmoid nerves). These fibers carry sensation, temperature, and pain. There are also fibers associated with the incisive artery that supply the vomer and maxillary crest as well as anterior palate and central incisors. Disruption of these fibers may occur during septoplasty and lead to decreased sensation of the anterior hard palate and central incisors, normally lasting < 6 weeks.

The autonomic system governs swelling of turbinates, vascular tone, and mucous production. These functions are mediated by sympathetic and parasympathetic innervation of arterioles, venous sinusoids, and seromucinous glands. Parasympathetic innervation arises from the superior salivatory nucleus, travels with the facial nerve becoming the greater superficial petrosal nerve at the geniculate ganglion. The greater superficial petrosal nerve joins the deep petrosal nerve forming the Vidian nerve (also known as the nerve of the pterygoid canal). The parasympathetic fibers synapse at the sphenopalatine ganglion before sending post synaptic fibers to the nasal lining. The primary neurotransmitters are acetylcholine and vasoactive intestinal peptide.

Sympathetic innervation arises from the thoracic spinal nerves (T1–T3), synapses at the superior cervical sympathetic ganglion, and ascends along the ICA. Deep petrosal fibers join the greater superficial petrosal nerve to form the Vidian nerve. The sympathetic fibers pass through the pterygopalatine ganglion without anastomosing and travel with branches of the sphenopalatine nerve to reach the nasal cavity. The primary neurotransmitters are norepinephrine and neuropeptide Y.

Two distinct lymphatic drainage systems are identified, largely based on anterior versus posterior location. The nasal vestibule and anterior nasal cavity drain through facial, submandibular, and parotid lymph nodes, all of which eventually reach the jugulodigastric lymph nodes. The majority of the nasal cavity and the paranasal sinuses drain to the retropharyngeal lymph nodes and eventually to the deep cervical lymphatic chain.

Lateral Nasal Wall and Nasal Turbinates

The lateral nasal wall is defined by the paired inferior, middle and superior nasal turbinates, and their respective spaces termed meati (Fig. 4.3). A fourth turbinate, termed the supreme turbinate, is present in a small subset of people. The bony scroll of the turbinates is covered by fibrovascular erectile submucosal tissue and respiratory epithelium. The turbinates have important anatomic, physiologic, and surgical relationships. Each turbinate is oblong in shape with the long axis parallel to the floor of the nose.

Inferior Turbinate and Inferior Meatus

The inferior turbinate is an independent bone projecting into the nasal cavity from the lateral wall. As the largest of the turbinates, it provides the most significant amount of temperature regulation, humidification, and filtration of inspired air. Its position and size additionally confer the most significant impact on nasal airflow. Hypertrophy of the inferior turbinate may arise from soft tissue and/or bony enlargement and may be congenital or, more commonly, related to inflammatory rhinitis. Pneumatization within the inferior turbinate may also rarely occur. The inferior meatus is the space underneath the inferior turbinate and medial to the lateral nasal wall. It houses the nasal opening of the nasolacrimal duct. A mucosal fold covering this opening in the nasal cavity is termed Hasner's valve. The maxillary sinus can be accessed through the lateral nasal wall in the inferior meatus.

Middle Turbinate and Middle Meatus

The anatomy of the middle turbinate has important implications for sinonasal physiology, inflammatory sinusitis, and endoscopic sinus surgery. Three separate attachment points of the middle turbinate are described. The anterior most attachment is oriented sagittally and connects to the cribriform plate, lateral nasal wall, or uncinate process. The mid-portion of the middle turbinate is oriented coronally and attaches to the lamina papyracea. The posterior portion is oriented axially and attaches to the posterior portion of the lamina papyracea. The mid and posterior attachments comprise the basal lamella, also termed the ground lamella. This is the embryologic and anatomic separation between the anterior and posterior ethmoid cells.

The middle turbinate normally either lacks significant curvature or has a convexity toward the nasal septum with the tip pointing laterally and the body curved medially. Paradoxical curvature is defined by the reverse relationships with the body curved toward the infundibulum. This configuration may potentially obstruct the physiology of the infundibulum, but the true degree to which this occurs is controversial.

The size of the middle turbinate may vary as a result of embryologic development, compression by surrounding structures, inflammatory polyposis, or presence of a concha bullosa. The latter has often been described as a pneumatization of the middle turbinate, implying that it is purely a pocket of air. This is neither fully accurate nor a complete definition of this process. A concha bullosa is better characterized as an aberrant ethmoid cell within the middle turbinate. Like other ethmoid cells, a concha is composed of mucosal lined bony shell, with an outflow tract. Variability exists with regard to the location of the cell within the middle turbinate, including lamellar, bulbous, and extensive variants.[4] The presence of an ethmoid cell within the middle turbinate has important disease and surgical implications. The cell may be air filled in the normal state, but can become involved with infectious and inflammatory changes including mucosal edema, polyposis, mucopurulence, and mucocele formation. In fact, a complete opacified ethmoid cell within the middle turbinate is still a concha bullosa, even in the absence of any air. Surgical management of ethmoid sinusitis in a patient with a concha bullosa cell should, therefore, be performed by exteriorization of the concha as is done with other cells. The practice of ignoring or crushing the middle turbinate in this setting is not supported. A bulky concha bullosa may additionally obstruct the ipsilateral ethmoid infundibulum (Fig. 4.9). An additional pattern that may occur in the setting of a large concha bullosa is contralateral deflection of the nasal septum and narrowing of the contralateral middle meatus. The cause versus effect debate for this phenomenon has been argued both ways. However, it would seem logical, but difficult to be proved, that the aberrant position of the ethmoid air cell would be the inciting embryologic event.

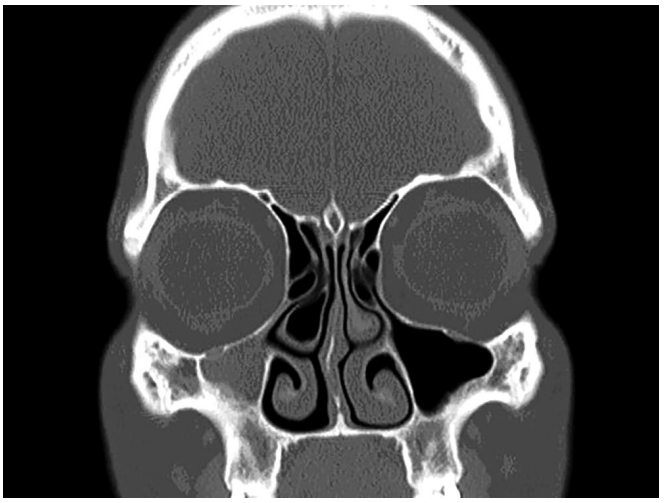


Fig. 4.9: Coronal computed tomography scan of a patient with a concha bullosa of the right middle turbinate, hypoplasia of the right maxillary sinus and atelectasis of the uncinate process.

The middle meatus encompasses the agger nasi cell, uncinate process, hiatus semilunaris, maxillary sinus ostium (SO), frontal recess, and ethmoid bulla. Physiologically, the middle meatus is a critical area for clearance of mucociliary flow from the anterior ethmoid, frontal, and maxillary sinuses.

Superior Turbinate and Superior Meatus

The superior turbinate is positioned posterior to and in continuity with the middle turbinate. Although the inferior portion of the superior turbinate is a discretely separate structure, the superior portion including the skull base attachment points are in continuity with the middle turbinate in the parasagittal plane. Therefore, the designation "superior" is somewhat misleading as the superior turbinate is conceptually better considered as mostly posterior and somewhat superior to the middle turbinate[5,6] (Fig. 4.3). The superior turbinate is a useful landmark for several endoscopic procedures. It is the medial boundary during dissection of the posterior ethmoid cells during endoscopic sinus surgery for inflammatory sinusitis. In this approach, the posterior edge of the superior turbinate in the ethmoid cavity is immediately proximal to the anterior face of the sphenoid sinus. Viewed from a different trajectory, the superior turbinate is the lateral boundary during transnasal, trans-sphenoidal approaches to the sella. Following the superior turbinate to its posterior limit in this trajectory leads to the superior meatus and sphenoethmoid recess. The posterior ethmoid sinuses and sphenoid sinus physiologically clear their secretions in this area. The natural ostium of the sphenoid sinus is located in this space and can be identified by identifying the posterior inferior edge of the superior turbinate.[7] Resection of the lower edge of the superior turbinate can bring the transnasal and transethmoidal corridors into continuity, as may be done for extended approaches to the sphenoid sinus. Of note, olfactory epithelium lines the medial surface of the superior turbinate to a variable degree and therefore injury, including over-resection, to this structure may lead to hyposmia. Similar to the middle turbinate, the superior turbinate may be involved with polypoid degeneration, concha bullosa changes, and hypoplasia.

A fourth turbinate, termed the supreme turbinate, exists in a subset of patients with an estimated incidence of 60%.[5] When present, it is located posterior–superior to the superior turbinate and is variable in size. The medial surface of the supreme turbinate is also lined by olfactory epithelium and resection should be avoided.

PARANASAL SINUSES

Maxillary Sinus

The paired maxillary sinuses are the most constant of the paranasal sinuses in terms of size, anatomic relationships and lack of variation. Each sinus is pyramidal in shape with the apex pointing towards the zygomatic process. The volume of each sinus in an adult is approximately 15 milliliters and is composed of a single, nonpartitioned cavity. The medial boundary of the maxillary sinus is composed of the lateral nasal wall constituents including the inferior turbinate, uncinate process of the ethmoid bone and projections of the maxilla, palatine and lacrimal bones. The natural ostium of the maxillary sinus measures approximately 3 mm in diameter and is positioned in the superior–posterior aspect of the medial wall. The mucociliary function of the maxillary sinus physiologically clears secretions to the natural ostia and infundibulum. Accessory openings into the maxillary sinus occur in the lateral nasal wall of approximately 25% of the population and are typically situated posterior to the natural ostia. Care is given not to mistake a fontanelle for the natural ostia during endoscopic sinus surgery. Failure to incorporate both the ostia and fontanelle into a single maxillary antrostomy can result in an island of isolated mucosa and potential recirculation phenomenon. The roof of the maxillary sinus is composed of the orbital floor. The infraorbital nerve, a sensory branch of the second division of

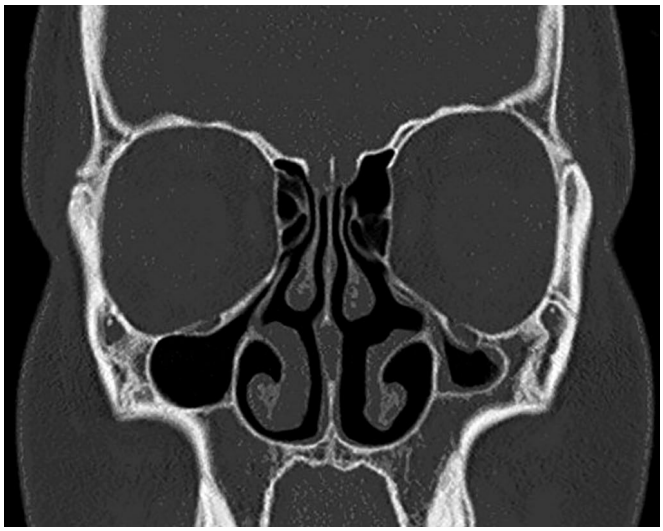


Fig. 4.10: Coronal computed tomography scan of a patient with bilateral maxillary sinus hypoplasia. A significant degree of atelectasis of the left uncinate process resulting in apposition against the orbital floor is noted.

the trigeminal nerve (V2), runs in the infraorbital canal, positioned approximately in the center of the orbital floor. The bony canal is often visible as a ridge in the roof of the maxillary sinus and in some cases may be dehiscent. The anterior face of the maxilla separates the malar soft tissues from the anterior border of the maxillary sinus. The infraorbital foramen transmits the infraorbital nerve to the facial soft tissues and is located in a superior–central portion of the anterior wall of the maxillary sinus. The bone over the canine tooth is typically the thinnest portion of the anterior wall. The floor of the maxillary sinus is composed of palatine and alveolar segments of the maxilla. In adults the floor is positioned approximately 1 cm inferior the nasal floor. The bony separation between the maxillary sinus and the upper dentition is variably thick and may allow for direct communication. The posterior wall of the maxillary sinus borders the PPF medially and the infratemporal fossa (ITF) laterally. Potential anatomic variants of the maxillary sinus include hypoplasia (Fig. 4.10) and septations.

Ethmoid Sinus

The ethmoid sinus is composed of multiple, individual cells separated by thin walled partitions within the ethmoid bone. The complexity and variability of this area has led many to refer to this area as a "labyrinth." Adding to the challenging nature of ethmoid sinus surgery is the proximity of critical neurovascular structures at the borders. The medial boundary is composed of the middle turbinate, superior turbinate and the olfactory fossa of the cribriform plate. The latter structure may be less than 1 mm thick, is tightly adherent to the underlying dura and has a variable depth in relation to the roof of the ethmoid cavity (fovea ethmoidalis). The distance between the lowest point of the olfactory fossa and the fovea ethmoidalis is classified based on the Keros classification[8]: type I 1–3 mm, type II 3–7 mm, type III 8–16 mm (Fig. 4.11). More important than a millimetric measurement, however, is understanding and identifying the potential hazard of a deeply recessed (type III) olfactory fossa when dissecting in the superior–medial aspect of the ethmoid sinus cavity. The superior boundary of the ethmoid cavity is predominantly composed of the fovea ethmoidalis segment of the frontal bone. This bone is typically thicker than the adjacent cribriform plate. Although the fovea ethmoidalis has a natural down sloping angle of approximately 15° in the anterior–posterior trajectory, this can vary to be either flatter or more steeply pitched (Figs. 4.12A and B). The latter variant places this structure at risk during ethmoidectomy. The fovea ethmoidalis also has a downward slope when viewed in a lateral to medial trajectory with the most inferior point corresponding to the junction of the lateral lamella of the cribriform plate. Asymmetry of the anterior skull base from side to side may also occur (Fig. 4.13). The lateral boundary of the ethmoid cavity is the thin-walled lamina papyracea portion of the ethmoid bone. The collinear position of the lamina papyracea with the maxillary sinus ostium serves as a useful landmark during ethmoidectomy. Additionally, close inspection of the lamina papyracea will often reveal a yellow coloration from the underlying orbital fat. Natural or disease related dehiscence of the lamina papyracea places the medial orbital structures at risk during endoscopic sinus surgery. The posterior boundary of the ethmoid sinus cavity is the anterior face of the sphenoid sinus.

An embryologic and anatomic distinction exists between the anterior and posterior ethmoid sinuses, including physiologic clearance points (middle meatus versus superior meatus), number of cells (greater number of anterior cells), and size of cells (larger posterior cells). The anterior and posterior cavities are separated by the ground lamella (also known as basal lamella) of the middle turbinate. The ethmoid bulla is a reliable landmark given that it is usually the largest of the anterior ethmoid cells and is positioned posterior to the uncinate process.

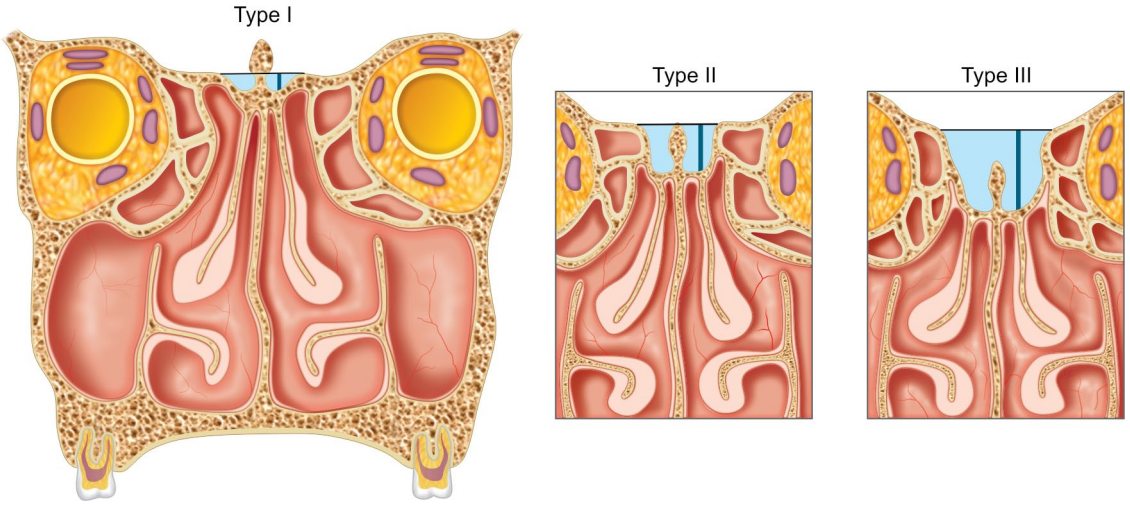
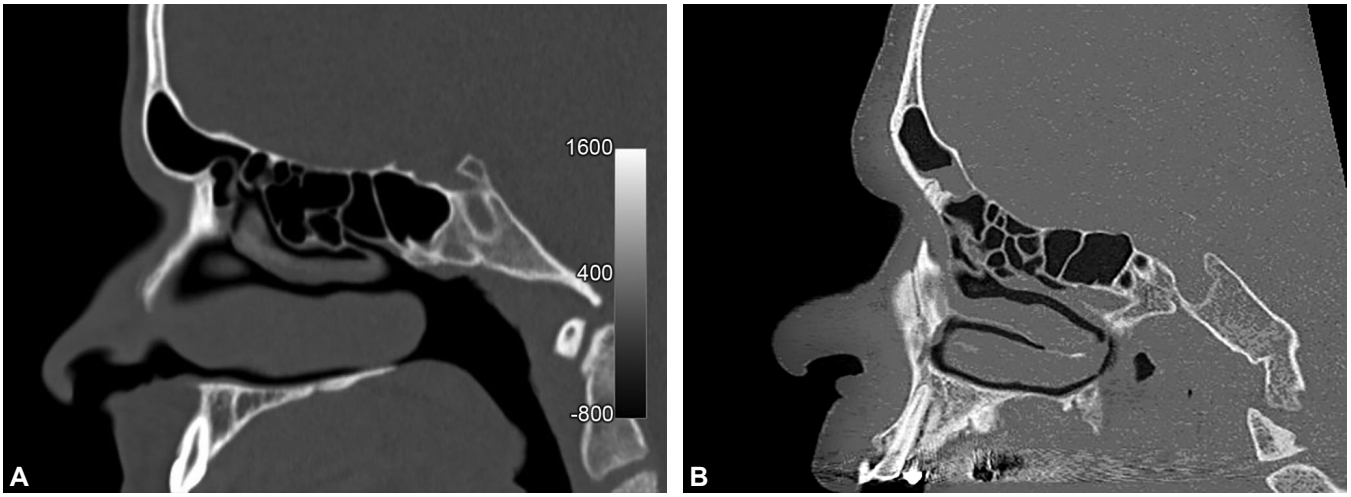


Fig. 4.11: The Keros classification describes the depth of the olfactory fossa in relation to the fovea ethmoidalis: type I (1–3 mm), type II (4–7 mm), and type III (8–16 mm).



Figs. 4.12A and B: Parasagittal computed tomography scan demonstrating a normal (A) and steeply pitched (B) fovea ethmoidalis. The latter is associated with increased risk of iatrogenic skull base injury.

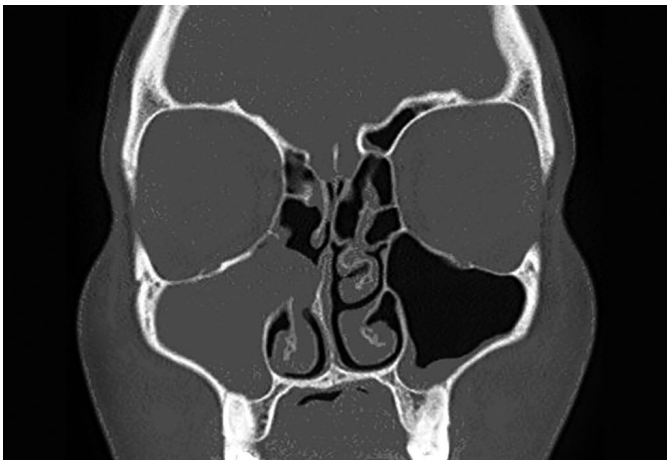


Fig. 4.13: Coronal computed tomography scan of a patient with asymmetric height of the fovea ethmoidalis. Attention to this potential variant is important when planning endoscopic ethmoidectomy to avoid inadvertent skull base injury (more likely on the lower side) while not leaving residual cell partitions (more likely on the higher side).

Tracing the anterior surface of the ethmoid bulla superiorly will lead to the frontal recess, as may be done with an "intact bullar" approach to the frontal sinus. The bulla may directly attach to the anterior skull base superiorly, may be attached by a single vertical lamella called the bulla lamella or may have a superior partition above which there is a space termed a suprabullar recess separating the bulla from the skull base. A vertical partition along the posterior surface of the ethmoid bulla may create a space between the bulla and the ground lamella, termed the retrobullar recess.

Agger Nasi, Uncinate Process, Infundibulum, and Hiatus Semilunaris

Agger (from Latin, meaning "mound") nasi are the most anterior ethmoid air cells and are identified as a rounded swelling in the lateral nasal wall, anterior to the middle turbinate. They are pneumatized in approximately 90% of individuals and have important spatial relationships to the frontal recess and frontal cells (anterior, lateral and inferior to the recess and frontal cells) and to the anterior superior attachment of the middle turbinate (anterior and above the attachment). Exteriorization of the posterior and superior surface ("cap") of a pneumatized agger nasi cell is important in the surgical management of chronic anterior ethmoid and frontal sinusitis.

The uncinate process is a crescent shape segment of the ethmoid bone that has important physiologic relationships. It is positioned lateral to the middle turbinate, anterior to the maxillary sinus ostia and ethmoid bulla. It attaches to the lateral nasal wall in multiple segments including the superior portion of the inferior turbinate, the maxilla, and the lacrimal bone. The superior most attachment is variable and impacts the drainage configuration of the infundibulum and frontal recess as described below in the frontal sinus section. Anatomic variants of the uncinate process exist and should be considered in preparation for surgery. An atelectatic uncinate process often occurs with a hypoplastic or nonventilated maxillary sinus and may be collapsed against the orbit (Figs. 4.9 and 4.10). This combination of factors may lead to negative pressure gas metabolism within the maxillary sinus and inward collapse of the surrounding walls including the floor of the orbit, termed silent sinus syndrome. A posterior to anterior, retrograde uncinectomy is indicated to prevent orbital injury in these cases. Medial displacement of the uncinate may also occur as result of polyposis and mass lesions filling the middle meatus and/or maxillary sinus. Lateral displacement of the uncinate may occur with a large concha bullosa, polyposis or other mass lesion. Pneumatization of the uncinate process may also occur.

The infundibulum is a three-dimensional space that serves as the physiological clearance area of the anterior ethmoid, maxillary and frontal sinuses. The hiatus semilunaris is the two-dimensional entrance on the medial aspect of the infundibulum. The uncinate process and ethmoid bulla define the anterior and posterior limits of the infundibulum, respectively. The other boundaries of the infundibulum include the lamina papyracea (lateral), frontal recess (superior), maxillary ostia (inferior).

Infraorbital (Haller), Sphenoethmoid (Onodi), and Supraorbital Cells

Haller cells (inferior orbital cells) are anterior ethmoid cells that are positioned along the medial portion of the orbital floor in the area of the maxillary sinus roof (Fig. 4.14). Their position and size may contribute to narrowing of the infundibulum and maxillary sinus ostium. The presence of these cells may increase the surgical complexity in performing a maxillary antrostomy. If the Haller cell is confused for the orbital floor, it may not be exteriorized and therefore outflow tract obstruction may persist. Conversely, if the orbital floor is confused for a Haller cell, attempted dissection of this area may result in an orbital injury.

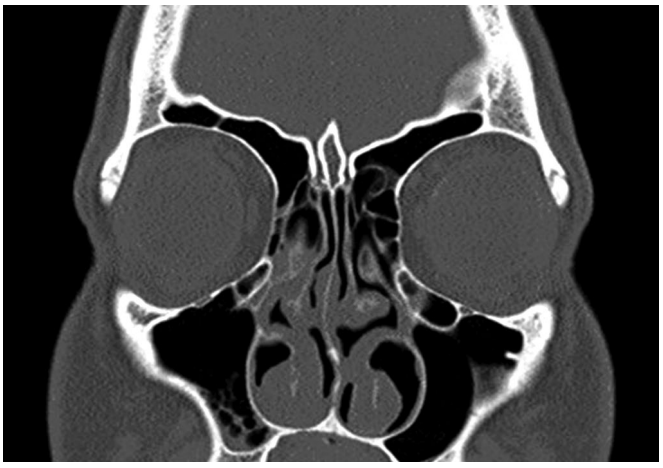
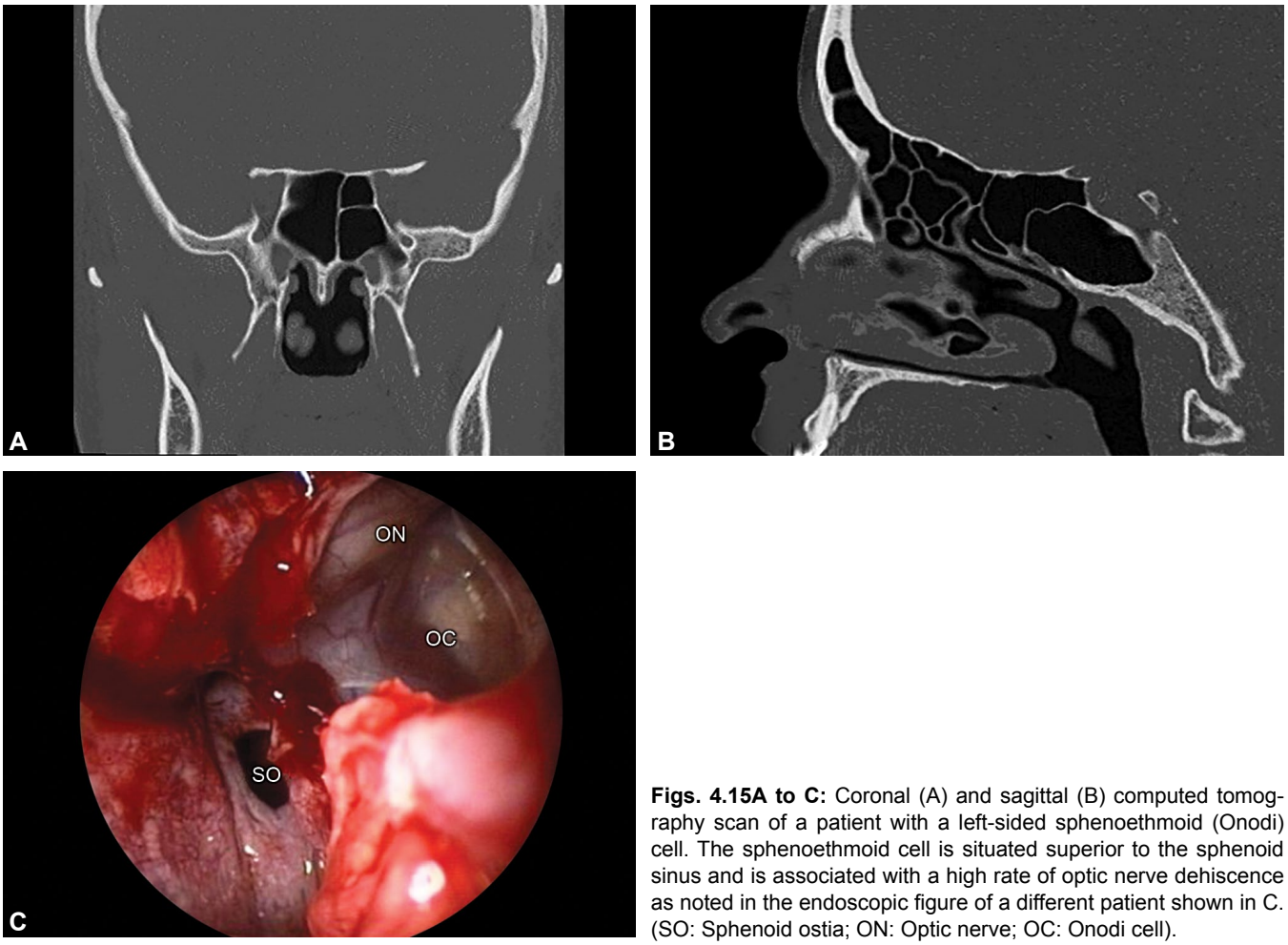


Fig. 4.14: Coronal computed tomography scan of a patient with bilateral infraorbital (Haller cells). These cells may potentially obstruct the infundibular outflow tract. Differentiation between these cells and orbital floor is necessary to allow for complete ethmoidectomy and preservation of the orbit.



Figs. 4.15A to C: Coronal (A) and sagittal (B) computed tomography scan of a patient with a left-sided sphenoethmoid (Onodi) cell. The sphenoethmoid cell is situated superior to the sphenoid sinus and is associated with a high rate of optic nerve dehiscence as noted in the endoscopic figure of a different patient shown in C. (SO: Sphenoid ostia; ON: Optic nerve; OC: Onodi cell).

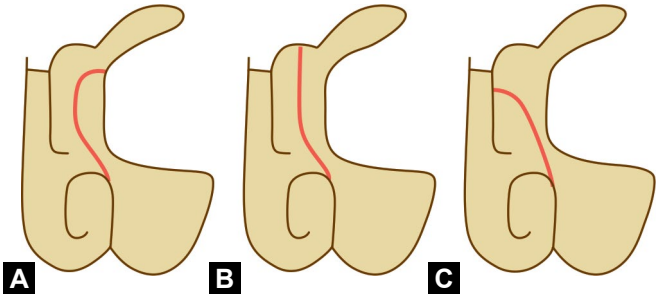
Onodi (sphenoethmoid) cells are posterior ethmoid air cells that pneumatize posterior, lateral and superior to the anterior face of the sphenoid sinus (Figs. 4.15A to C). These cells tend to displace the natural sphenoid sinus anteriorly, medially and inferiorly. On coronal and sagittal views, the Onodi cell is positioned above the sphenoid sinus. Recognition of the presence of an Onodi cell is necessary on preoperative imaging to avoid inadvertent skull base or optic nerve injury. The optic nerve typically runs in the superior–lateral surface of the Onodi cell and a significant rate of dehiscence has been reported. Differentiating an Onodi cell from the sphenoid sinus may be challenging especially in a transethmoidal trajectory.

A supraorbital cell is an ethmoid cell that pneumatizes into the orbital plate of the frontal bone. This cell is positioned over the orbit and can extend laterally to a variable degree. Given its position, it may be mistaken for a frontal sinus cell.

Frontal Sinus, Frontal Recess, and Frontal Cells

The anatomy of the frontal sinus and its outflow tracts are highly complex. The frontal sinus represents pneumatization within the frontal bone of the skull, defined by the thicker anterior table and the thinner posterior table. The posterior table separates the anterior horns of the frontal lobe of the brain from the frontal sinus. The floor of the frontal sinus corresponds to the orbital roof. The paired frontal sinuses are separated by an intersinus septation and are typically asymmetric. A variable number of sinuses may occur. Significant variability also exists in the pneumatization pattern of the frontal bone including unilateral or bilateral sinus hypoplasia and aplasia (approximately 10% of adults). Hyperpneumatization may also occur with far superior and lateral extension.

The frontal sinus outflow tract has an hourglass configuration. The three components of the outflow tract, from



Figs. 4.16A to C: Schematic representation of anatomic variants of the superior attachment point of the uncinate process. The frontal recess physiologically clears medial to uncinate process in patients where the superior attachment is the lamina papyracea (A). Conversely, the frontal recess clears lateral to the uncinate process in patients where the superior attachment is the skull base (B) or middle turbinate (C).

superior to inferior, are the infundibulum, frontal sinus ostium and frontal recess. The frontal sinus infundibulum is a funnel shaped space at the medial, posterior, inferior aspect of the frontal sinus that narrows towards the narrowest point of the hourglass, the frontal sinus ostium. The widening of the outflow tract inferior to the ostium and into the middle meatus is termed the frontal recess. The anatomic configuration of the frontal recess is defined by the surrounding structures: (1) the lamina papyracea laterally, (2) the anterior portion of the middle turbinate medially, (3) the ethmoid bulla or suprabullar recess posteriorly, and (4) agger nasi cell, frontal beak and frontal cells anteriorly. The relationship between the superior attachment of the uncinate and the frontal recess is variable. Additionally, the attachment of the uncinate process influences the drainage pattern of the frontal recess. Attachment of the uncinate process to the lamina papyracea results in the infundibulum terminating in a blind pouch superiorly termed the recess terminalis. The frontal recess in this situation opens medial to the infundibulum, between the middle turbinate and the uncinate process. In the second variant, the uncinate process attaches to the fovea ethmoidalis. In this situation, the frontal recess clears directly into the ethmoid infundibulum, lateral to the uncinate process. This is the same drainage pattern for the third variant in which the uncinate process attaches to the middle turbinate (Figs. 4.16A to C).

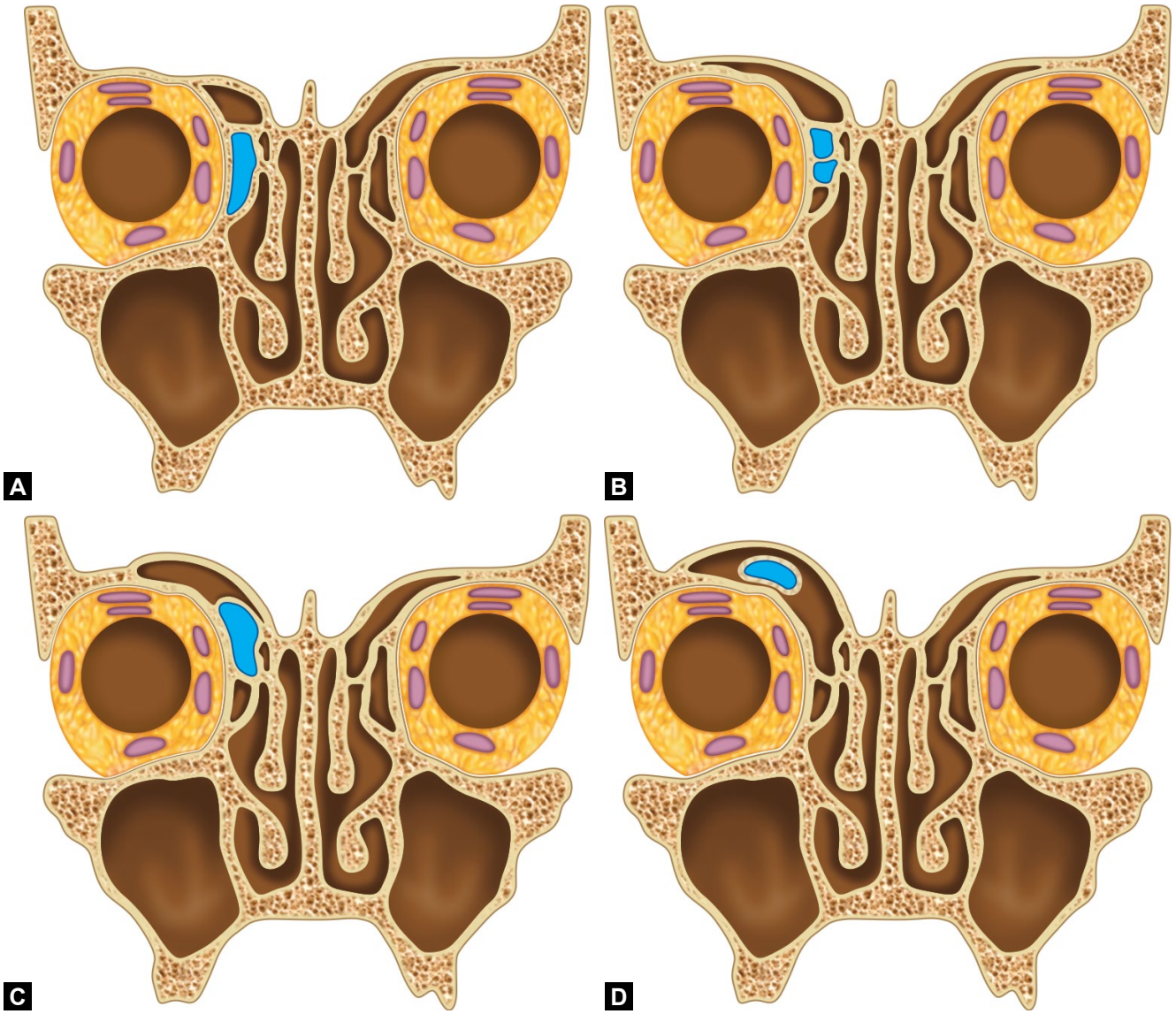
Frontal cells refer to anterior ethmoidal cells that originate in the infundibulum and pneumatize within the frontal sinus outflow tract. Originally classified by Bent and Kuhn,[9] the clinical significance of frontal cells relates to their potential for outflow tract obstruction. Additionally, understanding the pattern of frontal cells in a given patient is critical for successful endoscopic surgery of the frontal recess. Frontal cells are located above the agger nasi cell. A type 1 frontal cell is a single air cell within the recess. A type 2 cell is a group of two or more cells within the recess. A type 3 cell is a single cell that extends from the recess into the frontal sinus. A type 4 cell is an isolated cell completely within the frontal sinus (Figs. 4.17A to D).

Sphenoid Bone, Sphenoid Sinus

The sphenoid bone is a butterfly shaped bone that lies in the middle anterior cranial skull base. It comprises a central body, a single greater and lesser wing laterally, and pterygoid processes inferiorly. Each pterygoid process gives rise to a medial and lateral pterygoid plate, separated by a pterygoid fossa. The lesser wing of the sphenoid bone and the planum sphenoidale (PS) (roof of the sphenoid sinus) form the medial anterior cranial fossa, which houses the olfactory tracts and gyrus rectus. The medial portion of the middle cranial base consists of the sphenoid body, tuberculum sella (TS), sella turcica, middle and posterior clinoid processes, and dorsum sellae. The lateral aspect of the middle cranial base is formed by the lesser and greater wings of the sphenoid bone, which houses the temporal lobe.

Several critical neurovascular structures traverse through foramina contained within the sphenoid bone. The superior orbital fissure (SOF), positioned between the junction of the lesser and greater wings, transmits cranial nerves (CNs) III, IV, V-1 and VI, and the sympathetic fibers to the orbit. The optic canals carry the optic nerves, separated from the SOF by a ridge of bone called the optic strut. Other foramina located between the body and greater wing of the sphenoid include the foramen rotundum, pterygoid canal, foramen ovale and foramen spinosum. The foramen rotundum and pterygoid canal carry the maxillary nerve (V_2) and Vidian nerve, respectively, which lead into the PPF. The foramen ovale is located at the posterior aspect of the lateral pterygoid plate and transmits the mandibular nerve (V_3). The foramen spinosum transmits the middle meningeal artery and is located lateral to foramen lacerum on the infratemporal surface of the greater wing of the sphenoid bone (Fig. 4.18).

The sphenoid sinus is a large paired paranasal sinus located posterior to the ethmoid sinuses. The sphenoid sinus is often completely or incompletely divided into various compartments by bony septa. These septations



Figs. 4.17A to D: Schematic representation of frontal sinus cells. A type I cell (A) is a single air cell within the frontal recess. A type II cell (B) is a group of two more or cells confined to the recess. A type III cell (C) extends from the recess into the frontal sinus. A type IV cell (D) is an isolated cell completely within the frontal sinus.

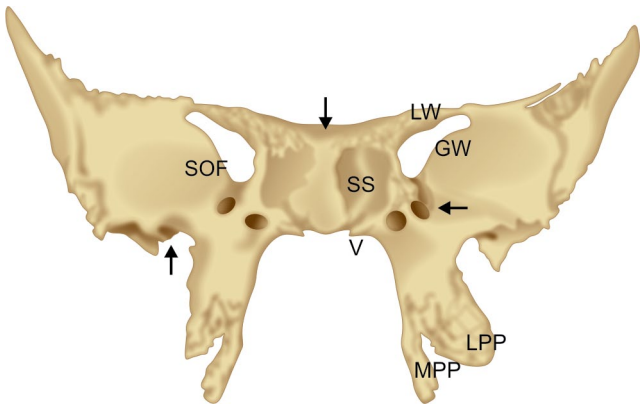
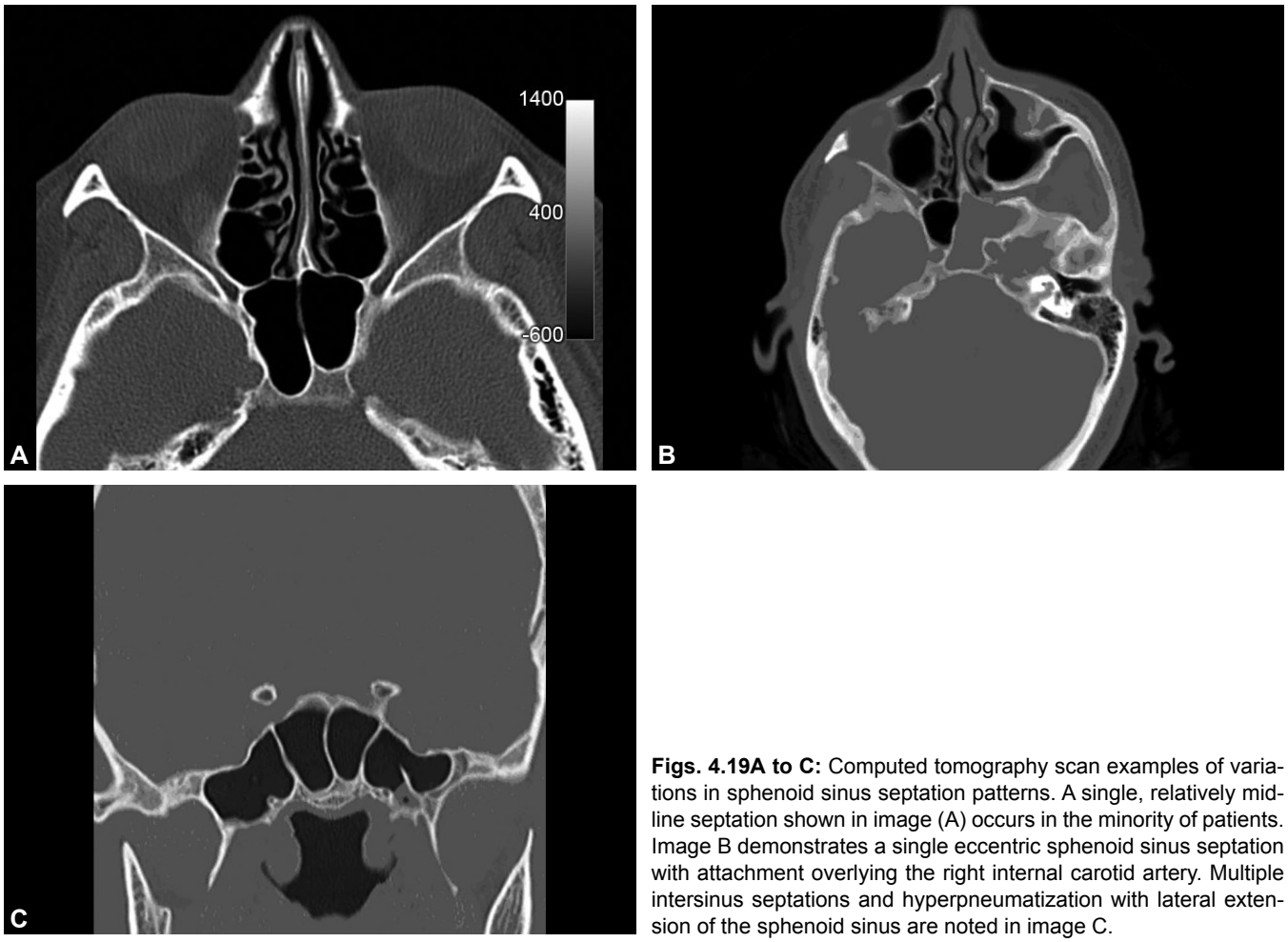


Fig. 4.18: Schematic representation of the sphenoid bone, anterior view. The sphenoid bone is a butterfly shaped bone that lies in the middle anterior cranial skull base. It comprises a central body, a single greater and lesser wing laterally, and pterygoid processes inferiorly. (LW: Lesser wing of the sphenoid bone; GW: Greater wing of the sphenoid bone; SOF: Superior orbital fissure; SS: Sphenoid sinus; LPP: Lateral pterygoid plate; MPP: Medial pterygoid plate; up arrow, foramen ovale; down arrow, planum sphenoidale; side arrow, foramen rotundum; V: Vidian canal).

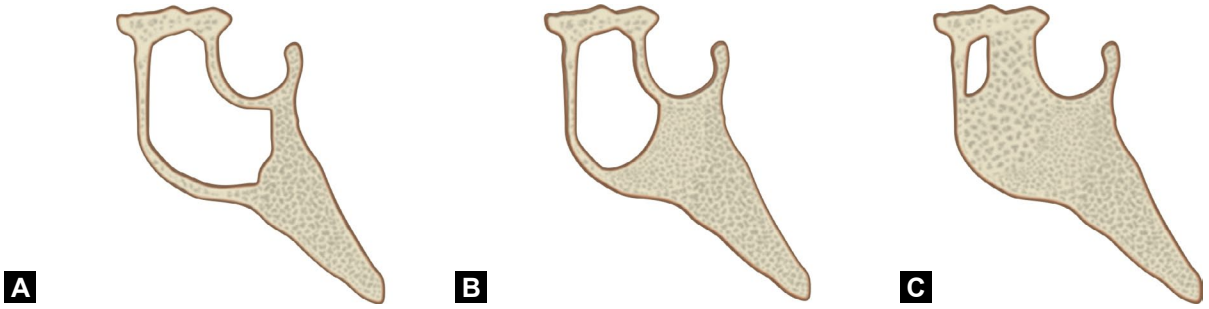


Figs. 4.19A to C: Computed tomography scan examples of variations in sphenoid sinus septation patterns. A single, relatively midline septation shown in image (A) occurs in the minority of patients. Image B demonstrates a single eccentric sphenoid sinus septation with attachment overlying the right internal carotid artery. Multiple intersinus septations and hyperpneumatization with lateral extension of the sphenoid sinus are noted in image C.

often adjoin the posterior wall of the sinus overlying the carotid artery, with as many as 87% of sphenoid septations inserting at the carotid artery, commonly in the parasellar and paraclival segments.[10] As such, caution should be exercised to ensure atraumatic removal of septations and avoidance of catastrophic vascular injury. In recent studies, as visualized on computed tomography scan and endoscopic dissection, 48–54% of sphenoid sinuses contain one septation, 33–41% contain two septations, and 13–18% contain 3 or more septations.[10,11] Only 11% of specimens have an isolated midline septation on endoscopic dissection (Figs. 4.19A to C).[10]

Pneumatization of the sphenoid sinus is highly variable and can extend as far laterally as the sphenoid wings, and inferiorly to the clivus and foramen magnum. Pneumatization occurs in a progressive fashion during childhood. Therefore, incomplete or partial pneumatization is far more common in the pediatric population. The historically accepted classification scheme for sphenoid sinus pneumatization patterns includes three types, sellar (80%), presellar (17%), and conchal (3%),[12] as originally proposed by Hammer and Radberg (Figs. 4.20A to C).[13] Preoperative imaging is crucial to evaluating such variations in sphenoid sinus anatomy in order to ensure safe entry into the sinus and access to the target lesions.

The sphenoid sinus ostium is located approximately two thirds up the anterior wall of the sphenoid sinus, positioned 21.21 ± 6.02 mm superolateral to the posterior choana and 4.85 mm ± 2.89 mm lateral to the midline.[14] The posteroinferior end of the superior turbinate is a useful reference point for localizing the sinus ostium. The sinus ostium resides approximately 10.6 ± 3.0 mm above the posteroinferior border of the superior turbinate, draining medial to the turbinate in 83% of cases (Fig. 4.21).[7] The sinus ostium can be visualized with gentle lateralization of the superior turbinate in the sphenoethmoid recess, enclosed by the



Figs. 4.20A to C: Schematic representation of sphenoid sinus pneumatization patterns including sellar (A), presellar (B), and conchal variants (C).

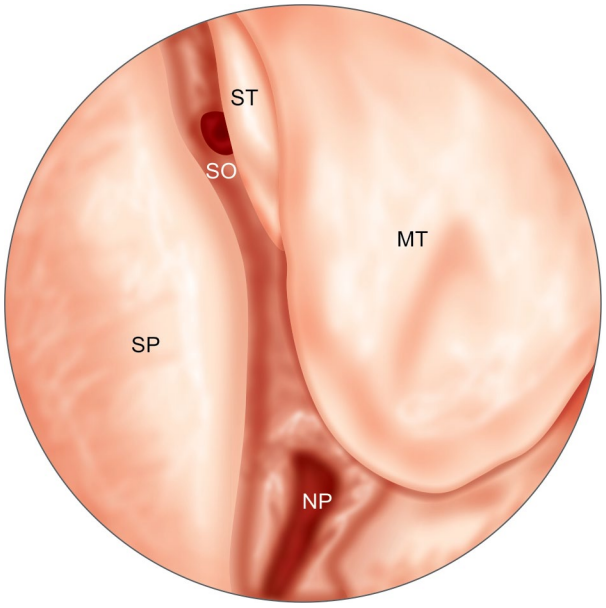


Fig. 4.21: Schematic representation of the left sphenoethmoid recess demonstrating the relationship of the sphenoid sinus natural ostia (SO) with the nasal septum (SP), nasopharynx (NP), middle (MT), and superior (ST) turbinates. The ostia is normally positioned approximately two-thirds up the anterior face of the sphenoid sinus.

septum medially, superior turbinate laterally, cribriform plate superiorly, and the nasal floor inferiorly. The sphenoid sinus can also be accessed past the posterior ethmoidal cells through the medial–inferior triangle of the sphenoid face. This approach avoids risk to the optic nerve and carotid artery in the superior–lateral triangle. The sphenoid sinus can also be accessed through a transpterygoid approach.[15]

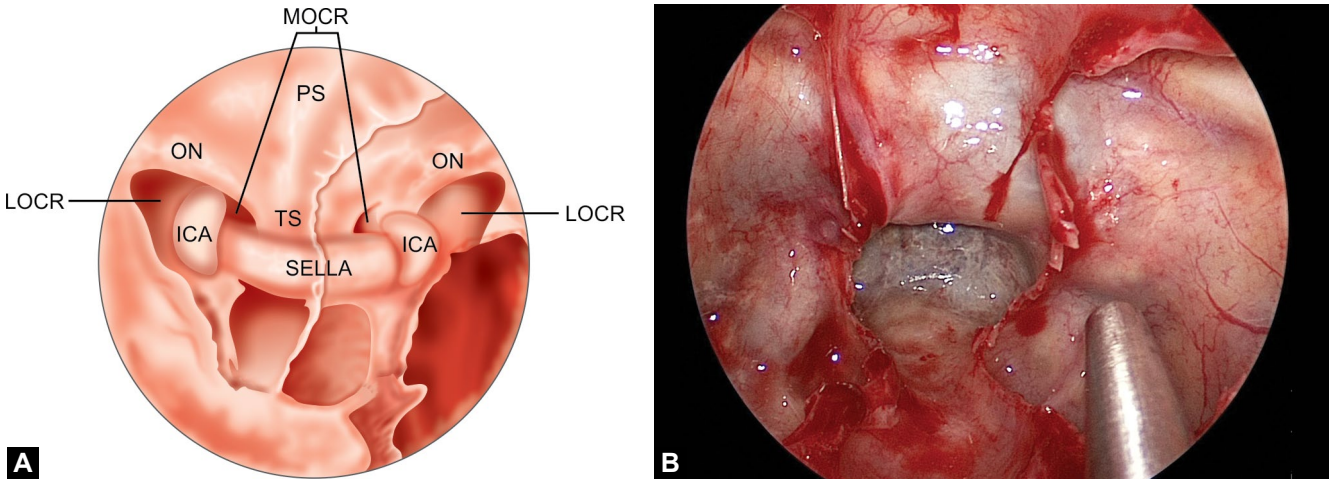
SKULL BASE

Anterior Skull Base

The osteology of the anterior skull base separates the cranial and sinonasal cavities. Medially, this consists of portions of the ethmoid bone and PS. The ethmoid bone is situated at the anterior base of the cranium between the two orbits. The medial component of the ethmoid bone is membranous bone composed of the crista galli, cribriform plate and perpendicular plate of the nasal septum. The crista galli is a piece of bone, resembling a "cock's comb" in shape, that extends intracranially to attach to the falx cerebri. This dural attachment is transected during endoscopic anterior craniofacial resection to allow for resection of the crista galli. The crista galli articulates inferiorly with the perpendicular plate of the nasal septum. The cribriform plate houses the paired olfactory bulbs and has numerous perforations through which the olfactory fibers pass to the nasal vault, superior and middle turbinates and the nasal septum (*see* Fig. 4.2). The lateral osteology of the anterior cranial base is composed of the fovea ethmoidalis, frontal bone and lesser wing of the sphenoid. The anterior to posterior span of the cranial component of the anterior skull base is defined by the posterior table of the frontal sinus anteriorly and the chiasmatic sulcus of the sphenoid bone and associated optic chiasm posteriorly. The anterior skull base houses the frontal lobes (gyrus rectus medially, orbital gyrus laterally) and cerebral vessels (anterior cerebral artery medially, middle cerebral artery laterally).

Sella and Suprasellar Regions

The sella lies within the midline posterior wall of the sphenoid sinus, superior to the intrasphenoidal clivus, separated by the sellar–clival junction. Superior and anterior to the sella lies the PS, separated from the sella by a thick bony ridge, termed the TS, which corresponds to the chiasmatic sulcus intracranially (Figs. 4.22A and B). The lateral wall of the sphenoid sinus involves four bony prominences and three depressions. The bony prominences from superior to inferior include the prominences of the



Figs. 4.22A and B: Schematic (A) and endoscopic (B) representations of the sellar anatomy as viewed within the sphenoid sinus. (TS: Tuberculum sella; PS: Planum sphenoidale; ICA: Internal carotid artery; ON: Optic nerve; MOCR: Medial opticocarotid recess; LOCR: Lateral opticocarotid recess).

optic nerve, parasellar ICA, maxillary (V2), and mandibular (V3) divisions of trigeminal nerve. The three bony depressions include the lateral opticocarotid recess (LOCR), the depression between cavernous sinus apex and V2, and the depression between V2 and V3. The LOCR is delineated superolaterally by the optic nerve and inferomedially by the parasellar ICA. The floor of the optic canal forms the LOCR superiorly, the SOF inferiorly, and the lateral border of the carotid prominence medially.[16] It corresponds to the optic strut and anterior clinoid processes intracranially. This bone that forms the LOCR can be thin or absent altogether, producing a dehiscence of the ICA.[17] The oculomotor nerve may also be found inferiorly within this recess. The next recess is a triangular region with the base located at the parasellar carotid and apex corresponding to the SOF. The third recess, between V2 and V3, represents an embryologic fusion plane of the basisphenoid called Sternberg's canal. Lateral sphenoid sinus encephaloceles and cerebrospinal fluid leaks can be found within this recess secondary to dehiscence.[17,18] Another recess, termed the medial opticocarotid recess (MOCR), is located at the intersection of the optic canal, carotid canal, sella and anterior cranial base, and corresponds to the medial clinoid intracranially. The MOCR has been described as an important "keyhole" landmark in skull base surgery. With its position at the medial aspect of the lCA sulcus, the MOCR offers an entry point for access to surrounding structures, while providing a safe border for prevention of injury to the adjacent paraclinoid ICA.[16]

The pituitary gland is located in the center of the cranial base, supported by a bony saddle, called the sella turcica ("Turkish saddle"). The diaphragma sellae forms a dural roof of the sella turcica, which covers the pituitary gland. The sella turcica is surrounded by a number of neurovascular structures including the optic nerves, optic chiasm and anterior circulation superiorly; the cavernous sinuses, ICAs and multiple CNs laterally; and the brainstem and posterior circulation posteriorly. Due to the high density of neurovascular structures located superiorly, laterally, and posteriorly in relation to the pituitary gland, anterior approaches have become the preferred approach to the sellar region.

The optic nerves pass through the suprasellar region and anterior incisural space. The anterior incisural space spans from the anterior border of the brainstem upward around the optic chiasm to the midline position of the subcallosal space.[19] The optic nerves exit the optic canals medial to the anterior clinoid processes and travel in a posterior, medial, and superior trajectory toward the optic chiasm. The optic tracts leave the chiasm and traverse posteriorly and laterally around the cerebral peduncles to enter the midline incisural space. The optic chiasm is positioned inferior to the junction of the anterior wall and floor of the third ventricle. Structures situated superior to the optic chiasm include the anterior cerebral and anterior communicating arteries, lamina terminalis and third ventricle. Laterally to the optic chiasm lie the ICAs, posteriorly lies the infundibulum, while the diaphragma sellae and pituitary gland are seated beneath the optic

chiasm. The infundibular recess lies at the base of the pituitary stalk behind the chiasm.[20]

Vascular Anatomy
Sellar/Suprasellar Region

The meningohypophyseal trunk, the largest branch of the intracavernous carotid artery, provides the majority of the bloody supply to the sellar region. The meningohypophyseal artery exits the cavernous portion carotid artery at the level of the dorsum sellae and gives rise to the inferior hypophyseal artery. The inferior hypophyseal artery travels medially, where it anastomoses with its counterpart from the contralateral side, and provides circulation to the posterior pituitary and dura of the sellar floor.

The perforating branches of the ICA also supply the optic nerve, chiasm, optic tract, infundibulum, and floor of the third ventricle. The superior hypophyseal artery originates from the supraclinoid portion of the carotid artery, and travels medially beneath the floor of the third ventricle, where it connects with its counterpart from the opposite side to form a vascular ring around the infundibulum (Fig. 4.23). The first branch of the ICA is the ophthalmic artery, which enters the optic canal just below the optic nerve. It most commonly arises from the supraclinoid portion of the carotid artery, but can also arise from the intracavernous carotid[21] and, rarely, from the middle meningeal artery.[22]

The suprasellar area harbors the circle of Willis. The anterior portion of the circle of Willis borders the anterior wall of the third ventricle and is composed of the anterior cerebral and anterior communicating arteries. The anterior cerebral artery arises from the ICA and passes anteromedially above the optic nerve and chiasm, where it typically anastomoses with the contralateral artery at the interhemispheric fissure. The convergence of the bilateral A1 segments typically occurs above the optic chiasm, forming the anterior communicating artery. Perforating branches arise from the anterior cerebral and anterior communicating arteries that supply the third ventricle, hypothalamus, fornix, and the anterior part of the basal ganglia and internal capsule (the recurrent artery of Heubner).[23]

The posterior communicating artery arises from the posterior wall of the internal carotid and travels posteromedially inferior to the optic tracts and floor of the third ventricle to join the posterior cerebral artery. Branches from the posterior communicating artery provide blood supply to the optic chiasm, thalamus, hypothalamus, and internal capsule. The anterior choroidal artery originates from the ICA posteriorly, above the origin of the posterior communicating artery. The anterior choroidal artery travels in close proximity to the inferior surface of the optic tract as it progresses posteriorly between the uncus and cerebral peduncle to ultimately supply the optic tract, globus pallidus, genu of the internal capsule, posterior part of the third ventricle and ultimately the lateral choroid plexus. The venous channels within the suprasellar region are not typically transgressed during surgical exposure and are therefore less of a concern for intraoperative bleeding. Tributaries of the basal vein of Rosenthal drain this region, traveling between the midbrain and temporal lobes feeding into the internal cerebral vein complex at the vein of Galen. The internal cerebral veins often travel in the roof of the third ventricle where they join caudally near the pineal body to form the great vein Galen, as mentioned. Fortunately the internal cerebral veins are rarely involved with suprasellar pathology, but great care must be exercised if preoperative imaging suggests any close anatomical relation with these structures.

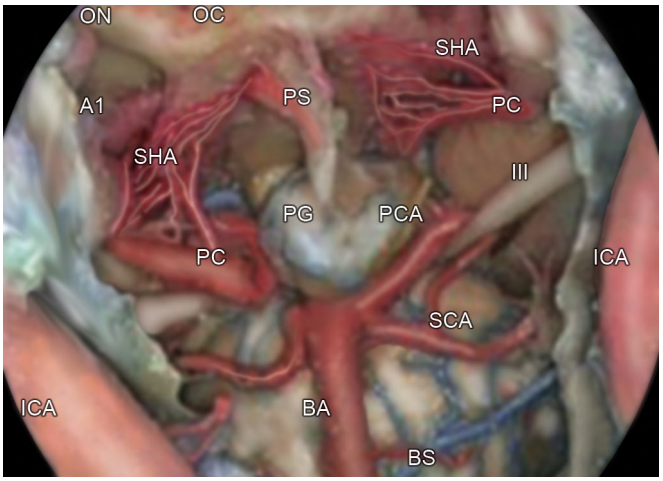


Fig. 4.23: Cadaveric representation of the parasellar vascular and neural anatomy following removal of the dural layers of the diaphragmatic sella and cavernous sinus. (ICA: Internal carotid artery; A1: A1 segment of the anterior cerebral artery; SHA: Superior hypophyseal artery; PC: Posterior communicating artery; PCA: Posterior cerebral artery; SCA: Superior cerebellar artery; BA: Basilar artery; III: Oculomotor nerve; OC: Optic chiasm; ON: Optic nerve; PG: Pituitary gland; PS: Pituitary stalk; BS: Brainstem).

Cavernous Sinus

The cavernous sinuses reside along the lateral aspect of the sphenoid sinus, sella and pituitary gland, spanning

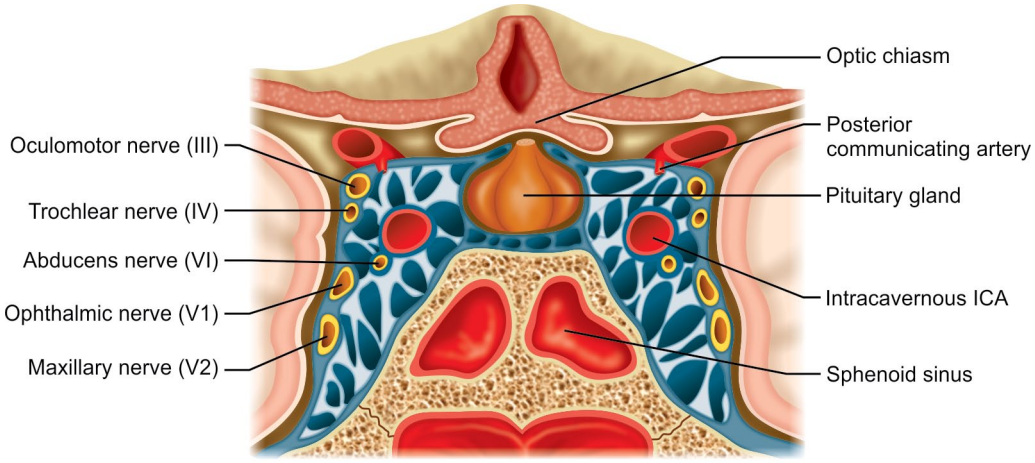


Fig. 4.24: Schematic representation of the cranial nerve anatomy of the cavernous sinus.

from the SOF anteriorly, to the petrous apex posteriorly. The medial walls of the cavernous sinus abut the lateral wall of the pituitary gland, often separated by a single layer of dura, thus allowing sellar tumors to extend laterally into the cavernous sinus. The ICA lies medially within the cavernous sinus. The artery enters the cavernous sinus after leaving the foramen lacerum and turning abruptly forward, traverses the cavernous sinus in a horizontal direction before passing upward along the lateral aspect of the anterior clinoid process. The intracavernous carotid artery is fixed at multiple points, which include bony rings of the anterior and middle clinoid processes and carotid sulcus. The intracavernous carotid artery provides blood supply to sellar contents via the meningohypophyseal trunk.[23]

Venous channels running along the border of the diaphragma sellae and pituitary gland connect the bilateral cavernous sinuses. These intercavernous sinuses are located anterior, posterior, and inferior to the pituitary gland. If the anterior and posterior intercavernous sinuses connect, the entire venous channel is called the circular sinus. The largest, constant, intercavernous sinus is the posterior basilar sinus located behind the dorsum sellae and upper clivus. The anterior intercavernous sinus is often larger than the posterior basilar sinus and can occasionally occupy the entire anterior sellar wall. This can result in intraoperative bleeding during a transsphenoidal procedure, which can be controlled with compression of the venous channel and use of hemostatic agents. Other multiple combinations of intercavernous sinuses may occur.[23,24]

Multiple CNs reside within the cavernous sinus including, superiorly to inferiorly, the oculomotor (CN III), trochlear (IV), ophthalmic division of the trigeminal nerve (V1), and abducens (VI) nerves. Cranial nerves III, IV and V1 lie between two dural leaves of the lateral sinus wall. Cranial nerve III enters the cavernous sinus anterior and lateral to the dorsum sellae, and lies slightly anteromedial to CN IV. V1 enters the sinus inferiorly and traverses upward to exit through the SOF. Cranial nerve VI penetrates the cavernous sinus at the posteroinferior border running medial and parallel to the ophthalmic nerve. Cranial nerve VI is bordered medially by the lateral wall of the intracavernous carotid (Fig. 4.24).[25] The ascending postganglionic sympathetic fibers to the eye, including Muller's muscles, enter the cavernous sinus with the carotid artery, follow the abducens nerve to the SOF and then follow V_1 to the orbit.

Clivus and Paraclival Region

The clivus is positioned at the center of the skull base and is formed by the posterior portion of the sphenoid body (basisphenoid) and occipital bone (basiocciput). It can be divided into thirds, composed of intrasphenoidal (upper one-third) and extrasphenoidal (lower two-thirds) components. The upper third of the clivus is formed by the basisphenoid and dorsum sellae, the middle third by the portion of the basiocciput above the petroclival fissures, and the lower third by the lower part of the basiocciput. The tectorial membrane overlies the clival dura in the basioccipital portion of the clivus. The largest intercavernous sinus, the basilar sinus, passes

from the dorsum sellae to the lower clivus connecting the posterior aspect of both cavernous sinuses.[24] Exposure through the inner dural layer and arachnoid reveals critical neurovascular structures including the vertebral arteries, basilar artery and its branches (superior cerebellar arteries, anterior inferior cerebellar arteries) posterior cerebral arteries, the brainstem and CNs III, IV, V, and VI (Fig. 4.23).

The oculomotor nerve (CN III) arises from the medial side of the cerebral peduncle, in the interpeduncular cistern, and courses between the superior cerebellar and posterior cerebral arteries. The oculomotor nerve travels in the lateral wall of the interpeduncular cistern, enters the roof of the cavernous sinus and traverses downward in the superior and lateral corner of the cavernous sinus. The trochlear nerve (CN IV) has a particularly long intracranial course, arising below the inferior colliculi and advancing around the dorsal midbrain, coursing under the tentorial edge, and piercing the roof of the cavernous sinus near the anterior tentorial attachment. The trigeminal nerve (CN V) arises from the midpons and divides into its three main branches, ophthalmic (V1), maxillary (V2), and mandibular (V3), at the anterior margin of the trigeminal ganglion. The ophthalmic division (V1) travels in the anteroinferior portion of the cavernous sinus. The medial aspect of the maxillary nerve (V2) flanks the sphenoid sinus as it courses inferior to the cavernous sinus, producing a prominence in the lateral wall of the sphenoid sinus. The abducens nerve (VI) originates near the lower margin of the pons and can pass either above or below the anteroinferior cerebellar artery. Cranial nerve VI passes through the prepontine cistern and pierces the dura of the clivus at Dorello's canal to enter the posterior aspect of the cavernous sinus near the superior border of the petrous apex.[24]

Pterygopalatine Fossa

The PPF is an inverted pyramidal space, which serves as a portal for a number of endoscopic approaches to the anterolateral skull base.[26-28] This pyramidal region is formed by the pterygoid plates posteriorly, the maxilla anterolaterally, the perpendicular plate of the palatine bone medially, and the body of the sphenoid superiorly. The PPF communicates with the ITF laterally via the pterygomaxillary fissure. This region is of particular importance given its intimate relationship with many critical structures, including branches of the IMA, the Vidian nerve, maxillary nerve, and pterygopalatine ganglion. The PPF can be divided into two compartments, with its anterior compartment containing fat and blood vessels and its posterior compartment containing neural components.

The pterygopalatine branches of the IMA include the posterior superior alveolar artery, infraorbital artery, descending palatine artery, pharyngeal artery, artery of the pterygoid canal, and SPA. The SPA branches carry blood to several vascularized pedicled flaps utilized for endoscopic skull base reconstruction. Specifically, the posterior lateral nasal artery supplies the nasal turbinates and the posterior septal artery, with its anastomoses with the ethmoidal arteries, supplies the posterior nasal septum (*see* Fig. 4.7). The pterygoid venous plexus, which is positioned between the masticator, temporal, and the internal and external pterygoid muscles, provides venous drainage from this region.

The pterygopalatine (sphenopalatine) ganglion, residing in the PPF, is one of four parasympathetic ganglia in the head and neck. The nerves associated with the ganglion include the Vidian nerve, pharyngeal nerve, descending palatine nerves, nasopalatine nerves, and the posterior superior nasal nerve. The Vidian nerve carries preganglionic parasympathetic fibers from the greater petrosal nerve and postganglionic sympathetic fibers from the deep petrosal nerve. The Vidian nerve travels through the Vidian canal and its parasympathetic fibers then synapse on the pterygopalatine ganglion. The parasympathetic branches then distribute to the nose, palate, and lacrimal gland through the foramina in the PPF. The Vidian nerve serves as a valuable surgical landmark for localizing the petrous ICA during supra- and infrapetrous transpterygoid approaches (Fig. 4.25). The maxillary nerve (V2) enters the PPF through the foramen rotundum, distributes its branches, and then continues as the infraorbital nerve through the infraorbital canal, which separates the PPF from the ITF laterally. Primary lesions of the PPF are rare. However, this region may contain metastatic disease or serve as a conduit for local extension of sinonasal or pharyngeal lesions into the ITF, petrous apex, orbital apex, or middle cranial fossa. There are eight different foramina that transmit various neurovascular structures through the PPF. The infraorbital nerve, zygomatic nerve, infraorbital vessels, and ophthalmic vein pass through the inferior orbital fissure (IOF) anteriorly to communicate with the orbit. Medially, the sphenopalatine foramen carries the SPA into the nasal cavity, and laterally, the maxillary vessels pass through

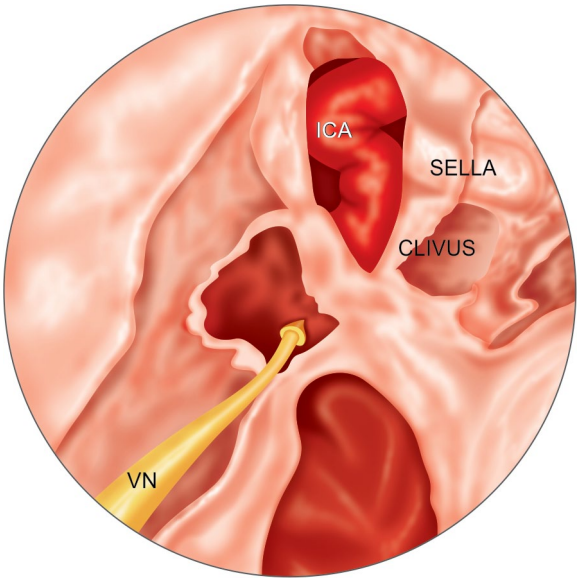


Fig. 4.25: Schematic representation of the Vidian nerve (VN) and its position relative to the paraclival internal carotid artery (ICA).

the pterygomaxillary fissure to communicate with the ITF. Inferiorly, the greater and lesser palatine canals transmit the greater and lesser palatine nerves and vessels, which supply the palate. Three of the eight foramina reside posteriorly within the PPF, including the foramen rotundum, the Vidian (pterygoid) canal, and the pharyngeal (palatovaginal) canal. The foramen rotundum transmits V2, while the Vidian canal, located 7–10 mm inferomedial to foramen rotundum, carries the Vidian nerve to the pterygopalatine (sphenopalatine) ganglion. Branches of the IMA supply the nasopharynx as they pass through the pharyngeal canal located at the lateral part of the posterior choanae.[27]

Infratemporal Fossa

The ITF fossa is a large irregular space located above the parapharyngeal space that is bound medially by the lateral pterygoid plate, the pyramidal process of palatine bone, and squamous portion of the temporal bone; laterally by the zygomatic arch and mandible; superiorly by greater wing of the sphenoid; inferiorly by the alveolar processes; anteriorly by the posterior surface of the maxilla; and posteriorly by the auricular tubercle of the temporalis bone, and spine of the sphenoid bone.

The ITF communicates superiorly with the temporalis fossa transmitting the temporalis muscle, nerve and vessels. It also contains the mandibular division of the trigeminal nerve traveling through foramen ovale and the middle meningeal vessels from the foramen spinosum. Anteriorly, it connects with the orbital cavity via the IOF that is located between the greater wing of the sphenoid and maxilla; and medially with the PPF via the pterygomaxillary fissure by sending through the terminal branches of the IMA.

The fossa contains a number of structures that are bound by fatty fibro connective tissue including the medial and lateral pterygoid muscles, the sphenomandibular ligament, the mandibular division of the trigeminal nerve, the chorda tympani nerve, the IMA and branches of its mandibular and pterygoid divisions, the middle meningeal artery, and the pterygoid venous plexus.

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CHAPTER

5

Physiology of the Nose and Paranasal Sinuses

Richard A Lebowitz, Whitney Pafford

REGULATION OF AIRFLOW

Both static and dynamic components play an important role in the regulation of airflow and overall nasal resistance. Normally, maximal nasal airflow is through the middle meatus, with the second greatest amount of airflow being through the inferior meatus. Except during active "sniffing," which increases airflow to the superior meatus, upper nasal cavity, and olfactory cleft region, these areas have relatively little airflow. Although nasal airflow is for the most part turbulent, it generally follows Poiseuille's law of physics for the flow of a liquid through a tube, which states that resistance is inversely proportional to the fourth power of the radius (Fig. 5.1). Therefore, the minimal cross-sectional area of the nasal cavity, i.e. the "radius" of the "tube" through which the air is flowing, is the most important factor determining nasal resistance and airflow.

The cross-sectional area of the nose at any point is determined by a number of factors. Septal deviations, turbinate medialization/pneumatization, and hypertrophy may all narrow the nasal cavity, leading to a baseline increase in nasal resistance. In addition to these anatomic structures, there are two nasal valves that may play a significant role in determining nasal resistance and airflow. The external nasal valve is composed of the columella, nasal floor (sill), and the caudal border of the lower lateral cartilage. This valve contributes little to airway resistance under normal circumstances due to its large size and dilation by the nasalis muscle during inspiration. However, deviation of the caudal end of the nasal septum/columella, alar (lower lateral cartilage) collapse during inspiration, or any other cause of vestibular stenosis can result in increased resistance at the level of the external nasal valve and reduced airflow through the nare. The internal nasal valve is the narrowest segment of the human airway and, as such, is responsible for about half of all airway resistance (*see* Poiseuille's law above). Its slit-like triangular opening is composed of rigid structures, including the anterior head of the inferior turbinate, the nasal septum, and caudal aspect of the upper lateral cartilage (Fig. 5.2). By significantly increasing nasal resistance and reducing nasal airflow, the narrow design of the internal nasal valve allows for greater contact of the inspired air with the inferior turbinate, thus facilitating the necessary warming, humidification, and cleansing of the air destined for the more sensitive lower airway. Venous sinusoids in the soft tissue of the inferior turbinate in this region may be quickly filled or drained to permit rapid variations in cross-sectional area of the nasal valve with subsequent variations in airway resistance and nasal airflow. The angle of the internal nasal valve varies among ethnicities. Caucasians have a more acute angle (normal range of 10–15°), leading to a larger impact on airway resistance in this population when compared with individuals of African or Asian descent.[1,2] Dynamic collapse may also be noted at the internal nasal

where:

$$R = \frac{8\eta l}{\pi r^4}$$

R = resistance
η = viscosity of the inspired gas
l = length of the airway
r = radius of the airway

Fig. 5.1: Poiseuille's law.

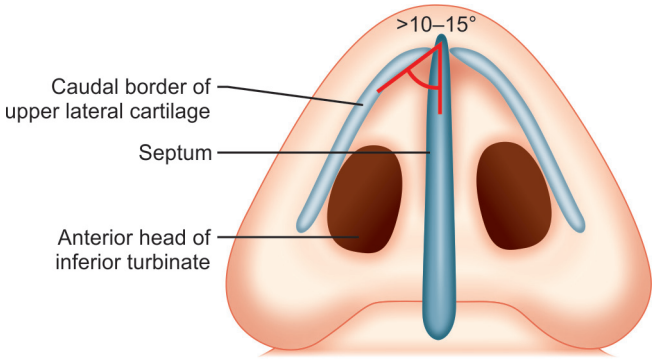

Fig. 5.2: Internal nasal valve.

valve, causing an increase in resistance. This occurs when the negative pressure in the nose exceeds the rigidity of the cartilaginous portion of the valve (upper lateral cartilage) during inspiration, resulting in collapse of the lateral nasal wall.

In addition to anatomic variations causing static narrowing of the nasal cavity, congestion of the nasal mucosa, neural tone, inflammation, and secretions all may further decrease the cross-sectional area. These dynamic changes in the nasal airway are achieved through the nasal mucosa. To understand the regulation of these functions, it is first necessary to understand the anatomy of the nasal mucosa.[3,4]

The nasal mucosa is a highly vascularized pseudostratified columnar ciliated respiratory epithelium containing both goblet cells and seromucinous glands, which lines the sinonasal cavity. The mucosal membrane is thickest and most vascular over the nasal conchae. It may also be thick over the nasal septum, particularly in the region of the septal body, but is normally thin along the floor of the nasal cavity and within the paranasal sinuses. The lamina propria is a thin, fibrous layer that forms the basement membrane. The submucosa of the sinonasal mucosa contains a dense layer of seromucinous glands, a dense vascular network and the nerve fibers that innervate the mucosa. Arterioles, capillaries, and venules are all found in the submucosal layer. The density of these vessels, as well as that of the goblet cells and seromucinous glands, varies with the location within the nose and paranasal sinuses.

The vasculature of the inferior turbinate is extremely dense. Unique to this region are venous sinusoids or capacitance veins. These small veins have a thick muscular layer allowing them to respond to neuronal regulation. The large capacity of this dense venous network allows for congestion and decongestion of the nasal tissues through a highly complex and highly regulated system. This may occur as part of the normal nasal cycle or in response to a variety of internal or external factors and stimuli.

INNERVATION

The nasal mucosa is innervated by both the trigeminal nerve (CN V) and the autonomic nervous system. The trigeminal nerve is predominantly a sensory nerve with three main branches: the ophthalmic nerve, maxillary nerve, and the mandibular nerve. The maxillary nerve exits the foramen rotundum at the skull base, enters the pterygopalatine fossa, and branches into the greater palatine nerve, the nasopalatine nerve, the zygomatic nerve, and the alveolar branches. These peripheral nerve fibers are made up of neurons with varying myelination. Heavily myelinated A-fibers have high-conduction velocities, while unmyelinated C-fibers have slower conduction velocities. A-fibers send rapid impulses to convey initial sharp pain sensations. Unmyelinated C-fibers have a more delayed response to pain and temperature. They are stimulated through inflammatory mediators or inhaled irritants such as nicotine or smoke. Prostaglandins modulate these fibers by lowering their depolarization threshold. Stimulation and subsequent depolarization of these neurons leads to the release of the neuropeptides substance P and calcitonin gene-related peptides. Both increase vascular permeability and submucosal gland release, resulting in nasal burning, itching, and rhinorrhea. Overactivity of this sensory pathway results in an exaggerated efferent response leading to oversecretion of mucous and increased nasal congestion through plasma extravasation into the nasal soft tissues.

The autonomic nervous system is made up of both parasympathetic and sympathetic nerve fibers. Parasympathetic fibers arise from the brain stem and travel with the facial nerve to the geniculate ganglion. They course with the Vidian nerve to the sphenopalatine ganglion. Then they enter the nose through the sphenopalatine foramen near the posterior wall of the maxillary sinus. These neurons synapse primarily at the precapillary arterioles. Acetylcholine is the primary parasympathetic neurotransmitter. Other less potent neurotransmitters also activate this pathway including vasoactive intestinal peptide. Stimulation of these nerves results in vasodilation, leading to engorgement of the nasal tissues and overall decrease in the nasal airway.

The sympathetic neurons arise from the spinal column and synapse in the superior cervical sympathetic ganglion. Nerve fibers then travel with the carotid artery and its branches into the nose, synapsing on arterial vessels, and venous sinusoids. Norepinephrine is the primary neurotransmitter. Other neuropeptides such as neuropeptide tyrosine also may stimulate these neurons to a lesser degree. Sympathetic activation leads to vasoconstriction decreasing the amount of blood in the rich vasculature of the nasal submucosa. Decongestion of the nasal mucosa increases the nasal airway and decreases nasal resistance. Sympathetic and parasympathetic components work together to create a net effect regulated through a brainstem reflex arc. The nasal cycle is one of these examples. The nasal cycle has been demonstrated in approximately 80% of individuals and refers to the alternating partial congestion/decongestion between nares. The length of time between nostril switching varies, depending on the individual and various other factors, but each cycle usually lasts from 40 minutes to several hours. The exact physiologic function or "purpose" of the nasal cycle is unknown but a number of theories have been proposed, all of which may have some validity. By reducing nasal airflow through one nostril, the selective autonomic activation nasal cycle is believed to increase humidification, filtering, and warming of the inspired air while keeping overall nasal congestion to a minimal. It has also been proposed that the intermittent "shutting down" of one nostril allows for a period of relatively minimal airflow during which trapped particulate matter can be cleared from the mucous blanket. Finally, the nasal cycle may have a role in olfaction by creating different rates of airflow through the two nasal passages. This difference is important because odorants vary in the amount of time they need to be in contact with the olfactory epithelium in order for them to be perceived. Odorants that diffuse more quickly through the mucous are able to interact with the olfactory receptors and can be more easily detected in a fast-moving airstream, while those that diffuse slowly may only be detected in a more slow-moving airstream. By creating differential rates of airflow between the two nostrils, the nasal cycle may allow for more detailed olfactory discrimination.

NASAL REFLEXES

The complexity of nasal innervation is demonstrated by the wide variety of nasal reflexes. Although some are primitive defense mechanisms, others are complex relationships between the nose and other physiologic systems that are still not fully understood. The nasonasal or sneezing reflex is an important defensive reflex controlled by the sensory nerves or trigeminal innervation. This reflex may be divided into two phases: the nasal or sensitization phase and the efferent or respiratory phase. During the nasal phase branches of the trigeminal nerve are stimulated through chemical stimuli or tactile/mechanical stimuli. Afferent signals are transmitted to the trigeminal ganglion via the anterior ethmoidal, posterior nasal, infraorbital, and ophthalmic branches of the trigeminal nerve and ultimately to the brainstem. Once a critical threshold has been reached the respiratory phase begins. This results in eye closure, deep inspiration, and an elevated intrapulmonary pressure caused by a forced expiration against a closed glottis. During this build up, the parasympathetic efferent pathways cause nasal vasodilation and secretion to trap irritating particles and prepare them for expulsion. Rapid dilation of the glottis results in an explosive exit of air, mucus, and debris through the nose and mouth.

Another defensive mechanism in the combined airway is the nasolaryngobronchial reflex or the nasopulmonary reflex. Although its significance is still disputed, nasal stimulation through this pathway may decrease respiratory rate, produce apnea, and induce laryngeal or bronchial constriction. This reflex is believed to explain how inflammatory pathways in the upper airway lead to changes in lower airway function. Sensory nerves in the nasal cavity, sinuses, and pharynx carry afferent signals through the trigeminal, facial, and glossopharyngeal nerves to the brain stem. The vagal nucleus carries efferent impulses to the lower airways by way of the vagus nerve leading to bronchoconstriction. This pathway is believed to contribute to the coexistence of allergic rhinitis with asthma and the incidence of nasal symptoms exacerbating asthma attacks. The corporonasal reflex or diving reflex is an example of how nasal reflexes extend beyond the respiratory system. Although it is most pertinent to aquatic mammals, it is still present to a weaker degree in other mammals. The reflex is triggered by cold water to the face and results in bradycardia and peripheral vasoconstriction. Trigeminal nerve stimulation results in an autonomic response shunting blood back to vital organs and slowing down the heart rate to conserve oxygen. This explains why an individual can survive longer without oxygen under cold water when compared with land. It is also one of the reflexes used to treat supraventricular tachycardia.

Two other cardiovascular reflexes exist, although less understood then the diving reflex, the nasovascular reflex and the nasocardiac reflex. The nasovascular reflex causes peripheral vasoconstriction with nasal stimulation. The nasocardiac reflex results in bradycardia and hypotension during nasal manipulation. This reflex can be quite severe and has been noted in nasal manipulation during routine office visits. Local anesthetics may decrease the threshold for this neurologic reflex. Gastric stimulation and irritation has been shown to cause nasal vasodilation in addition to an increase in nasal mucous production. Although the exact reflex is still being studied, it is believed to involve the esophagus and nasal cavity via the vagus nerve. Randomized controlled trials have shown a decrease in post-nasal drip with proton pump inhibitor therapy, supporting the existence of this reflex.[4,5]

A genitonasal reflex has even been described where sexual arousal or orgasm causes swelling of the nasal mucosa, especially the turbinates. This is believed to be caused by engorgement of erectile tissue found in the nasal mucosa, a side effect of the autonomic nervous system that triggers changes in the erectile tissue of male and female genitalia.

WARMING, HUMIDIFICATION AND FILTRATION

Those physiologic functions of the nose not related to the regulation of airflow can be considered collectively as "conditioning" inspired air, and include warming, humidification and filtration. The nasal mucous, or mucous blanket, plays an integral role in each of these physiologic functions, whose net effect is to improve the "quality" of the air by reducing drying effects, particulate matter, and antigenic load before inspired air reaches the lower respiratory tract. These benefits of nasal respiration are not absolute requirements but provide benefit to the lungs and serve as the basis for our preference for nasal respiration beyond the neonatal period of obligate nasal breathing.

Filtration of inspired air begins with larger particles (>3 μm) that are trapped by the nasal vibrissae at the level of the external nasal valve. Smaller particles (between 0.5 and 3 μm) are not filtered by the vibrissae but are removed from the inspired air by the mucous blanket, which traps these particles, particularly in areas of turbulent nasal airflow where contact with the nasal mucosa is increased. This two-stage filtration process reduces both the particulate matter and antigenic load to the lower airways, which are less efficient at clearing mucus.[5]

Mucociliary clearance or the movement of the "mucous blanket" is a constant process within the nose and paranasal sinuses and is an important component of the normal host defense system. Normal sinonasal function is dependent on mucociliary clearance to prevent mucous stasis as well as to remove any toxic, infectious, or particulate material that may have become trapped in the mucous during inspiration. Cilia on the surface of the respiratory epithelium beat and clear the mucus from the paranasal sinuses in specific patterns directed toward the natural sinus ostia.[9] With the exception of the frontal sinuses, the anatomic location of the natural ostia of the paranasal sinuses does not lie in a gravity-dependent position and, therefore, active mucociliary clearance is required. In fact, even within the frontal sinuses, mucous drainage is not gravity dependent and proceeds in a specific pattern that is ultimately directed toward the ostium. In the nose, nasal mucus is cleared from anterior to posterior along the nasal septum and lateral nasal wall, toward the nasopharynx where it is either swallowed or spit out.[6] Normal transit time from the anterior nasal cavity to the nasopharynx is less than 20 minutes. Conditions ranging from common viral upper respiratory tract infections to cystic fibrosis (CF) can affect ciliary function and/or mucous viscosity and impair normal mucociliary clearance.

Nasal mucous, produced by serous glands and goblet cells within the respiratory epithelium, consists of water, glycoproteins or mucin, salts, immunoglobulins (IgA), and lysozymes. It is made up of a deep, less viscous, periciliary (sol) layer, and a more superficial mucous (gel) layer into which the cilia extend in order to propel the mucous.[7] (Fig. 5.3). Mucous production is under autonomic control and can be influenced by stimulants, irritants, emotions, and a variety of medications that can affect the ratio of its serous and glycoprotein elements and thus affect mucous viscosity. The periciliary fluid (sol) layer is composed of nonviscous serous fluid, which is produced by active ion transport within the epithelial cells of the nasal mucosa. The balance between Cl^- secretion and Na^+ absorption determines the volume and ionic composition of the periciliary fluid and maintains the depth of this fluid at about 5–6 μm. When net NaCl transport into periciliary fluid is stimulated, water enters the periciliary fluid along the osmotic gradient that occurs transiently, thus maintaining normal fluid depth and ionic composition necessary for beating of the cilia and normal mucociliary clearance. CF, the most well-known disorder of mucociliary clearance, is an autosomal recessive genetic disease that is characterized

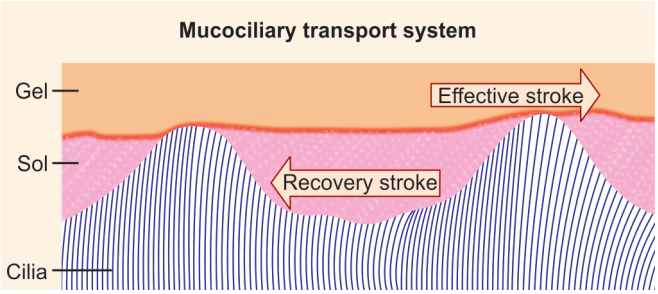

Fig. 5.3: Mucociliary clearance.

by thick, tenacious, airway secretions. In CF, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), which is a Cl^- channel, result in a decreased ability to secrete Cl^- and therefore enhance Na^+ absorption. This reduces the volume of periciliary fluid and results in thick mucus that cannot be properly cleared by the mucociliary clearance system.

There are approximately 250 cilia, measuring 2–5 μm in length, on the luminal surface of each epithelial cell within normal respiratory mucosa. Cilia are composed of nine microtubular doublets that surround two central microtubules held together by dynein arms, nexin links and spokes. The central microtubule doublet contains the enzyme adenosine triphosphatase, which is necessary to supply the energy required for ciliary motion Cilia beat in a coordinated, biphasic, pattern called metachronism. They beat at approximately 1,000 strokes/min, with a power forward stroke and a slow return or recovery stroke. During the forward stroke, the tips of the cilia extend upward into the viscous mucus layer and thereby propel it along with any entrapped particles. On the reverse beat, the cilia release the mucus and withdraw completely into the sol layer. Cilia in the nasopharynx beat in the direction that propels the mucus into the pharynx, whereas cilia in the trachea propel mucus upward toward the pharynx, where it is swallowed.

Warming of inspired air occurs by the transfer of heat from the nasal mucosa, specifically from the blood within the mucosal vessels, to the air that we breathe. It is also believed that nasal mucosa has the ability to dissipate heat as part of the body's thermoregulatory system.[10] The presence of mucous on the surface of the nasal lining helps to facilitate the dissipation of heat from the mucosa. Under normal physiologic conditions, inspired air is warmed or cooled to within 1° of body temperature as it passes through the nasal cavity. The lower airways also have the capacity to warm air before it reaches the alveoli, although less efficiently than the nasal passages. The ability of the nose to warm inspired air is enhanced by factors that increase nasal mucosal surface area and turbulent airflow, which increases contact time between the air and the nasal mucosa. Conversely, factors that decongest the nose, decreasing surface area, and transit time, while increasing laminar flow limit the ability of the nose to warm the air.

Even more important than the warming of inspired air is its humidification, which has a significant effect on gas exchange in the lower airways. This process occurs as a result of an exchange of moisture between the air and the serous component of the nasal mucus as well as due to direct extravasation of fluid from blood within the mucosal vasculature, which contributes some of the water content. As with the other components of "conditioning" of inspired air, humidification is dependent on contact with the nasal mucosa and is, therefore, influenced by factors that affect nasal mucosal surface area, transit time, and turbulent airflow.[8]

Nitric Oxide (NO)

Nitric oxide (NO) is a chemical neurotransmitter increasingly found to influence myriad physiologic functions including regulation of blood flow, platelet and macrophage activity, and mucociliary clearance in addition to possessing antiviral and bacteriostatic properties. The exact role of NO in sinonasal physiology/pathophysiology is not clearly understood. However, it is known that the paranasal sinuses and nasal mucosa are a major source of exhaled NO and significantly decreased concentrations of exhaled NO have been demonstrated in patients with chronic rhinosinusitis (CRS) potentially making it a measurable indicator of the disease state and suggesting a possible role in its pathogenesis.

As a biological messenger, NO has been demonstrated to be a cotransmitter to acetylcholine in parasympathetic nerve fibers and can modulate cholinergic effects in the vascular system and glands. It can also trigger vasodilation through relaxation of the vessel musculature. All of these make it capable of influencing common sinus and nasal physiologic functions. The distribution of NO within the nasal mucosa appears to vary by location, with some areas demonstrating high production while production in other areas is not detectable. However, studying and demonstrating the physiologic role of NO is difficult due to its extremely short half-life, making it unmeasurable in tissue. In order to demonstrate NO production in nasal

mucosa, methods of localizing NO metabolizing enzymes such as NOS or nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d) are used. There is also currently no known specific NO receptor, its effect being modulated through the activation of soluble guanylyl cyclase leading to increased levels of cyclic guanosine monophosphate (cGMP), which activates kinases through the cGMP effect in the cell. The cGMP effect causes the relaxation of smooth muscle cells; therefore, it has been postulated that NO could have a role in the physiologic regulation of nasal blood flow and, secondarily, influence nasal airflow, and the warming and humidification of inspired air. The presence of strong NOS immunoreactions in the cytoplasm of capillaries and endothelial cells of arteries has been shown in human nasal mucosa and lends strength to this theory.

Significant NOS immunoreactivity has also been demonstrated in periglandular and periductal axons as well as in the cytoplasm of acinus cells, suggesting that NO may also influence glandular secretion directly and/or through the regulation of the periglandular blood flow. Inducible nitric oxide synthase (iNOS) has also been shown experimentally to affect the ciliary beat frequency via increased NO production. This was able to be inhibited by dexamethasone or the application of L-Arginine methylester (L-NAME), which is a NOS inhibitor.

In addition to the circulatory and mucociliary effects, NO is known to be bacteriostatic at low concentrations and is known to have an antiviral effect. The concentration of NO in the maxillary sinus has been demonstrated at much higher levels than that measured in the nose, just as the presence of NOS has been found at higher levels in the ciliated epithelial cells of the paranasal sinuses than in the nasal epithelium. These findings suggest that NO may be involved in the maintenance of relative sterility in the paranasal sinuses, and that lack of NO may contribute to the pathogenesis of sinusitis. However, whether the reduced nasal NO observed in chronic sinusitis represents a cause or an effect of the disease process is still not known.

Nasal Immunity

Normal nasal physiology makes several contributions to both the innate and adaptive immune response and to the prevention of disease transmission via the respiratory tract. It begins with the filtration of inspired air and the trapping of particles in the nasal vibrissae and the mucous blanket, which contains antimicrobial enzymes, IgA, and opsonins. Nasopharynx-associated lymphatic tissue (NALT), located on the mucosal surface of the upper airway, is composed of both innate and adaptive immunity elements. The specific functions of this immune system are less well understood than those of gut-associated lymphatic tissue (GALT), but is accepted that a complex set of both innate and adaptive immune pathways are active at the nasal mucosal surface both constitutively and in response to specific challenges.[11]

Secretory IgA (SIgA) plays an important immunologic role in the upper respiratory tract, preventing microbial binding to epithelial cells and enabling the phagocytosis of potentially pathogenic viruses and bacteria through opsonization. SIgA is made by B cells located within the nasal mucosa; it is transported across the cell and excreted by exocytosis. In children, there is a relative lack of SIgA, a finding that has been postulated to help to explain the high number of upper respiratory tract infections during childhood.

Mucosal immunity can be broadly classified as either "adaptive" or "innate." Adaptive immunity is mediated by T and B lymphocytes and is characterized by antigen-based specificity and memory. Inhaled microbes interact, at the mucosal surface, with macrophages and dendritic cells through cell-surface receptors. Opsonization with antibody or complement allows for phagocytosis and neutralization of these potential pathogens. Polymorphonuclear leukocytes (PMNs) and other inflammatory cells—eosinophils, basophils and mast cells—also interact with opsonized foreign particles and microbes to activate extracellular release of potent antimicrobial enzymes. Innate immunity, formerly thought to consist of little more than nonspecific phagocytosis of pathogens by macrophages and leukocytes, has been shown to have considerable specificity. This is based on pattern recognition receptors (PRRs), such as the toll-like receptor, which recognize several hundred pathogen-associated molecular patterns (PAMPs) shared by entire classes of pathogens but not produced by host cells. While not as specific as the antigen-antibody-based adaptive immune response, the interaction between PRRs and PAMPs still confers the ability to discriminate between pathogens and self. The adaptive immune system, while more robust, may contain binding sites for environmental allergens and has been implicated as a potential contributing factor in the inflammatory pathogenesis of CRS.

MICROBIOLOGY

In order to understand the physiologic and pathophysiologic role of micro-organisms in the sinonasal tract, it is

necessary to characterize the microbiologic flora in both the healthy and the diseased states. The microbiome of the nose and paranasal sinuses has been studied extensively, as has the microbiology of both acute and CRS. Yet, the results of these myriad investigations vary so greatly that while each study's conclusion may be valid in its own right, in aggregate, the data lead to debate regarding virtually every aspect of the questions that we endeavor to answer: What is the "normal" flora of nose and paranasal sinuses? What are the pathogens responsible for rhinosinusitis? What is the role of bacteria in CRS? What is the role of fungus in rhinosinusitis?

A number of explanations have been put forth to explain the differences among the numerous studies conducted with the aim of elucidating the microbiology of sinusitis. The most fundamental weakness with many of these reports is their reliance upon standard culture techniques that have significant limitations. First, many bacterial species are refractory to culture, particularly those that exist surrounded by an exopolysaccharide matrix in a complex community known as a biofilm. Additionally, the use of standard nutrient media results in a bias toward the isolation of certain organisms with faster growth rates, often at the expense of other organisms whose growth may be inhibited, a phenomenon known as dysbiosis. Fungal culture is, likewise, felt to be highly technique dependent and results may underestimate the presence of fungal organisms or, conversely, demonstrate ubiquitous environmental organisms simply trapped in the mucous blanket following inhalation.[12] Thus, the true diversity of the microbes present in the environment being cultured is often not accurately reflected in the culture results. Despite these limitations, the common finding among these studies is that there exists a polymicrobial community within the paranasal sinuses in both the healthy and diseased states.

In an attempt to overcome the aforementioned technique-based limitations, Boase et al. analyzed sinonasal mucosa from 38 CRS patients and 6 controls.[13] Bacterial and fungal analysis was performed using conventional culture, molecular diagnostics (polymerase chain reaction coupled with electrospray ionization time-of-flight mass spectrometry) and fluorescence in situ hybridization (FISH). Their results demonstrated that (1) the healthy sinus is not sterile; (2) fungus was present uncommonly, and in a select group of CRS patients with nasal polyps; (3) *Staphylococcus aureus* was the most prevalent organism (in a typically polymicrobial community); (4) anaerobes were present in highly prevalent in both CRS (47%) and control (83%) patients, casting doubt on a direct pathogenic role; (5) *Haemophilus influenzae* was detected at relatively low levels (13%) in CRS patients, and was not detected in controls; (6) *Pseudomonas aeruginosa* was found infrequently (8%).

The high prevalence and concentrations of *S. aureus* among the CRS patients are consistent with the emerging theory of that organism as a significant pathogen and inflammatory disease modifying organism with the ability to form biofilms. This may contribute to the variable detection of *S. aureus* using traditional culture techniques, and may have significant clinical implications. The high prevalence of anaerobes is also consistent with prior molecular studies. However, the presence of *Propionibacterium acnes* in more than 80% of control patients suggests a role other than as a pathogen. *P. acnes* is known to produce bacteriocins, which have antibacterial and antifungal activity and may be protective against pathogens in the polymicrobial environment characteristic of CRS.

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SECTION 3

Evaluation of the Nose and Paranasal Sinuses

CHAPTER

6 Clinical Evaluation of the Nose and Paranasal Sinuses

Steven D Pletcher

INTRODUCTION

Symptoms related to the nose and paranasal sinuses are one of the most common reasons for medical evaluation. Appropriate diagnosis of sinonasal disorders requires a thorough evaluation of the patient and an understanding of the common and uncommon disorders of the sinonasal cavity. The patient's history, nasal examination, and the judicious use of radiographic studies all play an important role in determining the appropriate treatment for patients with symptoms of a sinonasal disorder.

HISTORY

A targeted and thorough history will help the clinician distinguish among a variety of sinonasal pathologic entities. While obtaining the history, the clinician should be mindful of symptoms that may help distinguish between inflammatory process in the nose and/or paranasal sinuses, neoplastic disorders affecting the sinonasal cavity, or nonsinus etiologies of symptoms the patient attributes to sinus disease.

Chief Complaint

The most important initial aspect of the history is to elicit a clear and concise chief complaint from the patient. It is critical to ensure that the chief complaint is a symptom rather than a suspected diagnosis. Patients will often describe that they have come to the doctor to be evaluated for sinusitis, but a key to establishing an appropriate diagnosis is to determine which symptom is most bothersome to the patient.

History of Present Illness

After establishing a chief complaint, a history of present illness should be obtained. The standard components of this section of the history include the initiation and duration of the chief complaint, associated symptoms, and aggravating or alleviating factors. The circumstances surrounding the initiation of symptoms often provide significant insight into the likely etiology of symptoms. Onset of symptoms in association with an upper respiratory infection (URI) may be indicative of rhinosinusitis. An association with dental work involving the alveolar molars is suggestive of an odontogenic sinusitis.

The duration of symptoms defines whether the patient is suffering from an acute or chronic process. Patients with symptoms for < 4 weeks are deemed to have an acute process while those suffering for > 12 weeks are categorized as having a chronic process.[1] Some patients will note recurrent symptoms with complete normalization between episodes. This may be indicative of intermittent rhinitis or recurrent acute rhinosinusitis. Patients with symptoms lasting between 4 weeks and 12 weeks are deemed to have a subacute process.

The duration of symptoms is particularly important in distinguishing acute bacterial rhinosinusitis from acute viral rhinosinusitis. Viral rhinosinusitis typically improves significantly within 10 days of onset. Patients who have persistence of symptoms beyond 10 days, or worsening of symptoms within 10 days after initial improvement of symptoms are presumed to have acute bacterial rhinosinusitis.[1]

Aggravating and alleviating factors may provide additional insight into the etiology of the patient's symptoms. Symptoms brought on by seasonal and situational exposures to pollen, animal dander, or other potential antigens strongly suggest an allergic etiology. Changes in climate may result not only in altered antigen exposure, but also differences in humidity, which may impact disease processes such as allergic fungal rhinosinusitis or epistaxis. An acute asthma attack brought on by exposure to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) is indicative of aspirin-exacerbated respiratory disease. Salicylate exposure often results in concomitant worsening of nasal symptoms. Patients with an "allergy" to aspirin or NSAIDs noted in their chart should be queried regarding these symptoms.

Evaluating associated symptoms is critical in establishing a diagnosis. Common associated nasal symptoms include congestion/obstruction, nasal drainage, anosmia and epistaxis. Patients with rhinitis alone generally note clear nasal drainage and nasal congestion/obstruction. Septal deviation or other structural narrowing of the nose frequently results in isolated nasal obstruction. Thick, discolored, or purulent nasal drainage is a hallmark of rhinosinusitis and is frequently accompanied by nasal congestion/obstruction, anosmia, and facial pressure or pain.[12] The presence of these two or more of these symptoms is sensitive in establishing a diagnosis of rhinosinusitis, but for chronic rhinosinusitis (CRS) the specificity of diagnosis with symptoms alone is very poor. Objective findings are required to confirm the diagnosis.[3]

Epistaxis is not frequently associated with rhinitis or rhinosinusitis. The majority of patients with epistaxis bleed from the anterior nasal cavity. Superficial vasculature within the septal mucosa is vulnerable to bleeding in response to nasal dryness or mild trauma. Patients with epistaxis in conjunction with nasal obstruction, epiphora, diplopia, or changes in facial sensation should be evaluated for a sinonasal neoplasm.

Clinicians should be wary of assigning a diagnosis of rhinosinusitis to patients who present primarily with symptoms of facial pain and headache.[2] While patients often arrive at the office convinced that these symptoms are evidence of sinus inflammation or infection, several studies have documented that the majority of patients who self-diagnose with "sinus headaches" suffer from headaches of neurologic etiology, most frequently migraine.[4-6]

Patients should be evaluated for the presence of orbital symptoms. Itchy, watery eyes are common in patients with allergic rhinitis. Tearing or epiphora may occur in conjunction with acute sinusitis, but persistence of this symptom should raise concern for a possible neoplastic process. Diplopia and proptosis are more concerning findings, which may represent complications from sinus disease or an expansile lesion: mucoceles, tumors, complicated acute sinus infections, and allergic fungal sinusitis may all present with proptosis or diplopia. Enophthalmos is less common, but it may occur in the setting of silent sinus syndrome.

Past Medical and Surgical History

A thorough evaluation of the patient's medical and surgical history often provides insight into likely etiologies of sinonasal pathology and helps guide appropriate therapy. A history of inflammatory or infectious pulmonary disease may be helpful in establishing a diagnosis for sinonasal disease. Allergic rhinitis and asthma are linked through both pathophysiology and epidemiology.[7-9] Eighty percent of patients with allergic asthma also suffer from allergic rhinitis. The presence of allergic rhinitis is a risk factor for the future development of asthma. Guidelines suggest screening patients with persistent allergic rhinitis for asthma and evaluating asthmatic patients for rhinitis.[89]

Chronic rhinosinusitis is also closely linked to asthma, particularly those patients with nasal polyps (CRSwNP). About 30–40% of CRSwNP patients describe wheezing and respiratory discomfort. Twenty-six percent of polyp patients report a diagnosis of asthma, compared with 6% of control patients.[10] Patients with asthma demonstrate a high incidence of sinus mucosal thickening on computed tomographic (CT) imaging.[11,12] While asthmatic patients demonstrate a high incidence of nasal polyps, nonatopic asthma demonstrates a significantly stronger association (13%) with nasal polyps than atopic asthma (5%).[13]

Recurrent pulmonary infections may suggest a congenital disease impacting both the upper and lower airways. Patients with recurrent infections of the upper and lower airways should be evaluated for cystic fibrosis, and ciliary dyskinesia, and immunodeficiency. Although these disorders are often diagnosed early in life, patients with milder phenotypes may present as adults.

Prior surgery of the nose or sinus cavities predisposes patients to a variety of sinonasal disorders. Surgical manipulation of the nasal cavity may result in septal perforations, disruption of the normal humidification function of the turbinates with resultant atrophic rhinitis, and the loss of structural support of the nasal framework. A history of

neurological surgery may also impact the sinuses. Many pituitary and anterior skull base approaches use the sinonasal cavity as an approach with significant resulting changes to the normal sinonasal anatomy. Craniotomy procedures may pass through the frontal sinus cavities or result in bony defects of the ethmoid or sphenoid roof.

Evaluating a patient's medication list provides insight into their current medical conditions and may identify factors contributing to the patient's symptoms. Decongestant nasal sprays are frequently used for symptomatic relief of nasal congestion and obstruction, but chronic use leads to rebound mucosal hypertrophy known as rhinitis medicamentosa. Multiple medications may contribute to recurrent or refractory epistaxis. Nasal steroid sprays may irritate the septum resulting in nosebleeds. Anticoagulant medications including warfarin, aspirin, NSAIDs, clopidogrel and dabigatran are often contributing factors in patients with refractory epistaxis. These medications must also be managed to limit postoperative bleeding after sinonasal surgery and may impact the decision to proceed with elective surgery. Disturbances in taste and smell are also common with chemotherapy treatment and have been noted with 5-fluorouracil, docetaxel and bevacizumab. Mucositis of the nasal cavity with symptoms of bleeding, crusting and discomfort, may also result from some chemotherapy combinations.

A patient's social history may provide valuable information when evaluating sinonasal symptoms. Pet ownership can be helpful in determining the etiology of sinonasal symptoms. Animal dander, particularly cats and dogs, is one of the most common perennial allergens contributing to allergic rhinitis. Patients are often able to identify this reaction without formal allergy testing.

Intranasal drug use may result in significant sinonasal pathology. A perforated nasal septum is the nasal finding most frequently associated with illicit drug use in the nasal cavity. Necrosis of the turbinates, saddle nose deformity, and synechiae with subsequent nasal obstruction are additional sinonasal findings, which may result from intranasal drug use.

Ethnicity and travel history may also be helpful in evaluating sinonasal symptoms. Leprosy remains endemic in some African, South American, and Asian countries. Nasal manifestations of leprosy include thickening of nasal mucosa, bleeding and tissue necrosis. Leishmaniasis is a parasitic disease transmitted by sand flies present in some tropical and subtropical countries. The cutaneous and mucosal forms of leishmaniasis frequently involve the nose or nasal cavity with symptoms ranging from nonhealing skin ulcerations to mucosal inflammation and septal perforation. Rhinoscleroma, a chronic bacterial infection of the nose caused by *Klebsiella rhinoscleromatis*, is endemic to tropical areas in Africa and Central America. Clinical manifestations range from nasal congestion and clear drainage to chronic purulent rhinorrhea with crusting. Progressive disease may result in destruction of nasal cartilage with subsequent nasal deformity.

Disease-Specific Quality-of-Life Questionnaires

Along with obtaining a history to establish a diagnosis, physicians are frequently asked to measure disease severity. Disease-specific quality-of-life questionnaires provide the most accurate information regarding the patient's burden of disease. Validated questionnaires are also critical in outcomes research as they allow an objective evaluation of patient symptoms, which may be used for comparisons across studies. Several questionnaires with complementary features have been designed to quantify the burden of disease for patients with sinonasal disorders.[14] The rhinoconjunctivitis quality-of-life questionnaire may be used for patients with allergic rhinitis.[15] Several validated questionnaires have been designed to evaluate patients with CRS: the most widely use surveys are the sinonasal outcomes test 22 (SNOT-22),[16] the rhinosinusitis disability index (RSDI),[17] and the chronic sinusitis survey (CSS).[18] The SNOT-22 and RSDI provide more detailed symptomatic evaluation of patients, whereas the CSS includes information about medication utilization.[19]

PHYSICAL EXAMINATION

General Examination

Physical examination of the patient begins with a general assessment. While focus on the head and neck region is appropriate in patients presenting with sinonasal symptoms, some systemic diseases may manifest initially in the nasal cavity. Particular attention should be paid to the presence of general symptoms such as fatigue, weight loss, and malaise in patients with sinonasal masses, septal perforations, or erosive lesions of the sinus cavity.

Evaluation of the facial structures may prove useful in determining the extent of sinonasal pathology. Patients who suffer nasal trauma may experience concomitant injury to the surrounding facial structures. Evaluation of

the bony orbits, the zygoma and zygomatic arch, and frontal bone may reveal additional injuries. In addition, a thorough evaluation of the contents of the orbit including gross visual acuity, extraocular movements, and basic visual field testing may provide valuable information. Dysfunction of facial sensation may signify injury to branches of the fifth cranial nerve.

A thorough examination of the head and neck including evaluation of the orbit, oropharynx, ears, oral cavity, facial structures, and neck provides a local and regional evaluation of the patient's symptoms. Sinonasal pathology may impact the eye and orbital contents. Expansile masses within the sinus cavities may encroach upon the orbit with subsequent proptosis or displacement of the eye. Conversely, orbital fractures, which resulted in significant increase in the orbital volume, may result in enophthalmos. Silent sinus syndrome, or atelectatic maxillary sinus, also results in expansion of the orbital volume and enophthalmos. In general, sinonasal pathology, which is suspected of causing orbital findings, such as proptosis, alterations in extraocular movements, or enophthalmos, should be evaluated with CT or magnetic resonance imaging (MRI).

Nasal Examination

Examination of the nose begins with evaluation of the structural elements. Deviation of the nasal bones, middle third of the nose, or nasal tip may all contribute to restrictive airflow through the nose. Collapse of the soft tissues of the nose, particularly in the mid and lower third of the nose, may result in dynamic nasal obstruction. The contribution of such collapse to nasal obstruction may be evaluated using the modified Cottle maneuver where the external nasal valve is supported during inspiration.

Examination of the nasal cavity typically begins with an anterior examination using a nasal speculum. As the nasal speculum is inserted, the closed speculum is used to elevate the soft tissues of the nasal ala. This allows opening of the speculum without undue pressure or on the floor of the nose, which may be uncomfortable for the patient. The use of a head mirror or headlight provides illumination for this anterior examination. The nasal septum is closely evaluated for evidence of significant deviation, spurs, septal perforations, or mucosal changes. The inferior turbinate may also be closely evaluated on anterior examination. The relationship between the inferior turbinate in the lower portion of the septum, in combination with the soft tissues of the external nasal valve, will determine the adequacy of the anterior nasal airway.

Mucosal changes of the inferior turbinate, most frequently fullness and edema, may contribute significantly to nasal obstruction and nasal congestion. These findings, particularly blue, boggy turbinate mucosa, may be related to allergies or other nasal irritants. In patients with normal anatomy of the septum, it is often possible to visualize the anterior aspect of the middle turbinate on anterior examination. Close inspection of this region may reveal the presence of polyps or thick mucus in patients with chronic sinusitis. Anterior examination of the nose is often complemented by nasal endoscopy, which provides enhanced illumination and magnification, resulting in a vastly superior view, particularly when evaluating the posterior nasal cavity.

Palpation and transillumination of the sinuses have been described to assist with diagnosis of acute and CRS. Overall, these evaluations are neither sensitive nor specific for sinonasal pathology and have little clinical utility.

Nasal Endoscopy

The use of a nasal endoscope allows enhanced illumination and magnification of structures within the sinonasal cavity. Endoscopy can be easily accomplished in the clinic with minimal patient discomfort. Decongestant and anesthetic sprays are frequently applied to the nasal cavity prior to endoscopic examination to minimize patient's discomfort. Rigid and flexible endoscopes may be used in the nose and paranasal sinuses. Rigid endoscopes often have better image quality, but even angled scopes do not provide the same ability as flexible scopes to look at various angles within the sinonasal cavity. Flexible scopes also provide the option for concomitant evaluation of the larynx and hypopharynx. The use of flexible endoscopes requires two hands to adequately hold and support the scope; rigid scopes may be used with one hand, freeing a hand for the use of functional instruments such as a suction or grasping device.

Classic rigid nasal endoscopy utilizes three passes through the nasal cavity: an initial pass along the floor of the nose back to the nasopharynx, a second pass angled higher in the nose to evaluate the middle meatus, and a third pass deeper and higher in the nose to evaluate the sphenoethmoid recess. This examination is frequently completed with a 30° endoscope, which can be rotated within the nose to visualize an area of interest.

Nasal endoscopy allows improved characterization of septum, visualization of the mid and posterior aspects of the inferior turbinate, improved visualization of the

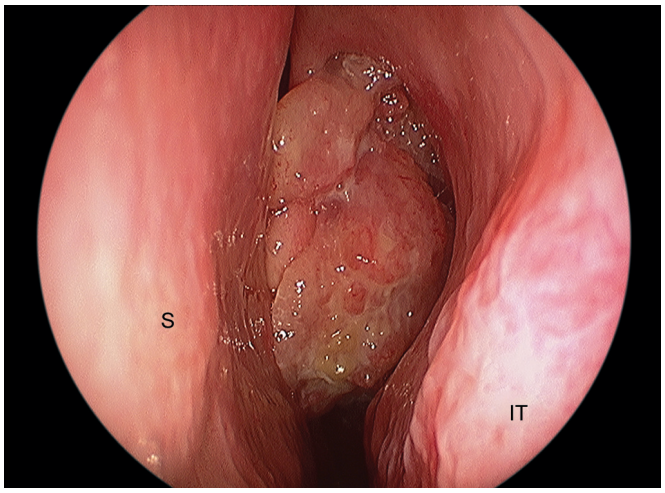


Fig. 6.1: Endoscopic view of the left nasal cavity demonstrating a sinonasal mass filling the middle meatus and obscuring the left middle turbinate. The septum (S) and inferior turbinate (IT) are normal in appearance. Biopsy of this lesion demonstrated an inverted papilloma.

middle turbinate, uncinate process, and ethmoid bulla. The superior turbinate and ostium of the sphenoid sinus are often visible with this technique. The nasopharynx may also be closely evaluated including the Eustachian tube, adenoid pad, and fossa of Rosenmuller.

Numerous common findings that may be identified with nasal endoscopy may not be appreciable with anterior examination of the nose. These include nasal polyps, mucopurulence emanating from the middle meatus or sphenoethmoid recess, adenoid hypertrophy, enlargement of the posterior end of the inferior turbinate (mulberry tip), and masses within the nasal cavity (Fig. 6.1) and nasopharynx. In patients who have not had prior surgery, endoscopic visualization of the sinus cavities is limited, but the nasal findings of polyps, mucosal edema, or thick mucus often alert the examiner to the presence of underlying sinus inflammation. Endoscopic access to the sinus cavities in patients with prior surgery is significantly enhanced and may allow clear endoscopic visualization of all sinus cavities. The adequacy of endoscopic visualization is dependent upon the extent of prior surgery. Several endoscopic grading systems have been described to quantify the extent of sinonasal inflammation.[20-22]

A variety of endoscopic interventions may be performed at the time of endoscopic evaluation. These include debridement of crusting (frequently in the postoperative setting), control of epistaxis with endoscopically targeted cautery or packing, and endoscopic biopsy of sinonasal masses. Appropriate caution is required for endoscopic biopsies as some nasal masses may be extremely vascular. Sinonasal masses in adolescent males are particularly concerning as clinic biopsy of a juvenile nasal angiofibroma may have disastrous consequences. Encephaloceles may also present as a sinonasal mass, and biopsy of these lesions may result in cerebrospinal fluid leak with risk for meningitis.

CONSIDERATIONS FOR THE DIAGNOSIS OF SINONASAL NEOPLASMS

Sinonasal neoplasms are rare disorders, which may present with subtle findings. The following symptoms should increase the level of concern for a neoplasm, particularly when they occur in combination: unilateral obstruction, epistaxis, facial numbness, diplopia, epiphora and proptosis. On physical or endoscopic examination, any unilateral nasal mass or polyp should raise the possibility of a neoplasm. Sinonasal neoplasms may also present as a perforation of the nasal septum. Typically, this is associated with soft tissue changes around the rim of the perforation.

Biopsy of nasal cavity masses may be helpful in the identification of sinonasal neoplasms, but it should be undertaken with care. Heavy bleeding may be encountered with biopsy of vascular lesions such as juvenile nasal angiofibromas. Because clinic fatalities have been reported after this procedure, nasal masses in young adult males should not be biopsied until this diagnostic possibility is excluded. For patients outside of this demographic, appropriate access to nasal packing and hemostatic materials as well as a familiarity with the management of epistaxis is critical. Masses of the nasal cavity may represent extensions of intracranial or vascular processes. If the entirety of the mass is not visualized on endoscopic examination, appropriate imaging should be performed prior to clinic biopsy. Cerebrospinal fluid leaks and intractable epistaxis from biopsies of encephaloceles and vascular pseudoaneurysms are preventable complications with appropriate preprocedure evaluation. The biopsy of a septal perforation is generally safe and well tolerated in clinic.

LABORATORY EVALUATION

The majority of patients with sinonasal symptoms do not require laboratory evaluation. Patients with complications

of sinus disease or symptoms refractory to standard treatment, however, may benefit from a variety of laboratory investigations.

Treatment of acute or chronic sinusitis may be enhanced with the use of culture-directed antibiotics. Endoscopic sampling of mucopurulence within the sinonasal cavity may be used to identify and characterize offending bacteria and often impacts antibiotic selection. This is particularly important in refractory of clinically aggressive infections. Overall, endoscopic cultures correlate well with cultures derived from more invasive sinus puncture procedures.[23]

For patients with acute suppurative disease refractory to initial treatment or with threatened complications, a complete blood count allows the monitoring of leukocytosis, a helpful metric to monitor disease progression. Chronic sinusitis may be associated with elevation of peripheral eosinophils or specific immunoglobulin such as IgE. An elevated eosinophil count in the setting of nasal polyps and peripheral neuropathy is suggestive of Churg–Strauss disease. Immunoglobulin deficiencies, particularly of IgG subtypes, have been identified in patients with refractory chronic sinusitis.[24]

Unexplained septal perforations or erosive lesions within the nasal cavity may indicate autoimmune or vascular disorders. While serologic evaluation including cytoplasmic antineutrophil cytoplasm antibodies, antinuclear antibodies, and angiotensin converting enzyme may be helpful in identifying systemic disorders, conditions such as limited granulomatosis with polyangiitis (PGA, formerly known as Wegener's granulomatosis) may not demonstrate serologic changes.

Allergies are a common contributor to sinonasal inflammation. Skin testing or radioallergosorbent sensitivity testing may be used to identify offending allergens. Patients may subsequently be counseled regarding allergen avoidance or treated with immunotherapy. For patients with suspected aspirin-exacerbated respiratory disease, an aspirin challenge may be performed in a monitored setting. This is typically accomplished by allergists with an interest in this disorder.

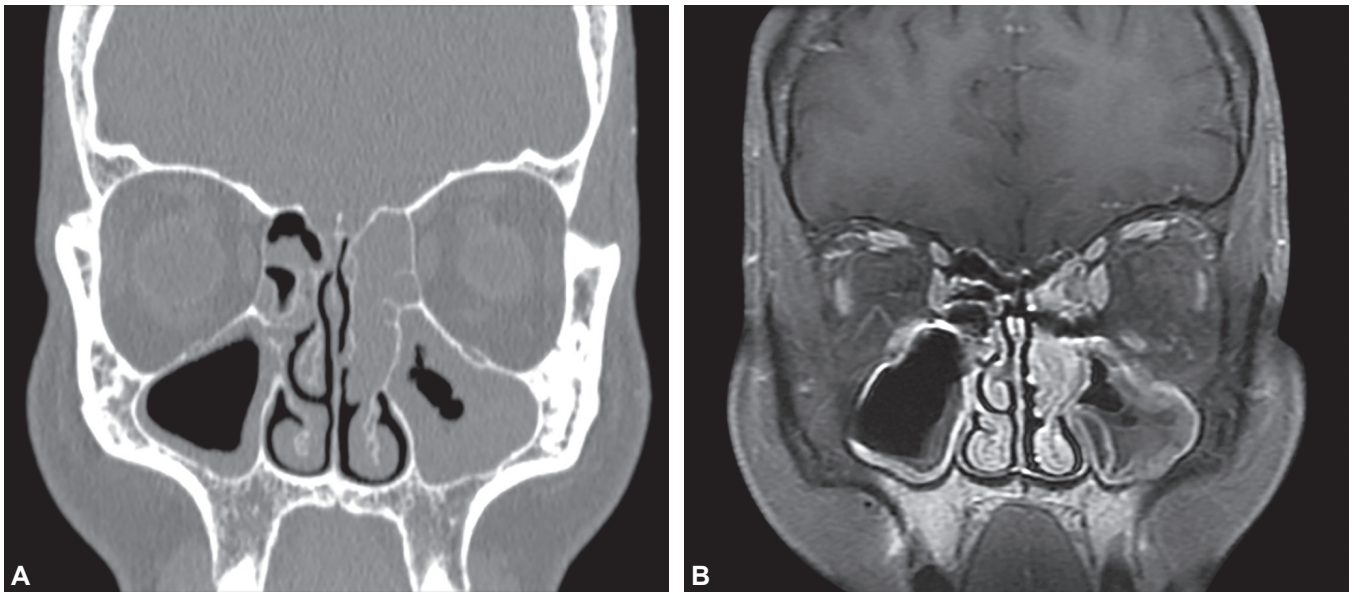
Imaging Studies

Radiographic studies, particularly CT and MRI, play a critical role in the evaluation of many sinonasal lesions. Judicious use of imaging studies is imperative as both increased cost and unnecessary radiation exposure may result from inappropriate utilization of these resources. Radiographic imaging should only be ordered when there is a clear question, which may not be answered with less costly or morbid interventions. Clinical practice guidelines suggest that radiographic evaluation should not be performed as part of the evaluation for uncomplicated cases of acute sinusitis. This is particularly important in the pediatric population due to an increased frequency of URIs and susceptibility to radiation exposure.[25]

Plain film X-rays of the sinuses are neither sensitive nor specific for the presence of sinonasal disease and have little clinical utility.[26,27] CT imaging provides excellent detail of the bony anatomy of the paranasal sinuses as well as a clear contrast between air and soft tissue or fluid. Because normal healthy sinuses are full of air, the presence of fluid or soft tissue within the sinus cavities is easily appreciable on CT images. MRI allows further detail of soft tissue and fluid; information that is frequently complementary to CT findings (Figs. 6.2A and B). MRI is particularly helpful in evaluating sinonasal tumors as MRI-generated images distinguish between tumor and inspissated secretions within the sinuses and are invaluable in determining the extent of skull base, intracranial and orbital invasion seen in aggressive lesions.

The diagnosis of chronic sinusitis requires both subjective and objective findings. Nasal endoscopy may not be available to all practitioners, and evaluation of the sinuses with this technique may be inadequate to rule out a diagnosis of chronic sinusitis. Therefore, CT imaging of the sinuses is frequently ordered to evaluate for the presence or extent of paranasal sinus inflammation. Noncontrast studies provide adequate information in the majority of cases. If the clinical scenario is suggestive of suppurative complications of sinusitis such as subperiosteal or epidural abscess, contrast-enhanced images are preferred. CT imaging must also be interpreted in the clinical context of the individual patient. Viral URIs have been demonstrated to cause inflammatory changes in the paranasal sinuses consistent with acute or chronic sinusitis.[28] CT imaging of patients with recurrent acute sinusitis between symptomatic flares is often normal. Variants of anatomy and mucosal changes without clinical significance may also complicate CT interpretation.[29]

Several approaches to quantify the extent of inflammation within the paranasal sinuses based on CT imaging have been described; The Lund–McKay scale is most frequently used. Although these scores are helpful in tracking response to treatment in individual patients and comparing disease burden across clinical studies,



Figs. 6.2A and B: Complementary evaluation of sinonasal tumors using computed tomography (CT) and magnetic resonance imaging (MRI). CT imaging demonstrates opacification of the left middle meatus and ethmoid regions and partial opacification of the left maxillary sinus (A). T2-weighted MRI and (B) gadolinium-enhanced T1-weighted images (B) demonstrate that the partial opacification within the left maxillary sinus is secondary to mucosal edema and fluid.

quantitative CT scores correlate poorly with symptom scores in patients with chronic sinusitis.[30-33]

SUMMARY

Sinonasal symptoms represent one of the most common reasons for presentation for medical evaluation. A careful clinical history, physical examination, and judicious use of radiographic evaluation allow clinicians to appropriately evaluate and treat patients with sinonasal symptoms.

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CHAPTER

Acoustic Rhinometry and Objective Measures of Nasal Airway Obstruction

7

Mohamad R Chaaban, Jacquelynne P Corey

INTRODUCTION

The nose is lined by the nasal mucosa, which is composed of the mucous layer, the epithelium, glands, arterioles, arteriovenous anastomoses, as well as the venous sinusoids. A critical area in the nose, the internal nasal valve (INV), is located at the anterior end of the inferior turbinate; the lining epithelium changes from squamous to transitional and then to respiratory epithelium. Upon nasal breathing, the nose provides humidification, filtering, and warming of the air as it enters the nasopharynx. Nasal airway resistance represents around 50% of the total resistance of the upper and lower airways.[1]

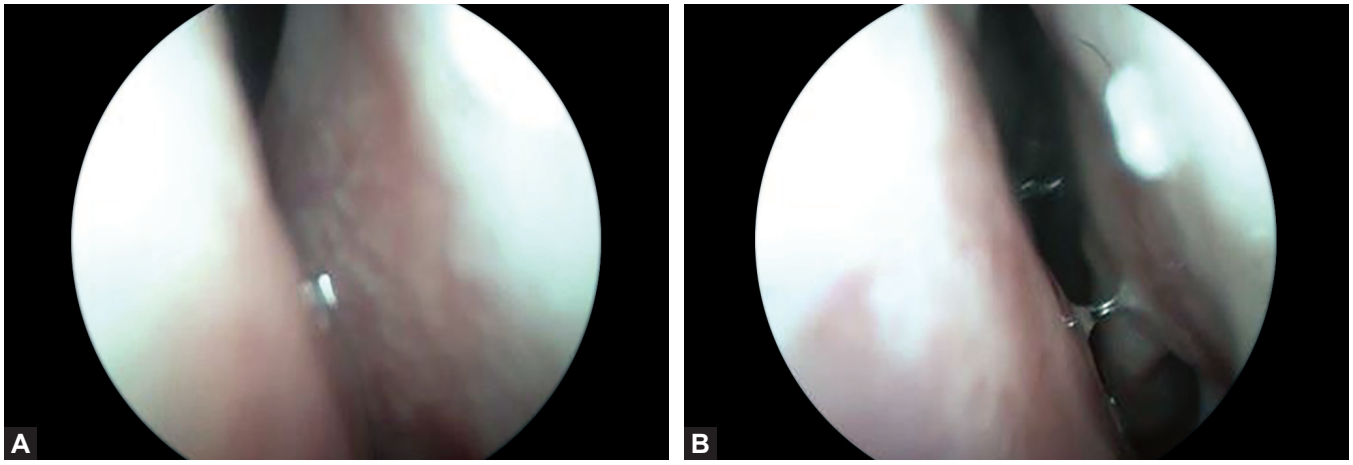
Various subjective as well as objective tests to assess nasal airflow have been developed to complement the history and physical examination performed by the physician. Some of these tests were validated and can provide documentation for comparisons between patients as well as to follow-up following medial or surgical treatment.

NASAL CYCLE

The nasal cycle is the physiologic alteration in nasal congestion on opposing sides of the nose, resulting in similar airflow, resistance, as well as amplitude.[2] Although there are wide variations, the most commonly reported scheme is that of reciprocal and spontaneous changes in unilateral nasal airflow.[3,4] Ideally, both sides of the nose have equal resistance, amplitude and similar airflow during the nasal cycle in a reciprocal fashion.[3,4] In certain individuals, there is no cycle or the nasal cycle may be very shortened or elongated. It typically lasts between 4 hours and 6 hours in most individuals; however, it can be as short as 10 minutes and as long as several days.[5]

Subjective Assessment of the Nasal Airway

Nasal congestion or fullness appears to be the most bothersome symptom in patients with allergic rhinitis.[6] The differential diagnosis of patients with nasal obstruction includes allergic rhinitis, acute and chronic nasopharyngitis and sinusitis, deviated nasal septum, nasal polyposis, rhinitis, NV collapse, and lesions and masses in the nose.[7] Several methods to subjectively measure the magnitude of sinonasal symptom, including nasal congestion, include questionnaires such as the Rhinosinusitis Outcome Measurement (RSOM-31), SinoNasal Assessment Questionnaire (SNAQ-11), Sinonasal Outcome Test 22 (SNOT-22), or use of an ordinal 10-point or 100-mm visual analog scale (VAS)[8] as well as others.[9,10] Seventy-seven percent of patients suffering from viral rhinitis are able to distinguish between high and low nasal flow; however, the percentage of correct responses drops to 50% when the nasal flow is less than 100 cm^3/s.[11] The sensation of fullness may not be secondary to the objective presence of obstruction in the nasal airway, but may also be functional or neurologic. Neurogenic causes occur via the trigeminal nerve as evidenced by the topical application of menthol, camphor, as well as other irritants resulting in an increase in the sensation of nasal patency.[12] Because of this variability, objective methods of nasal airway patency are sometimes needed to identify the cause of obstruction.



Figs. 7.1A and B: Inferior turbinate before (A) and after (B) decongestion using oxymetazoline spray.

Objective Assessment of the Nasal Airway

Objective assessment of the nasal airway begins with the physician's assessment of the patient's subjective complaints. This will include a complete rhinologic history and physical examination coupled with nasal endoscopy. Historically, two tests were used to objectively measure nasal airway patency. The first test, "hygrometry",[13] measures the diameter of the fog created by breathing into a mirror. The "hum" test is the other, developed by Spiess in 1902, that measures the change in the timbre of the sound produced in by the nose while occluding the decongested side with the patient humming.[14] Another objective method is utilizing computed tomography (CT) in the form of CT volumetry to assess for nasal obstruction, which carries with it the increased risk of radiation exposure. The commonly objective tests include peak nasal inspiratory flow (PNIF), acoustic rhinometry (AR), rhinomanometry (RM), and Odiosoft Rhino (OR).

History and Physical Examination

The initial assessment of a patient with nasal airway obstruction is to obtain a complete rhinologic history and physical examination. The history should address the possibility of an allergic cause of the nasal obstruction. Important questions to ask include symptoms of nasal congestion, such as rhinorrhea, postnasal drip, sneezing and itching.

Examination of the patient may also be helpful to check for the possibility of an allergic source. The presence of allergic shiners or salute may be helpful to identify allergic patients. External appearance of the nose is helpful in identifying nasal deflections as well as tip ptosis. Examination of the INV is also performed. This is aided by the use of a Cottle maneuver, which consists of retracting the cheek and checking to see if the nasal airflow improves subjectively. A positive test indicates an obstruction at the level of the INV. Anterior rhinoscopy is also helpful to assess the size of the inferior turbinates and to check for static causes of nasal obstruction such as a deviated nasal septum. Nasal endoscopy is also helpful to identify potential causes of this nasal obstruction. This is best performed before and after topical application of a vasoconstrictor or decongestant (Figs. 7.1A and B). Reversible inflammatory causes usually reverse with decongestion and hence a response to the decongestant may indicate an inflammatory cause,[15] whereas a lack of response may indicate a structural problem such as a deviated nasal septum or bony hypertrophy of the inferior turbinates.

ACOUSTIC RHINOMETRY

Acoustic rhinometry is the most commonly utilized objective test for the nasal airway.[16] It is a noninvasive, quick test that relies on acoustics to measure the cross-sectional area (CSA) of the nose relative to the distance from the nostril. Unlike PNIF, AR requires only minimal patient cooperation. It can be performed on adults and children and does not require sedation. It is very helpful to measure the volumes of the nasal passage and hence detect anatomical problems such as a deviated nasal septum or space-occupying lesions such as polyps.[16-18] The validity of this technique has been provided by comparing it with other methods including nasal endoscopy,[15] CT[19] and MRI.[15]

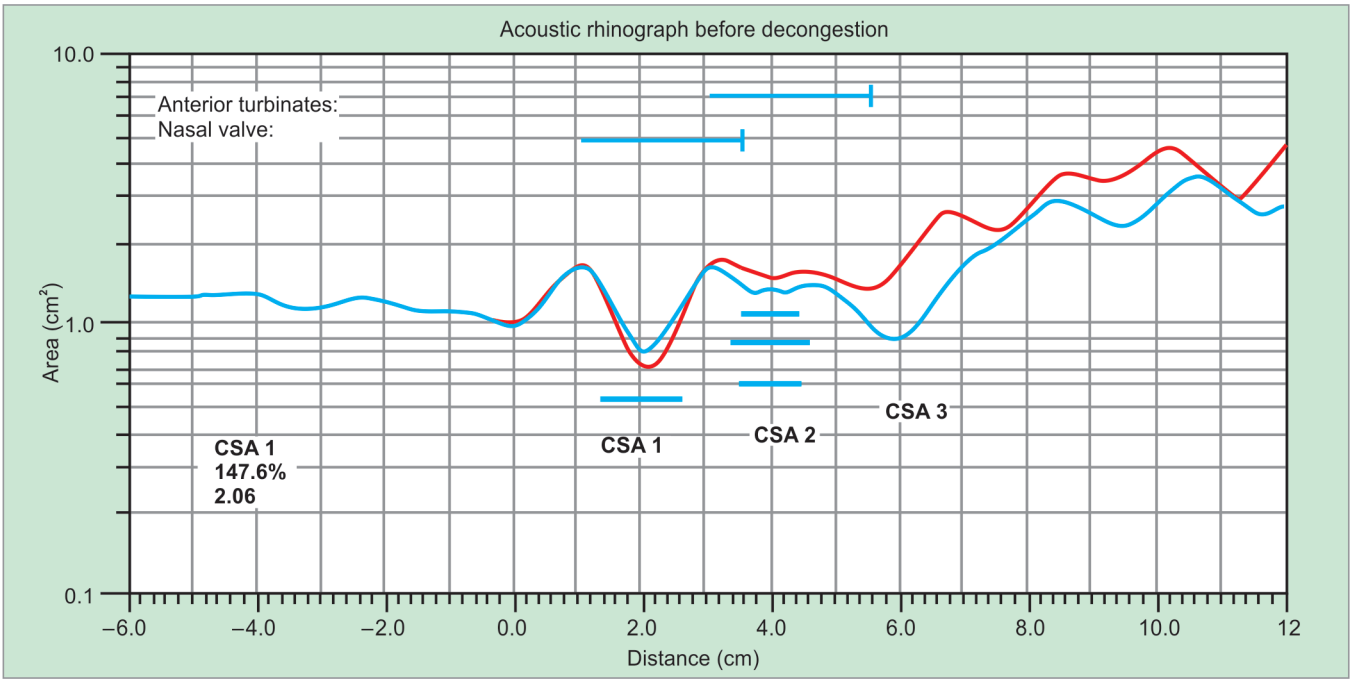


Fig. 7.2: Acoustic rhinograph with the x-axis representing the distance from the nostril in centimeter and the y-axis representing the area. The three notches seen on this graph represent the corresponding cross-sectional areas (CSAs) inside the nose at the given distance. CSA 1 is thought to arise from the nasal valve area and CSA 2 is identified at around 4 cm and usually represents the anterior half of the inferior turbinate as well as the anterior edge of the middle turbinate. The third notch visible is CSA 3 is at 6 cm from the nostril and usually corresponds to the middle portion of the middle turbinate.

Principle

Acoustic rhinometry relies on acoustics in assessing the nasal airway. Sound travelling into the nose is reflected as a result of the variations in the anatomy. The location of obstruction is inferred from the time when these deflections occur, which are then constructed into a rhinograph by the computer as shown in Figure 7.2. AR is typically accurate in the first 5–6 cm from the nostril[20] and hence is best suited for the measurement of the NV.[21,22]

Equipment and Technique

In addition to the nosepiece and the source, the equipment required for AR includes the wave tube, microphone, filter, amplifier, analog-to-digital converter, and a computer to generate the waves. Several nose pieces are available depending on the size. The technique is started in a quiet room with the patient first acclimating to room temperature for a period of 10–20 minutes. The equipment has to be calibrated first by passing a test wave. Following acclimation, the patient is instructed to fixate straight on a distant point. The nose piece is placed parallel to the long axis of the nose with the use of lubricant to provide a seal. Care must be taken to avoid distortion of the nose with the nose piece (Fig. 7.3). Three signals are sent, each 10 seconds long on each side, and these are averaged by the computer. Decongestion of the nose is then performed and the test repeated after 10 minutes to help quantify a potential mucosal reversible cause for the congestion.[16,18]

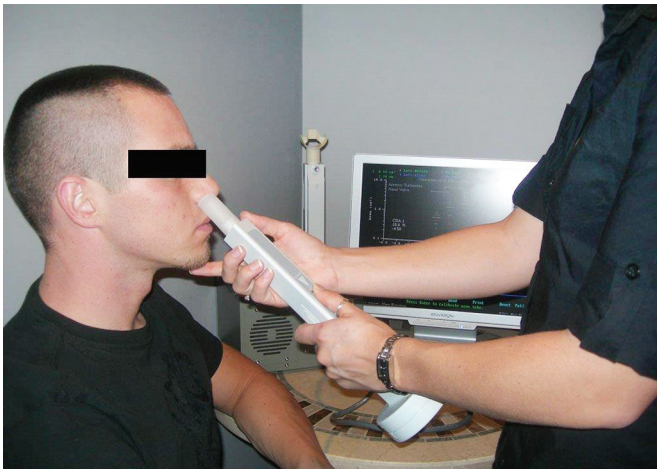


Fig. 7.3: Acoustic rhinometry being performed in the office.

Interpretation

The tracing seen on Figure 7.2 is the rhinograph obtained by the computer. The first 6 cm only are used for interpretation, as previously mentioned. The curves reflect the sound waves that were reflected, with the estimated distance in centimeter being measured on the x-axis and the estimated CSA being measured on the y-axis. The narrowest areas or "valleys" are referred to as CSA 1, 2 and 3, corresponding to each of these valleys.

CSA 1 usually correlates with the location of the INV, CSA 2 correlates with the location of the anterior head of either the middle or inferior turbinate, while CSA 3 correlates to the midposterior end of the middle turbinate around 6 cm away from the nostril.

Clinical Applications

It would be of great value to be able to identify a potentially reversible cause of congestion. The senior author (JPC) developed a method to calculate the "congestion factor".[23] The method used takes decongestion into consideration. The values are obtained before and after the application of a topical decongested as mentioned in the technique section.

Congestion factor = (decongested CSA 2 value – baseline CSA 2 value/baseline CSA 2 value).

The value obtained is then compared with a grading scale and rated as either normal, mild, moderate, severe, or markedly severe.[24] Usually, two standard deviations at CSA 2 before and after application of the decongestion are considered abnormal.[23]

Acoustic rhinometry can be utilized to identify locations of nasal airway narrowing secondary to static factors such as a deviated nasal septum, as well as dynamic factors such as the presence of inferior turbinate hypertrophy. It has also been used in various other areas such as for comparison of preoperative as well as postoperative values for patients undergoing septoplasty, turbinate reduction, cleft lip, and palate as well as facial cosmetic surgeries.[25-29] In addition, its use has been helpful in predicting the tolerance of nasal continuous positive airway pressure (CPAP) in patients with sleep apnea.[30-32] A CSA of less than 0.6 cm^2 at the level of the head of the inferior turbinate correlates with the inability to tolerate nasal CPAP.[32] This, however, is still controversial as other studies have shown no correlation between CSA and adherence to CPAP.[33]

Limitations

Several limitations exist for the utility of AR. The ideal and gold standard test for objective measurement of the nasal airflow is one that is reliable, reproducible, and that strongly correlates with subjective complaints of nasal obstruction. Accuracy of AR is limited to the first 5–6 cm from the nostril.[33] In addition, breathing and swallowing may affect the results obtained, and thus patients should be instructed to avoid these maneuvers since they may change CSA estimates[34] or provide high rate of artifactual traces.[35]

Rhinomanometry

Rhinomanometry is another objective method used in the measurement of nasal airway resistance and is considered a dynamic test. There are different modes that are used; these include active anterior, passive anterior, as well as posterior RM. Objective measures obtained with RM generally do not correlate well with the subjective symptoms.[36,37] Both PNIF and RM are useful in evaluating the severity of nasal congestion.

Principle

Nasal flow can either be turbulent or laminar.[38] As the velocity increases, nasal flow tends to be more turbulent, which corresponds to airflow between 250 cm^3 and 500 cm^3. Factors that affect airflow include nasal length, transnasal pressure, CSA, and whether the flow is laminar or turbulent.[39] Nasal resistance is related to the nasal flow as well as to the pressure. In laminar flow, the relationship between these variables is linear whereas in turbulent flow, it is nonlinear. RM measures simultaneously intranasal pressure as well as airflow. Nasopharyngeal pressure changes between inspiration and hence leads to nasal airflow. Nasal airflow is affected by multiple factors, including CSA, length of the nose, transnasal pressure, as well as the nature of the nasal flow.

Equipment and Technique

A mask is attached to a pneumotachometer that has a pressure transducer measuring transnasal pressure. The transducer converts the pressure difference to an electrical voltage signal that is sent to a connected computer and recorded. In general, there are three different methods used for RM. The pressure detector is placed depending on the type of RM being conducted. In the anterior method, which is the most commonly used method, the pressure detector is placed anteriorly at the opening of the nostril that is not being actively tested. In the posterior method, it is placed transorally or at the level of the posterior oropharynx, and in the postnasal method it is placed in one of the nostrils posteriorly.[40] The International Committee

on Standardization of Rhinomanometry (ICSR) concluded that the method of choice is the active anterior RM.[41,42]

The technique is started following acclimation of the patient to the room for 20 minutes. It is important to calibrate the equipment in the beginning. The test is started with the patient spontaneously breathing. It is prudent to note any leaks in the connections to the mask that can be detected while examining the flow volume loops obtained on the computer. In the active technique, the patient breathes through one nostril while the contralateral nasal pressure is assessed. The passive technique measures the pressure for each side separately at airflow of 250 cm^3/s.

With the recordings of the flow and pressure simultaneously, the work of breathing can be obtained (pressure × flow) along with resistance (pressure/flow) for each breath. Although other results can be used, most commonly used reporting is the nasal resistance that is abbreviated as NAR or Rn. The ICSR recommended that RM values should be in standard units (SI) with pressure expressed in pascal (Pa) and flow in cm^3/s. The resistance is reported in $Pa/cm^3/s$.[41-43]

Interpretation

On a typical graph that is produced by the computer (Fig. 7.4), the x-axis reflects the pressure differential and the y-axis reflects the flow. The standard representation of active RM is a four-quadrant representation of both the right and left nostril during inspiration as well as expiration. The most important measure from this technique is the nasal airway resistance. In anterior RM, the resistance is reported on each separately; however, in the posterior RM, total nasal airway resistance since both sides are assessed simultaneously. The more obstructed the nose, the greater the pressure is needed to generate airflow. For this reason, the greater the resistance, the closer is the curve to the pressure axis. In order to compare results of the nasal airway resistance, a specific point on the curve is needed. According to the International Standards Committee, the designated two options are either at a pressure of 150 Pa or at radius 2.[41,44] The use of this designated pressure is limited by the patient's ability to reach it. For this reason, another important measure is the resistance at the peak pressure or flow point, which is called maximum resistance or the vertex resistance,[44] which does not require a set pressure.

Clinical Applications of RM

Just like AR, RM is an excellent research tool. Either technique can be used in nasal challenge studies.[45,46] RM can also be used to measure resistance before and after decongestion. If there is less than 35% reduction in resistance, then static or irreversible causes such as deviated nasal septum can be the reason for the nasal airway obstruction.

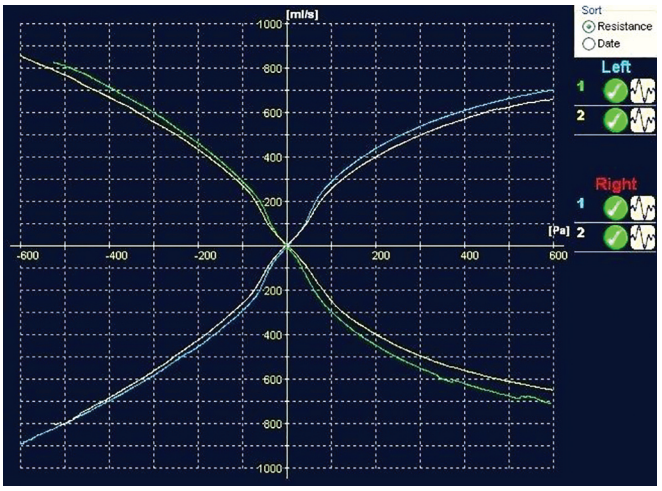


Fig. 7.4: Typical rhinomanometry graph as produced by the computer. The x-axis reflects the pressure differential and the y-axis the flow. On this graph, there are two trials on each side of the nose demonstrating flow in relation to pressure.

AR or RM: Which One Is Better?

There are multiple factors to take into consideration when comparing those two tests. Patients tolerate AR better than RM.[47] When used as a screening tool, both these tests were comparable.[47] Both techniques are operator dependent and are also unable to diagnosis tip ptosis or alar collapse because their measurements reflect obstruction located posterior to the external nasal valve.

NASAL PEAK FLOWMETRY

Compared with AR and RM, this technique is very simple and cost-effective. This test has high sensitivity and has been shown to variably correlate with patient symptoms as well as the other methods of airflow measurement.[46,48-51] The test measures, in liters per minute, the airflow through the nose during maximal forced nasal inspiration.[52]

Equipment and Technique

This test highly depends on the instructions given by the investigator.[52] The test requires only the use of a peak flow meter, the type of which depends on whether NPIF or nasal peak expiratory flow (NPEF) is being measured. The meter is equipped with an airtight face mask to prevent

Fig. 7.5: Inspiratory flow meter used by a patient.
Source: Adapted with permission from Clement Clarke International, Harlow, United Kingdom.

air leak. In NPEF, the patient is asked to hold the device horizontally and then instructed to inspire maximally while the lips are closed, followed by expiring maximally through the nose (Fig. 7.5). Three readings are usually required with the highest being recorded. There are different sizes of the mask to be used by various age groups. In NPIF, the patient is asked to close his/her mouth; the equipment first is calibrated and the red cursor is reset to its initial position.

Interpretation

At least three readings are obtained and the highest is recorded. So far there are no standard limits on what nasal airflow should be as measured by NPIF or NPEF. In one study on healthy subjects, it was determined that no symptoms were apparent when NPIF or NPEF is higher than 2.5 L/s.[53]

Clinical Applications

Since there is no standard limit on the values for NPIF or NPEF, these are best used on the same patient and compared over time.[54] Compared with NPEF, NPIF has better reproducibility and is the one that is most studied and well validated. A linear increase in NPIF occurs with age, height and weight.[55] It has also been compared with other objective methods such as RM and was found to correlate in studies assessing nasal patency following allergen and/or histamine challenges.[56,57] In addition, NPIF has been used for the assessment of nasal airflow following septal or alar surgery[58,59] as well as for the evaluation of patients following medical management of seasonal allergic rhinitis.[60,61]

Limitations

Since this test can only be performed with maximal inspiration, it is not a good test for patients with respiratory disturbances. The test also may be inaccurate since it heavily relies on patient cooperation as well as investigator's instructions. A disadvantage with NPIF is the alar collapse that is observed on forced inspiration. Both NPIF and NPEF rely on a normally functioning lower airway,[53] and thus assume its normal function. During NPIF, the Eustachian tube may open and hence cause discomfort and thus a decrease in the expiratory effort.[62] Similar to AR, no information is obtained regarding the location of the airway obstruction. NPIF is also not as sensitive as the other objective methods and is unable to detect small changes in nasal resistance that could be detected with RM.[48] When flow rates are less than 30 L/s, it is best to use other objective methods as NPIF may not be able to utilized. In addition, repeating this test may change the blood content of the nasal mucosa and hence may result in alterations of the nasal airway resistance over time.[63]

ODIOSOFT RHINO

Odiosoft Rhino is a noninvasive technique that is similar to AR in relying on acoustic signals. The main difference between the two is that in OR, no external sound stimuli are used and the test is performed while the patient is spontaneously breathing. This technique, developed by Seren,[64] converts the frequency of sound generated by the normal nasal breathing into CSA measurements with the aid of the computer. The narrower the area is, the more turbulent is the flow and hence a higher frequency sound is produced.[64]

Similar to AR, each side is tested separately. The equipment needed for this method includes a nasal probe, microphone, sound card, and a computer (Fig. 7.6). The technique begins by occluding the non-test side and placing a nasal probe that is connected to a microphone located 1 cm anterior to the nostril.[65] When comparing this technique to the other objective methods, OR correlated better with symptom scores compared with AR.[66] The accuracy of these results were also shown to be comparable to those obtained with RM.[65]

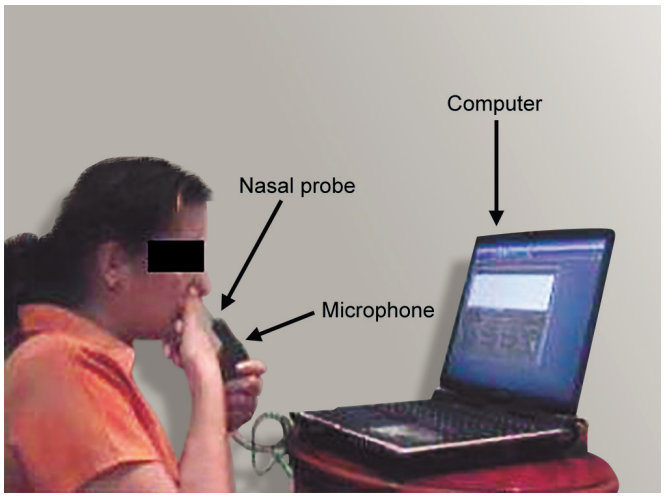


Fig. 7.6: Basic requirements of Odiosoft-Rhino include a nasal probe, a microphone, and a computer.

Limitations

Placement of the tubing in the posterior method and postnasal method requires the patient's compliance. In addition to the requirement of the tubing, the posterior method requires that the patient be instructed on maneuvers for keeping the tongue in position while the nasopharynx and oropharynx remain open. This method was found to be unsuccessful in around 15% of patients due to its positioning requirement.[67] There are multiple factors that affect both AR and RM, including host and external factors (Table 7.1).

RHINOSTEREOMETRY

This is an optical method developed to evaluate the thickness of inferior turbinate mucosa. This method has a high correlation with subjective symptoms of patients following a nasal challenge[68]; however, no significant correlation has been found with it as well as AR during nasal cycling[69] or in subjects with vasomotor rhinitis.[70] This method is relatively new and used only in few centers and is still subject to standardization.

Equipment and Technique

This technique requires the use of a microscope placed on a micrometer table. The patient is fixed on the micrometer table and the microscope, which has a small depth of focus, is brought in. It is usually able to detect as little as 0.18 mm of inferior turbinate mucosal changes.

Table 7.1: Factors that influence acoustic rhinometry and rhinomanometry (AR and RM)

Factor	*Effect on nasal resistance*
Aging	Decrease
Exercise	Decrease
Hyperventilation	Increase
Posture	Supine—increase
	Upright—decrease
Time of the day	Early morning and night—increase
Medications	Decongestants—decrease
Smoking	Increase

Clinical Applications

The technique so far has only been used as an experimental tool[53] due to the lack of standardization and paucity of use. It has been studied in outcome studies such as with detecting effects of nasal decongestants,[71] intranasal steroids,[64] and for nasal hyperactivity.[65]

Limitations

Perhaps the most limiting step in the use of this technique is the time that is required to complete the evaluation as well as the need for a microscope. The patient needs to be fixed to the micrometer table, which is time consuming. In addition, the technique depends on the visual assessment of the investigator.

CONCLUSION

Assessment of nasal airway obstruction starts with an adequate history and physical examination that includes nasal endoscopy. Enhanced information about the nature of the nasal airway obstruction can be obtained by performing objective tests of the airway, which most commonly include AR and RM. Obtaining these tests may help assess the nature of the airway obstruction and its reversibility. Future studies are also needed to provide further evidence documenting the results obtained for these tests, particularly for postoperative patients.

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CHAPTER

Clinical Evaluation and Treatment of Smell and Taste Disorders

8

Richard L Doty, James B Snow, Jr

INTRODUCTION

Although commonly taken for granted, the chemical senses of taste and smell are important for everyday living and, when dysfunctional, significantly impact the safety, nutrition, and quality of life. These senses play a key role in a number of occupations, including those associated with cooking, chemical manufacturing, medical practice, perfumery, plumbing, firefighting, police work, and public works. In fact, anosmia (loss of smell function) is a cause for dismissal from the United States Armed Forces, including the Coast Guard, attesting to the importance of a normally functioning sense of smell in aeronautics, maritime activities, and battlefield situations.

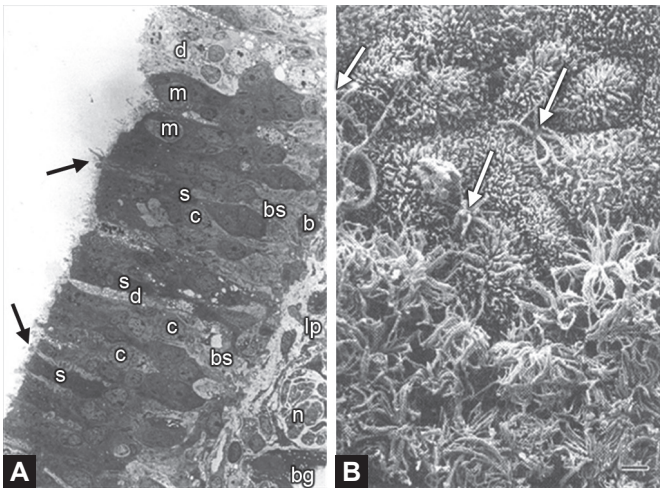
Of 750 consecutive patients presenting to the University of Pennsylvania Smell and Taste Center with chemosensory complaints, 68% reported altered quality of life, 46% changes in appetite or body weight, and 56% adverse influences on daily living or psychological well-being.[1] In a Virginia Commonwealth University study of 445 patients with chemosensory disturbances, at least one lifetime consequential hazardous event (e.g. food poisoning or failure to detect fire or leaking natural gas) was reported by 45.2% of those with anosmia, 34.1% of those with severe hyposmia, 32.8% of those with moderate hyposmia, 24.2% of those with mild hyposmia, and 19.0% of those with normal olfactory function.[2] Recently, a longitudinal study of 1162 nondemented older persons performed at Rush Medical Center in Chicago found that mortality risk was 36% higher in those with low scores than in those with high scores on a 12-item odor identification test after adjusting for such variables as sex, age and education.[3] Of particular importance to the medical practitioner is the fact that chemosensory function can be an index of neurological health. As described in detail later in this chapter, olfactory disturbances are among the early "preclinical" or "presymptomatic" signs of such neurological disorders as Alzheimer disease (AD) and Parkinson disease (PD).[4]

In this chapter, we review the basic anatomy and physiology of the senses of taste and smell and describe diseases associated with the malfunction of these senses. The sections of the chapter are divided into anatomy and physiology, chemosensory disorders, clinical evaluation, quantitative testing, and patient management and treatment. Somewhat more emphasis is placed on olfaction than on gustation, in part because of more information on smell than on taste disorders and because most complaints of decreased "taste" function reflect lessened smell function.[1] Thus, flavor sensations from such beverages or foodstuffs as coffee, chocolate, strawberry, pizza, licorice, steak sauce, and vanilla largely depend on stimulation of the olfactory receptors by molecules that enter the nasopharynx during deglutition, a process called retronasal olfaction. The taste system mediates such discrete flavor sensations as sweet, sour, bitter, salty and savory (umami), although, as noted later in this chapter, taste receptors are found outside the oral cavity, including the respiratory system and the alimentary tract.

ANATOMY AND PHYSIOLOGY

Olfaction

During inhalation an estimated 10–15% of the air entering the nose reaches the olfactory epithelium, a



Figs. 8.1A and B: (A) Low-power photomicrograph of cross section of the human olfactory neuroepithelium showing the four major types of cells: bipolar receptor cells (arrows point to cilia at their dendritic knobs. bg, Bowman's gland; bs, basal cell undergoing mitosis; c, cell body of receptor cell; d, duct of Bowman's gland; lp, lamina propria; m, microvillar cell; n, collection of axons with an ensheathing cell; s, sustentacular (supporting) cell. By courtesy of Dr David Moran, Longmont, CO, USA. (B) A transition zone between the human oflactory epithelium (bottom) and the respiratory epithelium (top). Arrows signify two examples of olfactory receptor cilia dendrites with cilia that have been cut off. Bar = 5 µm. *Source*: With permission from Menco and Morrison.[92] Copyright © 2003 Richard L Doty.

pseudostratified columnar neuroepithelium that overlies the cribriform plate, superior sections of the septum, and portions of both the superior and middle turbinates. Sniffing increases the numbers of molecules that reach this epithelial region. In addition to harboring the dendrites, cell bodies, and initial axon segments of 6–10 million olfactory receptor cells, this epithelium contains sustentacular (supporting) cells, microvillar cells, duct cells of Bowman glands (the major source of mucus in the region), and basal cells, which are the progenitor stem cells of the other cell types (Fig. 8.1A). When damaged, the cells of the epithelium can be replaced by the stem cells, although such replacement is rarely complete and does not occur if the stem cells are damaged.

Odorant molecules are absorbed into the mucus covering the olfactory epithelium and reach receptors located on the cilia by either diffusion or transport via specialized "carrier" proteins[5] (Fig. 8.1B). The types of olfactory receptor proteins found on the cilia are extremely diverse, numbering around 400 in humans. Such receptor diversity exceeds that of all other sensory systems, e.g. vision relies on only four different types of receptors: three types of cones and one type of rod. Remarkably, the olfactory subgenome spans 1–2% of the total genomic DNA, and odor receptor genes are found in ~100 locations on all of the chromosomes except 20 and Y. Interestingly, each olfactory receptor cell expresses only one type of olfactory receptor.[6] Since most olfactory receptors are activated by multiple chemicals, there is overlap among the responsiveness of the receptor cells to the same chemical.

It is important to point out that the olfactory receptor cells can serve as conduits for the movement of xenobiotics, including nanoparticles and viruses, from the nose into the brain. Unlike most receptor cells, olfactory receptor cells are both the receptor cell and the first-order neuron, synapsing not at the periphery but within the brain. Indeed, it was found in the 1930s that the polio virus commonly gained access to the brain via this route, leading to public health initiatives in Canada and elsewhere to cauterize the olfactory region of school children with zinc sulfate in attempts to prevent the contraction of polio.[7]

After coalescing into bundles (fila) within the lamina propria, the olfactory receptor axons pass through the foramina of the cribriform plate and are distributed across the surface of the olfactory bulb. The olfactory bulb, a cortex-like layered ovid structure illustrated in Figure 8.2, is composed of afferent and efferent nerve fibers, multiple interneurons, microglia, astrocytes, and blood vessels. The receptor cell axons selectively enter the sphere-like olfactory glomeruli located within an outer layer of the bulb (Fig. 8.2), where their activity is influenced presynaptically by dopamine and GABA (Fig. 8.3). Note in this figure that the main neurotransmitter of the olfactory receptor cells is L-glutamate and that there are many types of influences on the secondary neurons, most notably mitral cells. Each glomerulus receives axons from receptor cells that express the same receptor protein, making them, in effect, functional units representative of the specific classes of such proteins. Although younger persons have over a thousand glomeruli, these structures become less distinct in older persons. In fact, many elderly lack distinguishable glomeruli altogether.

The activity of the mitral and tufted cells, the output neurons of the olfactory bulb, is modulated not only by receptor cell inputs, but by centrifugal fibers from outside of the bulb as well as by numerous local interneurons. For example, their secondary dendrites have reciprocal synaptic contacts with GABAergic granule cells, which make up much of the core of the olfactory bulb and which

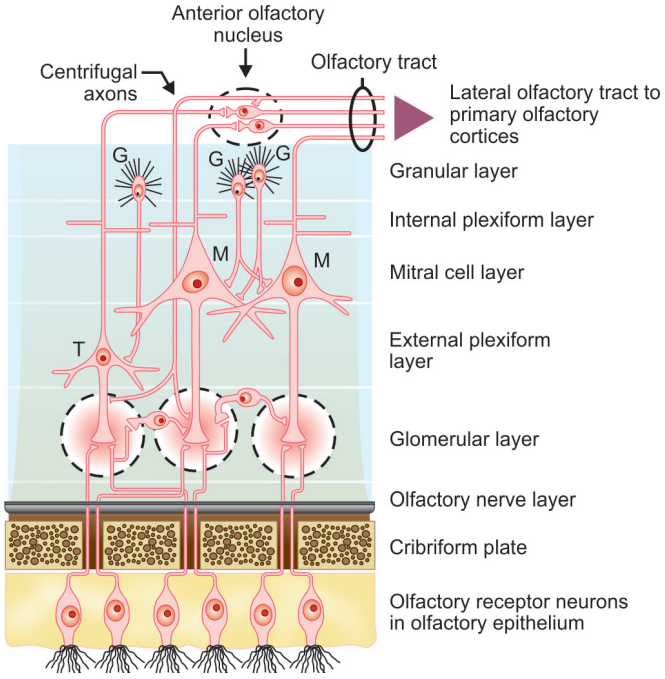


Fig. 8.2: Schematic representation of the major layers of the olfactory bulb and their interactions among cell types therein.
(G: Granuel cells; M: Mitral cells; T: Tufted cells).
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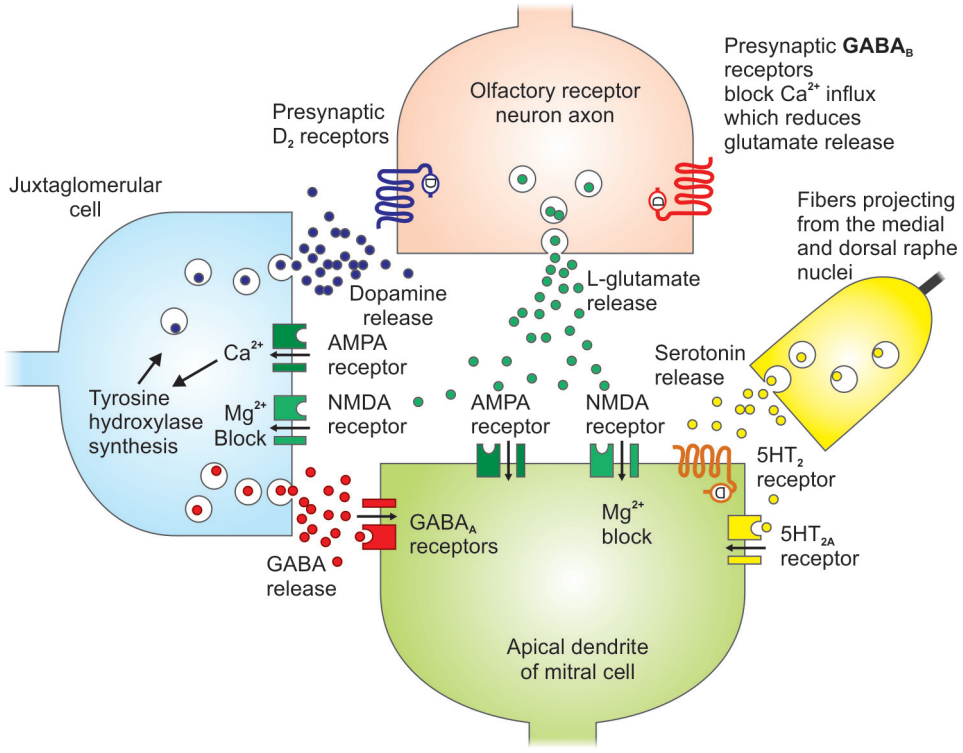
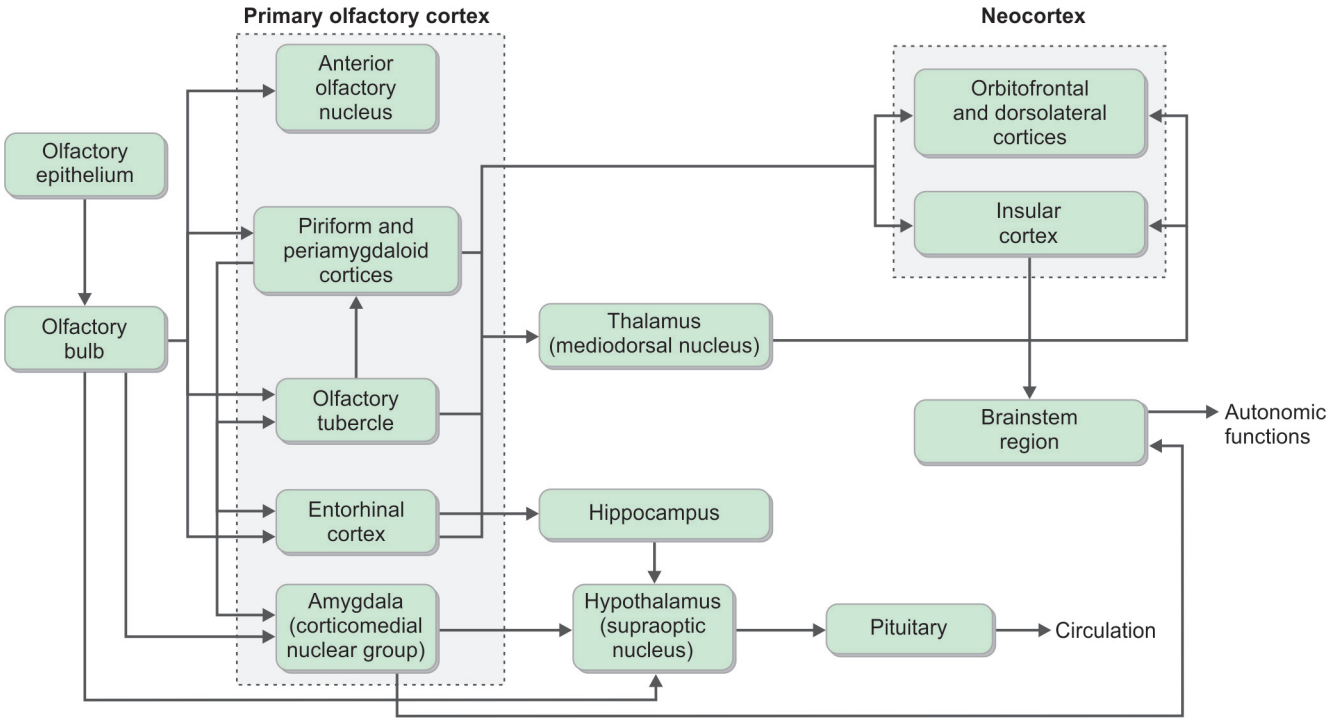


Fig. 8.3: Glomerular synapses showing the variety of receptors. The axons from the olfactory receptor neurons form the olfactory nerve and synapse with the primary apical dendrites of the mitral cells. L-glutamate is the primary excitatory transmitter at this synapse that binds to AMPA and NMDA receptors on the postsynaptic membrane. Juxtaglomerular cells are inhibitory GABAergic/dopaminergic interneurons that mediate inhibition between glomeruli. Centrifugal fibers project from the raphe nuclei to the glomeruli modulating the mitral cell activity via postsynaptic 5HT (serotonergic) receptors.
Source: Reproduced with permission from O'Connor and Jacob.[94]

Flowchart 8.1: The major central afferent olfactory projections of the olfactory system. Reciprocal efferent projections are not shown. Direct connections between the olfactory bulb and hypothalamus may not be present in humans and some other mammals. Copyright © 2010 Richard L. Doty.



themselves are modulated by inputs from central brain regions. Although most centrifugal fibers terminate on granule cells, others enter into the external plexiform, internal plexiform, and glomerular layers.

Cells within the olfactory bulb, like the olfactory receptor cells, undergo replacement over time.[8] These include the granule cells and the largely dopaminergic periglomerular cells. Large numbers of neuroblasts are generated from astrocyte-like stem cells within the subventricular zone of the brain. Some of these neuroblasts undergo restricted chain migration along the rostral migratory stream, terminating within the granule cell layer of the olfactory bulb.[9] Some differentiating neuroblasts then migrate more peripherally within the bulb, thereby repopulating periglomerular cells.

A number of central brain structures receive the projections from the mitral and tufted cells via the lateral olfactory tract. These include the anterior olfactory nucleus, the piriform cortex, the anterior cortical nucleus of the amygdala, the periamygdaloid complex, and the rostral entorhinal cortex (Flowchart 8.1). These structures have reciprocal relations with one another and numerous other brain centers. For example, fibers from the entorhinal cortex innervate the entire length of the hippocampus. Pyramidal cells from the anterior olfactory nucleus project to numerous ipsilateral and contralateral brain structures, the latter via the anterior commissure. Although the olfactory system projects directly to cortical structures without first synapsing in the thalamus, connections via the thalamus are present, for example, between the entorhinal cortex and the orbitofrontal cortex.

The functions of the central olfactory structures are poorly understood and appear to be overlapping. The posterior piriform cortex likely mediates basic odor perception and detection, whereas the anterior piriform cortex seems to be involved in odor hedonics.[10] Although the amygdala responds to both pleasant and unpleasant odors, limited data suggest it may be slightly more activated by unpleasant stimuli. The orbitofrontal cortex may be more involved in the perception of concepts in which odors play a role, integrating information about such concepts (e.g. an orange) across several modalities (e.g. color, touch, taste and smell).

Gustation

The sense of taste plays a critical role in the detection, acceptance, or rejection of nutrients (e.g. sugars) and

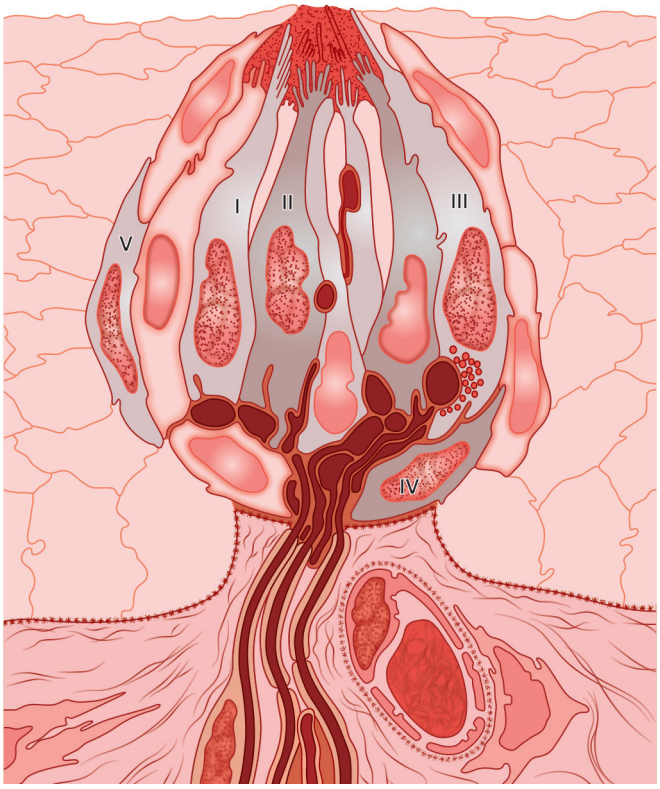


Fig. 8.4: Idealized drawing of longitudinal section of mammalian taste bud. Cells of type I, II and III are elongated and form the sensory epithelium of the bud. These cells have different types of microvillae within the taste pit and may reach the taste pore. Type IV are basal cells and Type V are marginal cells. Synapses are most apparent at the bases of type III cells. The connecting taste nerves have myelin sheaths.
Source: With permission from Witt et al.[95] Copyright © 2015 Richard L. Doty.

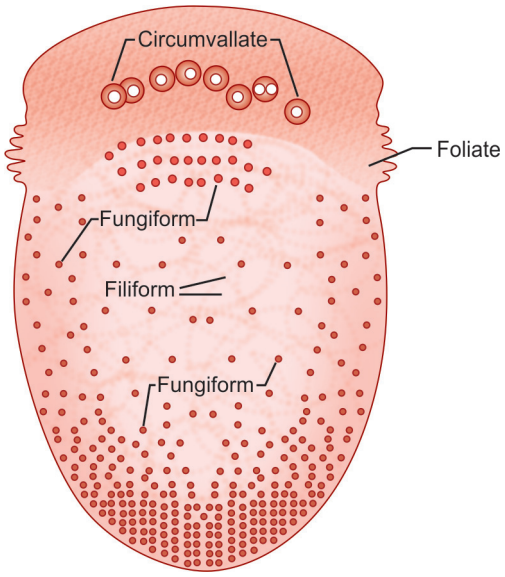


Fig. 8.5: Schematic representation of the tongue demonstrating the relative distribution of the four main classes of lingual papillae. Note that the fungiform papillae can vary considerable in size and that they are more dense on the anterior and lateral regions of the tongue. Copyright © 2006 Richard L. Doty.

poisons (e.g. bitter tasting alkaloids). Sweet and bitter taste-related receptor proteins are distributed within the oral cavity, as described in detail below, as well as within the stomach, intestine, oropharynx, larynx, and the upper esophagus, where they serve multiple functions.[11,12] These include facilitation of digestion, bacterial inactivation (via secretion of nitric oxide), chemical absorption, insulin release, and the metabolism of swallowed foods and beverages. Interestingly, one specific taste receptor (T2R38) is expressed in human upper respiratory epithelia where it is associated with release of nitric oxide. This receptor responds to acyl-monoserine lactone, quorum-sensing molecules secreted by *Pseudomonas aeruginosa* and other gram-negative bacteria. Differences in T2R38 functionality, as related to TAS2R38 genotype, are associated with susceptibility to upper respiratory infections.[13] Taste-related receptor proteins located in the gut provide one explanation as to why more insulin is released from the pancreas when glucose is ingested than when it is injected into the blood stream and why gastric bypass patients have an immediate decline in their underlying insulin resistance.[14]

Most of the oral taste receptor cells involved in the conscious perception of taste are found within flask-like taste buds located on lingual papillae (Fig. 8.4). Humans possess approximately 7500 taste buds. Those on the fungiform papillae and the anterior foliate papillae are innervated by the chorda tympani division of the facial nerve (CN VII), whereas those on the posterior folliate papillae and on the large circumvallate papillae are innervated by the glossopharyngeal nerve (CN IX) (Fig. 8.5). Taste receptors found in the throat and digestive tract are supplied by the vagus nerve (CN X), whereas those on the soft palate are supplied by the greater superficial petrosal division of CN VII. The small and somewhat pointed filiform papillae, which cover the entire tongue, harbor no taste buds. Although not involved in taste perception, per se, elements of the trigeminal nerve (CN V) project into the papillae and other oral mucosa surfaces and participate in the formation of flavor by signaling sensations of touch, pain and temperature. Thus, the fizziness of carbonated soft drinks and the warmth of coffee are dependent upon the stimulation of this nerve.

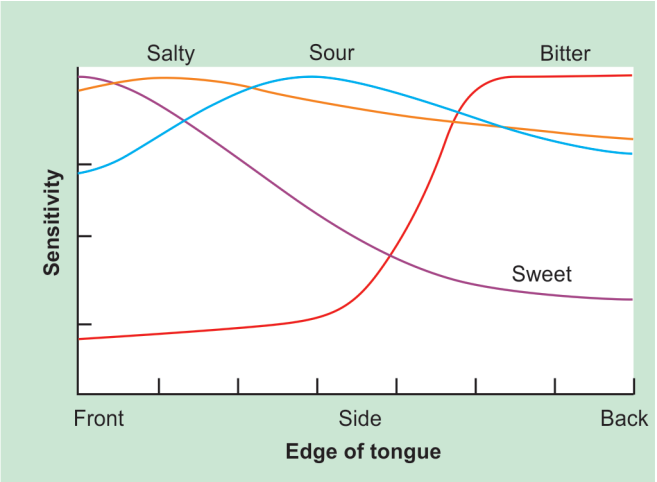


Fig. 8.6: Relative sensitivity of the edges of the tongue to the four classic taste qualities. Sensitivity reflects the reciprocal of the threshold value and is plotted as a ratio of maximal sensitivity = 1. Threshold data are from Hänig (1901). Note that all regions of the tongue that were evaluated were responsive to some degree to all stimuli, but that the anterior edge of the tongue was most sensitive to sweet, sour and salty, and least sensitive to bitter. The back (base) of the tongue was relatively more sensitive to bitter.
Source: Adapted from Boring.[96]

Individuals differ markedly in terms of the number and distribution of their taste buds which are distributed largely in the edges and back sections of the tongue (Fig. 8.5). Although all tongue regions respond to most tastants, the front of the tongue is more sensitive to most taste qualities save bitter, to which the back of the tongue is more sensitive. The relative average sensitivity of tongue regions to the four prototypical taste qualities is shown in Figure 8.6. It must be kept in mind, however, that considerable variation exists among people.

Three general classes of taste-responsive cells within taste buds have been identified on the basis of structure (Fig. 8.4).[15] Type I cells are largely responsible for salt taste. These cells are activated by the entrance of Na^+ ions via specialized membrane channels such as the amiloride-sensitive Na^+ channel.[16] Type II cells are responsive to sweet, bitter and savory (monosodium glutamate-like) sensations. Some Type II cells express a family of three G-protein-coupled receptors (GPCRs) responsible for sweet and savory taste sensations, namely, the T1R1, T1R2, and T1R3 receptors, whereas others express a family of ~30 GPCRs, the T2R receptors, responsible for bitter sensations.[17-19] Type III cells appear to be specialized for detecting sour tastes. H^+ ions pass through specialized proton channels of Type III cells that do not involve GPCRs.[20] A number of types of ion channels are responsive to acids, including acid-sensing ion channels, potassium channels, and epithelial sodium channel-like channels.[21]

The taste nerves of the oral cavity and pharynx (i.e. CN VII, IX, and X) project to the nucleus tractus solitarius of the brainstem, the first relay station of the taste system. Connections are then made via the medial lemniscus to the upper regions of the ventral posterior nuclei of the thalamus. From there, projections are sent to the amygdala and other structures, most notably the anterior-insular cortex and the primary somatosensory cortex. Neurons within these higher brain regions respond to taste, touch, and in some cases odors, often reflecting conditioning, which occurs from the pairing of activation of these modalities during deglutition. There is evidence that hedonic responses to tastants can occur at the level of the brainstem, although for identification of a tastant, the matching of information coming from the taste pathways must be made at some point with the remembered sensation to allow for its recognition or identification. The gestalt of flavor perception clearly requires multimodal integration of information and the participation of a number of brain regions.

CHEMOSENSORY DYSFUNCTION IN HEALTH AND DISEASE

Total loss of smell function is termed anosmia, whereas that of taste is termed ageusia. Terms used to describe less than total loss of smell or taste function are hyposmia and hypogeusia, respectively. Dysfunction can be on both sides of the body (bilateral) or only on one side (unilateral). Distorted or strange smells, such as those described as "chemical- or garbage-like," that depend upon an odorant for their elicitation are termed dysosmia or parosmia, whereas those that spontaneously appear in the absence of an apparent stimulus are termed phantosmias (olfactory hallucination). Equivalent terms of distorted tastes are dysgeusia, parageusia and phantogeusia. When an olfactory sensation is fecal like, the term cacosmia is sometimes used.

Numerous nondisease factors influence the ability of healthy persons in the general population to smell and taste, including age, gender and smoking behavior. Cigarette smoking can have a cumulative, albeit modest, adverse effect on smell function, which is typically reversible, with return to normal function after cessation dependent upon to the degree of previous smoking in pack years.[22]

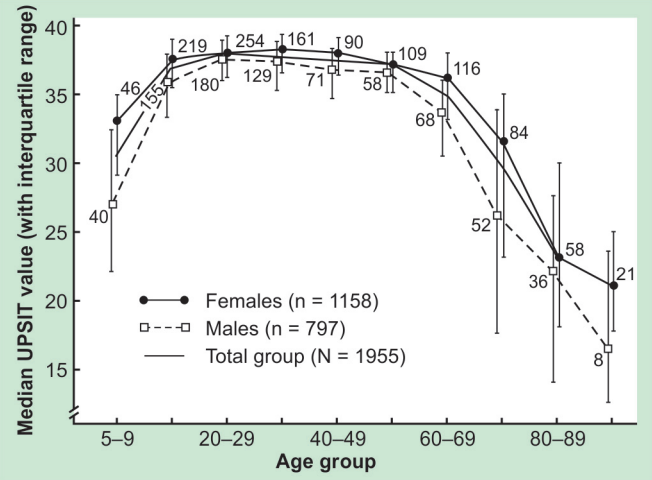


Fig. 8.7: Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of age and gender in a large heterogeneous group of subjects. Numbers by data points indicate sample sizes.
Source: With permission from Doty et al.[26] Copyright © 1984 by the American Association for the Advancement of Science.

Similar influences of smoking on taste sensitivity have also been reported, although the reversibility of the deficits has not been established.[23-25] Women generally have better senses of taste and smell than men, effects which are accentuated in later life, most notably for the sense of smell (Fig. 8.7). Decreases in olfaction occur in over half of persons between the ages of 65 and 80 years, and in over three quarters of those >80 years.[26] Although age-related whole-mouth taste deficits can be demonstrated in older persons, regional taste deficits are much more marked.[27] Such losses help to explain why many elderly find food distasteful and are more likely to succumb to nutritional deficiencies and, in rare instances, to natural gas poisoning or fires.

As noted in the beginning of the chapter, most patients with complaints of taste loss have olfactory dysfunction, not taste dysfunction, reflecting a lesser degree of fragility of the taste system and the importance of retronasal olfactory stimulation in establishing flavor sensations. Nonetheless, taste dysfunction can occur from (a) viral invasion of one or more taste nerves as in Bell palsy, (b) altered transport of tastants into the taste buds (e.g. scaring of the lingual surface, mucosal drying, inflammatory conditions, infections), (c) taste bud damage from local trauma, invasive carcinomas, and iatrogenic outcomes as with radiation therapy, (d) damage to taste nerves (e.g. middle ear infections or operations, third molar extractions, radiation therapy), (e) damage to taste-related central nervous system structures from multiple sclerosis, neurodegenerative diseases, tumors, epilepsy, stroke, and iatrogenesis, and (f) generalized metabolic disturbances that arise from diabetes, chronic renal failure, end-stage liver disease, thyroid disease, hypothyroidism, medications, and vitamin and mineral deficiencies. A number of anticonvulsant drugs have been reported to produce severe dysgeusias, including carbamazepine, felbamate, phenytoin, and lamotrigine.[28-31] In addition, foul-tasting materials can be introduced into the oral cavity as a result of rhinosinusitis, gingivitis, and purulent sialadenitis.

Lesions dorsal to the pons produce ipsilateral deficits, whereas those within the pons can produce ipsilateral, contralateral, or bilateral deficits. Both ipsilateral and contralateral taste deficits have been noted in patients with lesions of the insular cortex, reflecting the bilateral representation of taste function at this level.[32] CN IX, unlike CN VII, is relatively protected along its path, although iatrogenic interventions can damage this nerve (e.g. tonsillectomy, bronchoscopy, laryngoscopy, and radiation therapy), and this nerve is not immune to damage from neoplasms, vascular lesions and infection. On rare occasion, epilepsy or migraine can produce a gustatory prodrome or aura, and some tastants may actually trigger seizures or migraine attacks. Importantly, several hundred medications have been associated with taste dysfunction in patients, including antineoplastic agents, antirheumatic drugs, antibiotics, and blood pressure medications.[33] Terbinafine, a popular antifungal, can produce long lasting loss of sweet, sour, bitter, and salty taste perception.[34] One double-blind study found that eszopiclone (Lunesta), a widely used sleep medication, induces a bitter dysgeusia in approximately two-thirds of individuals tested.[35] This sensation was related to the time since drug administration, was stronger for women than for men, and correlated with both saliva and blood levels of the drug.

The three most common causes of long-lasting smell loss are upper respiratory infections, head trauma, and chronic rhinosinusitis (CRS),[1] with smell loss being part of defining diagnostic features of CRS.[36] The next most common causes are congenital, iatrogenic, and toxic exposures to chemicals. While smell loss secondary to head trauma is usually assumed to reflect coup, contrecoup movement of the brain, resulting in tearing or shearing of the olfactory fila at the level of the cribriform plate,[37] more than one pathophysiological process may be involved since return of function from anosmia seems to segregate into two different functions (Fig. 8.8).

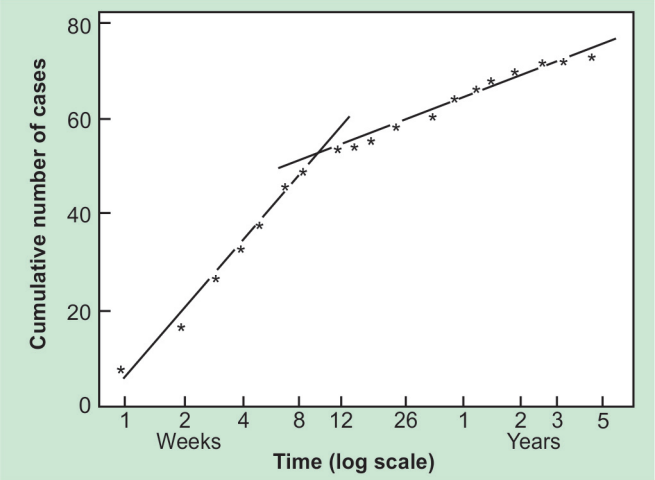


Fig. 8.8: The number of patients reported by Sumner[90] who recovered smell function over time since injury onset. Note abrupt change in slope of function at 9–10 months. This may reflect two different underlying factors, i.e. the shorter term disappearance of compression, edema, and blood clot formation and longer term neuronal recovery.
Source: Reprinted with permission from Sumner.[90] Copyright © 1964 Oxford University Press.

Other causes of taste and smell dysfunction include iatrogenic interventions (e.g. middle ear operations, third molar extractions, turbinectomy, septoplasty, rhinoplasty, sinus surgery and radiotherapy), intranasal or intraoral neoplasms (papilloma, hemangioma, ameloblastoma, etc.), intracranial space occupying lesions (Foster Kennedy syndrome, olfactory groove meningioma, frontal lobe glioma), epilepsy, psychiatric disorders, exposure to environmental chemicals, hypothyroidism, and renal or liver disease. Anosmia or hyposmia is a well-recognized primary and, in some cases sole, feature of an olfactory groove meningioma.[38] Although some medications alter chemosensory function, little empirical data are available on this point, and most cases of drug-induced dysfunction appear to affect the taste system, not the smell system. A listing of diseases associated with smell loss is presented in Table 8.1.

It is important to note that some viruses are able, under certain circumstances, to enter the brain after incorporation into the olfactory receptor cells.[7] Examples include *Herpes simplex* types 1 and 2, polio, the Indiana strain of wild-type vesicular stomatitis, rabies, mouse hepatitis, borna disease, and canine distemper viruses. Several viruses that are not ordinarily neurotropic may become so after entering the nose. For example, when the NWS strain of influenza virus is injected intraperitoneally in mice, viral antigen is restricted to the meninges, choroid plexus, ependymal cells, and perivascular regions within the brain parenchyma. However, when inoculated into the nose, this virus can spread through the olfactory and trigeminal nerves and invade the brain.[39]

A number of neurodegenerative diseases are associated with smell loss early in their course, in some cases years before the expression of the classical disease phenotype, i.e. during the so-called "presymptomatic" or "preclinical" phase.[4,40] Examples of such diseases are AD and PD. Disorders often confused with these two diseases, such as major affective disorder, essential tremor, and progressive supranuclear palsy, rarely exhibit meaningful olfactory dysfunction, making smell testing of potential use in differential diagnosis.[41] Idiopathic rapid eye movement (REM) sleep behavior disorder, a disease, which typically develops into PD, multiple system atrophy, or Lewy body dementia, is associated with olfactory dysfunction analogous to that of PD.[42] Narcolepsy, which is independent of REM behavior disorder, is also associated with similar olfactory dysfunction.[43] The basis for the olfactory deficit of nacrolepsy has been suggested to be damage to hypothalamic cells expressing the excitatory neuropeptide hormone orexin A (hypocretin-1). Such cells project to multiple regions of the olfactory system.[44] This hormone is decreased or undetectable in the cerebrospinal fluid of patients with narcolepsy and cataplexy, and intranasal administration of orexin A to narcoleptic patients with cataplexy reportedly improves their olfactory function.[45]

Many idiopathic cases of smell or taste loss are likely due to viruses but are not recognized as such. During seasonal epidemics the number of serologically documented influenza or arboviral encephalitis infections exceeds the number of acute cases by several 100-fold,[46] and cases of influenza-related smell dysfunction are much higher during the winter months.[47] In rare instances, smell dysfunction, but not taste dysfunction, has been reported to occur after influenza vaccine innoculations in a manner seemingly analogous to vaccine-related cases of Bell's palsy and Guillain-Barré syndrome.[48,49] Such losses may reflect a subtle but defining influence on an already compromised olfactory epithelium, although coincidental viral infection cannot be excluded from consideration.

Most cases of dysosmia or phantosmia reflect inflammation of, or damage to, the olfactory epithelium, although in some instances bacterial infections within the nose or sinuses can produce foul smells that produce this condition. Olfactory agnosia—the inability to recognize odors by an otherwise intact olfactory system—may occur

Table 8.1: Disorders and conditions associated with compromised olfactory function, in most cases documented by olfactory testing

22q11 deletion syndrome	Lubag
AIDS/HIV infection	Medications
Adenoid hypertrophy	Migraine
Adrenal cortical insufficiency	Multiple sclerosis
Age	Multiple system atrophy
Alcoholism	Multi-infarct dementia
Allergies	Myasthenia gravis
Alzheimer disease	Narcolepsy with cataplexy
Amyotrophic lateral sclerosis	Neoplasms, cranial/nasal
Anorexia nervosa	Nutritional deficiencies
Asperger syndrome	Obstructive pulmonary disease
Ataxias	Obesity
Attention deficit/hyperactivity disorder	Obsessive compulsive disorder
Bardet–Biedl syndrome	Orthostatic tremor
Chaga's disease	Panic disorder
Chemical exposure	Parkinson disease
Chronic obstructive pulmonary disease	Parkinson dementia complex of Guam
Congenital	Pick disease
Creutzfeldt–Jakob disease	Post-traumatic stress disorder
Cushing syndrome	Pregnancy
Cystic fibrosis	Pseudohypoparathyroidism
Degenerative ataxias	Psychopathy
Diabetes	Radiation (therapeutic, cranial)
Down syndrome	Rapid eye movement behavior disorder
Epilepsy	Refsum disease
Facial paralysis	Renal failure/end-stage kidney disease
Frontotemporal lobe degeneration	Restless leg syndrome
Gonadal dysgenesis (Turner syndrome)	Rhinosinusitis/polyposis
Guamanian ALS/PD/dementia syndrome	Schizophrenia
Head trauma	Seasonal affective disorder
Herpes simplex encephalitis	Sjogren syndrome
Hypothyroidism	Stroke
Huntington disease	Tobacco smoking
Iatrogenesis	Toxic chemical exposure
Kallmann syndrome	Upper respiratory infections
Korsakoff psychosis	Usher syndrome
Leprosy	Vascular disorders (e.g. aneurysms, hemorrhages)
Liver disease	Vitamin B12 deficiency

secondary to some brain lesions, although distinguishing this problem from other forms of dysfunction is challenging. Hypersensitivity to odorants (hyperosmia) has been reported, although many persons claiming hypersensitivity are experiencing dysosmias and show decrements in function upon testing. Others are emotionally reacting to the odors, and enhanced sensitivity, per se, is not evident.

CLINICAL EVALUATION

Like many disorders, the etiology of chemosensory disorders usually can be determined from the nature, onset, duration, pattern of fluctuations, and potential precipitating events of the symptoms. Information regarding previous injuries, smoking habits, drug and alcohol use

(e.g. intranasal cocaine), exposures to chemicals, pesticides, and other toxic agents, and prior medical interventions can be informative. The possibility of interactive or cumulative effects of multiple infections, head trauma, or other factors should be explored. A determination of medications that were being taken prior to or at the time of symptom onset is important, as are comorbid medical conditions such as renal failure, liver disease, hypothyroidism, diabetes, and dementia. Particularly in teenagers, delayed puberty in association with apparent congenital anosmia (with or without midline craniofacial abnormalities, deafness, and renal anomalies) suggests the possibility of Kallmann or related syndromes. Recollection of epistaxis, rhinorrhea (clear, purulent, or bloody), nasal obstruction, allergies, and somatic symptoms, including headache or irritation, have potential localizing value. Questions related to memory, parkinsonian signs, and seizure activity (e.g. automatisms, occurrence of black-outs, auras, and déjà vu) should be posed. The possibility of malingering should be considered, particularly if litigation is involved. In the case of olfaction, intermittent loss usually implies an obstructive disorder, such as from rhinosinusitis or other inflammatory problem. Sudden loss alerts the practitioner to head trauma, ischemia, infection, or a psychiatric condition, although in some cases the effects of head trauma can appear long after the insult, presumably reflecting long-term degeneration of the olfactory neurons. Gradual loss can be a marker for the development of a progressive obstructive lesion, cumulative drug effects, or simply presbyosmia or presbygeusia.

Some taste problems, most notably dysgeusias, can be identified by taste-specific complaints, such as the presence of a persistent salty or bitter taste. Surprisingly, simple questions such as whether salt can be detected in potato chips, or whether sweetness can be detected in soda, cookies, or ice cream, are relatively insensitive in detecting true taste losses, although affirmative answers to such questions usually imply that a taste problem does not exist.[50] In some cases where the patient complaints of dysgeusia or hypogeusia, smell loss is present and the patient is noticing the saltiness or bitterness of a food or beverage that previously went unnoticed because of the salience of its associated olfaction-related flavor. While it is well known that damage to the chorda tympani nerve, as occurs in some middle ear disorders or operations, can produce metallic dysgeusias, one cannot always attribute complaints of metallic tastes to the taste system, per se. In one study, for example, reports of metallic sensations following oral stimulation with $FeSO_4$ solutions were reduced to baseline when the nose was occluded, whereas no reduction occurred with $CuSO_4$ or ZnSO solutions, which were more bitter and astringent.[51] The authors suggested that the reduction in metallic sensation with $FeSO_4$ solution may reflect a lipid oxidation reaction within the mouth that produces volatiles sensed retronasally by the olfactory system and perceived as metallic in nature.

The physical examination should thoroughly assess the intranasal architecture and mucosal surfaces within the nose and oral cavity. Polyps, masses, and adhesions of the turbinates to the septum may compromise the flow of air to the olfactory receptors, since less than a fifth of the inspired air traverses the olfactory cleft in the unobstructed state. Computed tomographic imaging of the sinuses as well as a brain magnetic resonance imaging can rule out nasosinus or brain lesions that may be responsible for the loss or distortion of smell function. The neural evaluation should focus on cranial nerve function, with particular attention to possible skull base and intracranial lesions. Visual acuity, visual field, and optic disk examinations aid in the detection of intracranial mass lesions that induce intracranial pressure resulting in papillodema and optic atrophy, especially when considering their ipsilateral appearance in the Foster Kennedy syndrome due to an optic nerve meningioma. Blood serum tests may be helpful to identify such conditions as diabetes, infection, heavy metal exposure, nutritional deficiency (e.g. B6, B12), allergy, and thyroid, liver, and kidney diseases that may have gone unnoticed.

CHEMOSENSORY TESTING

As with all sensory systems, an accurate assessment of a patient's dysfunction is critical before therapy is undertaken. Many persons, particularly the elderly and those with cognitive deficits, are unaware of their dysfunction or are inaccurate in assessing its magnitude.[52,53] Hence, quantitative testing is essential for (a) establishing the validity of a patient's complaint, (b) characterizing the specific nature of the chemosensory dysfunction, (c) detecting malingering, (d) monitoring medical and surgical interventions, (e) establishing appropriate disability compensation, and (f) referring a patient for appropriate specialty care. Whereas accurate olfactory testing can be performed easily in the clinic, taste testing is more complicated.

Olfactory Tests

Olfactory tests can be divided into three general classes: psychophysical, electrophysiological, and psychophysiological.[54] Psychophysical tests include tests where a conscious response is required, such as in tests of odor adaptation, detection, recognition, identification, discrimination, memory, hedonics, and suprathreshold scaling of various sensory dimensions. Electrophysiological tests measure stimulus-induced electrical changes from sensory receptors or the brain, such as those measured from the surface of the olfactory epithelium or the scalp, such as event-related potentials. Psychophysiological tests generally assess autonomic nervous system-related processes, such as changes in heart rate or respiration after odorant presentations.

Psychophysical tests, most notably those of odor identification and detection, have been most widely employed in the clinic, reflecting considerations of reliability, practicality, and cost.[54]

In identification tests, the patient is asked to identify the quality of each of a series of odorants, usually from a list of names or pictures. Forced-choice procedures are preferred, i.e. requiring the subject to make a response even if no smell is perceived or the perceived smell does not correspond to any of the response alternatives. In the most widely used odor identification test, the University of Pennsylvania Smell Identification Test (UPSIT), a series of 40 microencapsulated (scratch and sniff) odors is presented and the subject's task is to chose, for each odorant, its name from a list of four response alternatives (Fig. 8.9).[55] The number of correct answers is determined and compared with norms based on thousands of normal subjects. This allows for an absolute (i.e. normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia) and relative (i.e. percentile rank relative to normal persons of the same age and sex) classification of function or dysfunction. Forced-choice testing makes it possible to detect malingerers on the basis of improbable responses. On the UPSIT, pure guessing, as would be expected from someone with no smell function, should result in ~25% of the items being correctly identified, i.e. a score near 10/40. Scores significantly below this number suggest the likelihood of malingering, i.e. avoidance of the correct responses. Interestingly, unlike malingerers of psychiatric symptoms who typically exaggerate their health problems, chemosensory malingerers underreport the presence of health problems that might conflict with the cause of their condition for which they are seeking remuneration (e.g. trauma) such as the number of allergies,

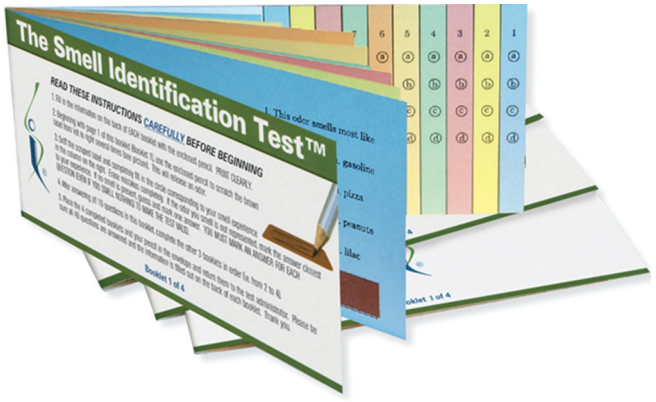


Fig. 8.9: The University of Pennsylvania Smell Identification Test (known commercially as the Smell Identification Test).[91] This test, developed in the early 1980s, is composed of 40 microencapsulated odorants located next to forced-choice questions on each page of 10-page booklets. A subject's test score can be compared to peers employing norms based upon ~ 4000 persons, allowing for a determination of absolute loss (mild, moderate, severe, total) as well as a percentile rank relative to the age and gender of the subject. Copyright © 2004, Sensonics International, Haddon Heights, NJ.

dental problems, cigarettes smoked, prior surgical operations, nasal sinus problems, and the use of medications.[56] They tend to exaggerate putative symptom-related psychological duress, interference with daily activities, weight loss, decreased appetite, and taste loss.

In olfactory threshold tests, the goal is to establish the lowest concentration of a target odorant that can be detected (detection threshold) or recognized (recognition threshold). In one paradigm, the detection threshold is established from a series of trials in which stimuli of different concentrations are presented. The subject is asked to report, on a given trial, which stimuli, one containing the odorant and one a blank, smells strongest. In one paradigm, the stimulus series begins well below threshold. When a trial is missed, the next higher concentration is presented and this is continued until a concentration is reached where reliable detection occurs a set number of times. A preferred procedure is to present stronger stimuli when a miss occurs and weaker stimuli when a hit occurs following a defined algorithm and averaging a number of "reversal" points to obtain the measure. This "staircase procedure" produces a more reliable measure than simply establishing a single transition point from not detecting to detecting. With the exception of tests of hedonics and suprathreshold scaling, scores on tests of odor identification and detection, as well as discrimination and memory,

are correlated with one another, with the size of the correlations being dependent upon the less reliable of the intercorrelated tests.[57] It is for this reason that a rather complete characterization of smell function can be obtained by simply administering a reliable odor identification test.

Taste Tests

For most patients, only olfactory testing is needed to identify their chemosensory deficit. Nonetheless, taste testing should be performed when possible. The most practical clinical taste tests use small stainless steel electrodes and present 0.5 to 1.5 second duration stimuli (< 100 mA) to localized tongue regions. Although, unlike chemical tests, electrogustometry tests do not produce all taste qualities (e.g. sweetness is never induced by an anodal electrode),[58,59] electrogustometric thresholds correlate well with chemical thresholds[60] and the number of underlying papillae.[61] Recently, normative electrical threshold data have been published for thresholds determined using staircase procedure on the anterior, posterior, and palate regions from 74 male and 82 female nonsmokers ranging in age from 10 years to 80 years.[62]

One clinically useful suprathreshold chemical taste test employs a micropipette to administer tastants to anterior and posterior regions of both the left and right sides of the tongue.[34] The stimuli are thickened in cellulose to minimize migration to other tongue regions, and the subject is required to rate the intensity of each stimulus. Such testing is very sensitive to age, sex, and a number of diseases. The influences of an orally ingested antifungal agent on taste identification scores obtained by this test for sucrose (sweet), citric acid (sour), sodium chloride (salty), and caffeine (bitter) stimuli are shown in Figure 8.10.

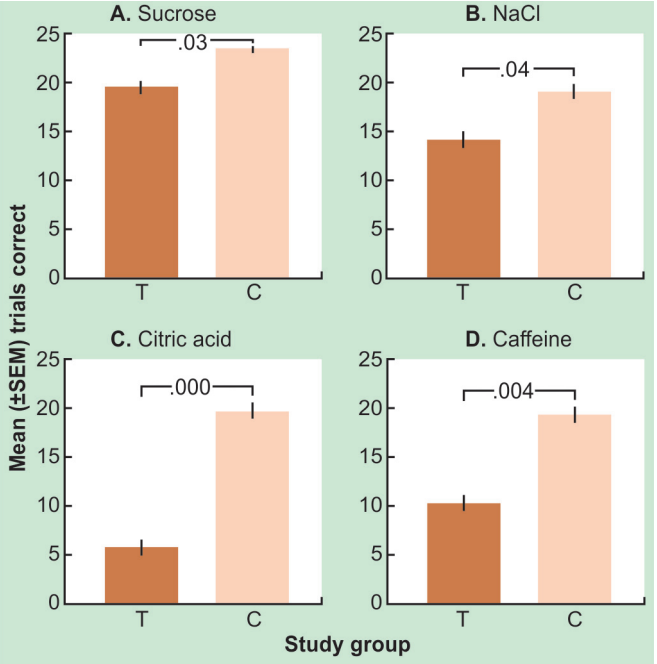


Fig. 8.10: Influence of terbinafine (Lamisil) on taste identification test scores for stimuli representing the four major taste qualities. The tastants were presented to left and right anterior and posterior regions of the tongue using micropipettes. The test scores represent the summation of scores across all four lingual regions. (C: Controls; T: Terbinafine patients).
Source: With permission from Doty and Haxel.[34]

PATIENT MANAGEMENT AND TREATMENT

Approaches to the management and treatment of chemosensory disorders are condition specific. Inflammatory or obstructive disorders (e.g. allergic rhinitis, glossitis, polyposis, intranasal, or intraoral neoplasms) are often amenable to medical or surgical interventions. A number of oral infections and inflammatory problems that alter taste function can be treated with appropriate antibiotic or anti-inflammatory medications. Oral mucosal function and comfort can be provided to some patients with xerostomia and excessive dryness using artificial salivas such as Xerolube. In the case of rhinosinusitis, a prednisone oral taper can usually reduce the general inflammation which, in some cases, can be maintained subsequently by topical corticosteroid administration via spray or irrigation directed to the olfactory meatus. Topical corticosteroids applied using a squirt system are more effective in this process than standard sprays.[63] Positioning the head in an inverted position, such as the Moffett position,[64] for a few minutes during and after topical administration also increases the likelihood that the corticosteroid reaches the olfactory mucosa. This appears more effective in treating olfactory dysfunction than traditional spraying.[65]

Dysgeusias or phantogeusias are among the most distressing and least understood chemosensory disorders. Most spontaneously remit over time without treatment, typically within 2 years.[66] Cessation or decreased dosage of drugs associated with dysgeusias, such as antifungal agents, ACE inhibitors, and some antiepileptic agents, can eliminate the dysgeusia, but a tradeoff obviously exists between maintaining the drug's function and the degree to which the dysgeusia is detrimental or can be tolerated. Unfortunately, little empirical data are available for most

drugs, and some drug-related effects on the taste system appear to be long lasting and not reversed by short-term drug discontinuance.[33] Some mouthwashes, such as those containing chlorhexidine digluconate or dyclonine HCl, have been reported to be effectual in some patients with dysgeusia.[67] When the dysgeusia is secondary to thyroid problems, adjustments in thyroxine levels can be beneficial.[68,69] In a 3-month-long double-blind randomized trial employing zinc gluconate (n = 26; 140 mg/day) and placebo (n = 24), more dysgeusics in the treatment arm (50%) reported improvement than in the placebo arm (25%).[70] Scores on a taste identification test improved significantly in the treated subjects relative to the controls. It should be pointed out that the patients of this study were carefully selected patients for idiopathic dysgeusia and those with dysgeusia from other causes were excluded from study.

A number of antioxidants, such as alpha-lipoic acid, have been claimed to be effective in some cases of hyposmia, ageusia and dysgeusia,[71] although double-blind evidence for efficacy is lacking. Despite being widely mentioned in the medical literature, zinc and vitamin A therapies have no beneficial effect on smell disturbances.[72-75] A recent report that theophylline improved olfactory function lacked a control group and was not double blinded,[76] failing to consider that some meaningful improvement occurs without treatment. Indeed, the percentage of patients said to be responsive to the treatment was similar to the percentage shown in other studies who improve without treatment over a similar time period.[77] In a longitudinal study of 542 patients with smell loss from a variety of causes, modest improvement occurred over an average time period of 4 years in about half of the participants.[77] Although normal age-related function returned in only 11% of the anosmic patients, 23% of the hyposmic patients had such return. The amount of dysfunction present at the time of presentation, not etiology, was the best predictor of prognosis. Other predictors were patient's age and the time between dysfunction onset and initial testing.

Recent reports claiming positive effects on smell function from acupuncture and transcranial magnetic stimulation[78,79] suffer from a number of methodological problems.[80,81] Although there are claims that antiepileptic drugs and some antidepressants (e.g. amitriptyline) may improve olfactory function, particularly after head trauma, such claims lack empirical support and, in the case of amitriptyline, distortions in taste function appear, probably from anticholinergic effects.[82] Donepezil, an acetylcholinesterase inhibitor, has been suggested to improved odor identification scores in patients with AD, leading to the suggestion that smell identification testing may be useful in assessing treatment responses to this medication.[83] It is of interest that repeated exposure to odorants may increase sensitivity to them in both animals[84] and humans.[85,86] Such observations provide a rationale for therapies in which patients smell a number of odors before going to bed and upon arising in the morning.[87] This approach, however, has not been confirmed using appropriate controls and double-blind protocols, and the amount of improvement appears to be about the same as that appears without such therapy.[77] Although there is some evidence from rodent studies that applying nerve growth factor onto the olfactory epithelium may alleviate axotomy-induced degenerative changes in the olfactory receptor neurons, it is not known whether this has any functional consequence or if such a procedure would be efficacious in humans.[88] Recent research also suggests that, in mice, intranasal administration of basic fibroblast growth factor for 6 weeks increases the proliferation of globose basal cells and supporting cells but does not change the number of mature olfactory receptor cells.[89]

A significant but largely overlooked element of therapy comes from chemosensory testing itself. Confirmation or lack of confirmation of loss is beneficial to patients, particularly those who worry that they may be "crazy" as a result of unsupportive family members or medical providers. Quantitative testing places the patient's problem into perspective. If less than total function is present, patients can be informed of a somewhat higher chance for a positive prognosis. Importantly, it is therapeutic for an older person to become aware that, while his or her smell function is not what it used to be, it still falls above the average of his or her peer group, a situation that happens, by definition, 50% of the time. Unfortunately, many such patients are simply told by their physician they are getting old and nothing can be done for them, commonly exacerbating or leading to depression and decreased self-esteem.

ACKNOWLEDGMENTS

Supported by USAMRAA W81XWH-09-1-0467, Richard L Doty, Principal Investigator.

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CHAPTER

9 Diagnostic Imaging in Rhinology

Mira Herman, Daniel Krieger, Andrew McClelland, Susan Sotardi, Ari Spiro, Jenna Le, Caitlin McMullen, Arel Golombeck, Jimmy Lee, Jacqueline A Bello, Joaquim Farinhas

DISCOVERY OF THE X-RAY AND APPLICATION TO THE PARANASAL SINUSES

On November 8, 1895, the German physicist Professor Wilhelm Conrad Röntgen (1845–1923) discovered the "new rays" in his laboratory at the Julius-Maximilian University of Wurzburg, Bavaria.[1] On December 28, 1895, he presented his findings to the local physics society of Wurzburg, entitled "On a New Kind of Rays" and was awarded the Nobel Prize in physics in 1901. John Macintyre (1857–1928) produced the first otolaryngology-related X-rays in Britain, March 1896.[1] These cases involved radiography of a cadaveric larynx and a foreign body in the esophagus. The sinuses were difficult to demonstrate, overshadowed by the bony skull.

Other pioneers in sinus radiography included Killian in 1903, the radiologist Eugene Wilson Caldwell [not to be confused with George Walter Caldwell (1866–1918) of the Caldwell-Luc procedure] and Cornelius Coakley, a New York otolaryngologist, in 1906.[2] These early investigators were radiologists, clinicians, and otolaryngologists with a special interest in the application of these new rays.[3]

In 1903, Caldwell wrote one of the first textbooks on diagnostic and therapeutic radiology. His interest in head and neck radiology is reflected by a radiologic view of the paranasal sinuses that still bears his name, "the Caldwell view." This view depicts the ethmoid and frontal sinuses and the orbits. The exposure time for acquisition of these early sinus X-rays was long and not uncommonly resulted in hair loss.

In the late 19th and early 20th century, infections of the paranasal sinuses and mastoid air cells were the major reasons for otolaryngologic operations. Before X-rays, it was not uncommon to operate on suspicious frontal sinus infections presenting as frontal headaches and opacity on transillumination, therefore mimicking an absent sinus. A major risk of surgery included violation of the cranial vault by a hammer and gauge. Clearly, there was a need to accurately delineate the frontal sinus.[1]

At that time, due to unacceptable complications of craniotomy for removal of pituitary tumors, it became necessary to better identify the sphenoid sinus, propelling the investigation for radiological definition of extracranial surgical approaches to the sella.[4] In 1907, Schloffer published an X-ray of his first transnasal approach using a metal probe to demonstrate the operative path.[1]

In 1912, in New York, Dr WH Luckett and Dr Stewart reported the first X-ray case of a fracture involving the posterior wall of the frontal sinus resulting in cerebrospinal fluid (CSF) rhinorrhea and air within dilated lateral ventricles.[5] This case report stimulated researchers to use air as a contrast agent. Walter E Dandy (1886–1946), a neurosurgeon at Johns Hopkins, also pursued this concept when he introduced air ventriculography in 1918,[6] and air encephalography and air-myelography.[6] Later, the introduction of air into the subarachnoid space for computed tomography (CT) air-meatography diagnosis of small acoustic neuromas was based on Dandy's work.

In 1912, Dr Hans Rhese, a German otolaryngologist, introduced an oblique view of the ethmoid sinuses that included the orbits, optic foramina, and sphenoid sinus.

Today, this radiographic projection, which bears his name, is occasionally used to survey orbital and optic foramen trauma.

In 1914, two British radiologists, Dr CA Waters and Dr CW Waldron, introduced a radiographic projection that better defined the paranasal sinuses and facial bones. Currently, the Waters view is used to survey sinus disease and facial fractures.

Contrast Administration

Lipiodol, discovered by Sicard and Forestier in 1921, was initially used for visualizing the epidural space; injection of Lipiodol into the paranasal sinuses was first described in 1926.[1] Subsequently, various methods were developed for the injection of contrast into the sinuses, including direct injection and an indirect method, sometimes referred to as "suffusion." In the latter technique, contrast was injected into the nasal fossa and manipulated into the sinuses by gravity during pressure changes in the nose, either self-induced by the patient or with applied suction.[7] Delayed films were obtained 48–96 hours after contrast injection in an effort to obtain physiologic or functional information about sinus emptying.[8]

Tomography

Bernard Ziedses Des Plantes of the Netherlands is credited with introducing tomography in the early 1930s.[9] In the late 1930s and early 1940s, tomography of the paranasal sinuses and temporal bones was described; however, it was the development of complex motion tomography in the 1950s that significantly advanced imaging of the paranasal sinuses, orbits, facial bones, temporal bones, and skull base.[9] Limitations of tomography included lengthy procedure time, high radiation doses, and high cost. Tomography is the premise for today's cross-sectional imaging, including CT and magnetic resonance image (MRI), which constitute otolaryngologic radiology.

Computed Tomography

In 1973, Sir Godfrey Hounsfield (1919–2004), an electrical engineer working for the Central Research Laboratories of EMI (Electric and Musical Industries), first introduced a clinical CT scanner for imaging the head. The foundation for CT was based on mathematic equations that had been formulated in 1963 and 1964 by AM Cormack, professor of physics at Tufts University, Boston.

In 1974, the ability to image the whole body and tilt the CT gantry made coronal imaging of the paranasal sinuses possible. The ability of CT to demonstrate clinically occult metastatic lymph nodes was superior to conventional radiographs. In 1979, Sir Godfrey Hounsfield and Allan Cormack shared the Nobel Prize in Medicine for their monumental invention, the clinical CT scanner.

Literature through the mid-1980s had proven that CT contributed to better otolaryngologic surgical outcomes due to more accurate staging and surgical planning, with associated decreases in morbidity and mortality.[9] A landmark article by Gatenby et al. demonstrated the utility of CT over clinical examination of head and neck cancers for staging of disease.[10]

With the introduction of functional endoscopic sinus surgery (FESS), in the early 1990s, coronal sinus CT became an important preoperative imaging technique.[9] Dr James Zinreich, a neuroradiologist and head and neck radiologist, developed the CT protocol for assessing the nasal cavity, osteomeatal complex, and paranasal sinuses in the coronal plane; this algorithm forms the basis for evaluation of the osteomeatal complex in presurgical planning for FESS.[11]

The development of spiral CT shortened examination time and allowed for thinner sections, suitable for three-dimensional reconstruction. Most recently, multidetector row CT with increased spatial resolution, section thickness as small as 0.5 mm and acquisition capabilities of eight images per second, has become the standard.

Positron Emission Tomography

The development of positron emission tomography (PET) is based on the creative genius of theoretical and experimental physicists, chemists, biologists, and physicians who did not initially foresee the benefits of the new technology,[12] reviewed more in depth in landmark communications.[12-15] PET/CT has revolutionized the evaluation of patients with head and neck cancer by contributing to more accurate staging, more focused treatment, earlier detection of recurrent disease, and identification of incurable disease.[16] The first prototype PET/CT scanner became operational in 1998, at the University of Pittsburgh, and the first commercial PET/CT scanner in early 2001, incorporating a four-slice CT scanner, the most advanced at the time.[15] PET/CT represents one of the fastest growing medical imaging modalities, rivaling the growth of MRI during the 1980s and 1990s. While the first commercial PET/CT scanner appeared in early 2001, PET-only scanners were

no longer available by 2006, as major medical centers and clinics opted for PET/CT to replace their PET-only scanners. Newly established diagnostic imaging centers support PET/CT.[15]

Magnetic Resonance Imaging

Felix Bloch (1905–1983) of Stanford and Edward Purcell (1912–1997) of Harvard shared the Nobel Prize for physics in 1952 for the discovery of nuclear magnetic resonance (NMR) in 1946.[17,18] An MRI of a mouse was obtained in Aberdeen, Scotland, in 1974; Peter Mansfield at Nottingham, England, imaged a finger in 1976;[1] and Raymond Damadian demonstrated images of the human thorax in 1977.[19] The first clinical application of MRI was achieved in the early 1980s as the size of the magnet bore increased to comfortably accommodate patients and surface coil technology improved. The contrast resolution of soft tissues with MRI is superior to CT. The sensitivity of neoplastic invasion into bone and cartilage is more conspicuous on MRI than on CT.[20] The introduction of gadolinium-based contrast in the early 1990s further increased MRIs sensitivity in diagnosing head and neck pathology.[21,22] Radiologists could follow pathology along a perineural course.[23] The conspicuity of head and neck pathology was further increased by the administration of gadolinium contrast material in conjunction with fat-saturated T1W MRI sequences.[24] MRI has become superior at detecting perineural tumor spread, complicated infections, and suspected intracranial and/or intraorbital extension of disease.[9]

IMAGING OF NORMAL AND VARIANT PARANASAL SINUS ANATOMY

The paranasal sinuses are air-filled extensions of the nasal cavity into frontal, ethmoid, maxillary, and sphenoid bones. The nasal cavity is bounded by the frontal, ethmoid and sphenoid bones superiorly, the nasal septum medially, lateral nasal wall, and the floor consisting of the palatine process of the maxilla and horizontal plate of the palatine bone.[25] The bilateral posterior openings of the nasal cavity are the choanae, which communicate with nasopharynx.

Sinus Development

At birth, only the maxillary sinus and ethmoid air cells are present. Maxillary sinuses develop in the 10th fetal week,[26,27] are small at birth and undergo biphasic growth. The first growth phase occurs during the first 3 years of life, whereas the second occurs between 7 and 18 years. With progressive growth, the maxillary sinus floor descends inferiorly such that at birth, it is above the level of the nasal cavity; in adults, it is below the nasal cavity. The roots of the first and second molar teeth extend superiorly toward the floor of the maxillary sinus, separated from the floor by a thin bony lamella through which dental infections involving the first and second molars involve the maxillary sinus.

Ethmoid air cells begin developing in the third fetal month and are well developed at birth. Pneumatization progresses in an anterior to posterior direction to reach adult size by age 12 years.[28] The posterior air cells are usually larger, less numerous, and are often involved in childhood sinusitis.

Frontal sinuses are absent or rudimentary at birth. Pneumatization begins around 2 years of age, and development continues throughout puberty.[28]

Sphenoid sinuses begin developing in the third fetal month. Rudimentary at birth, they pneumatize from age 2 to 3 years, and are complete at 17 years of age. Their rate of development is slower than other paranasal sinuses.

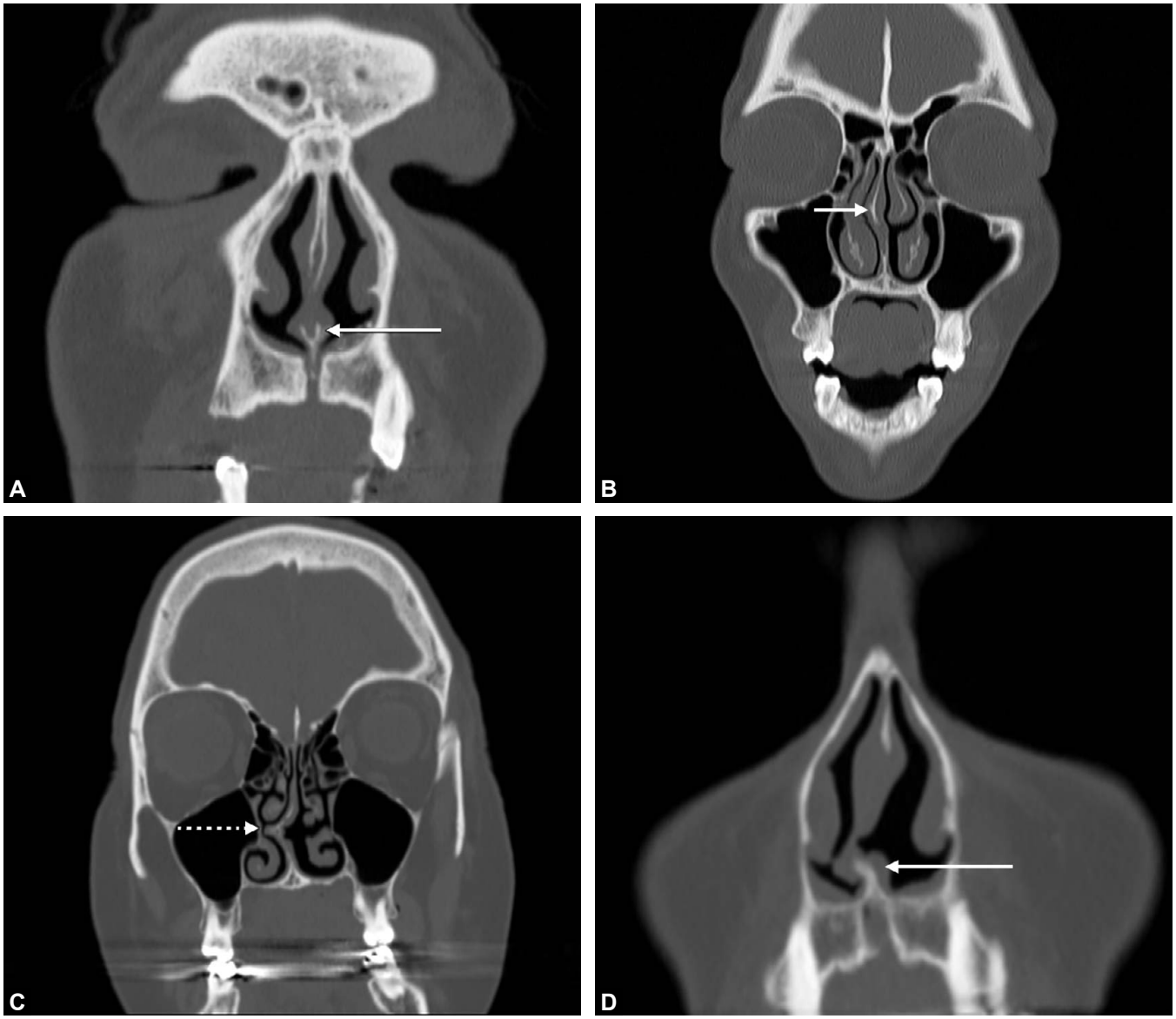
The nasolacrimal ducts drain the lacrimal sac along the medial canthus and course along the anterior and inferior portion of the lateral nasal wall, emptying into the inferior meatus.

Nasal Septum

The nasal septum has four components: The perpendicular plates of the ethmoid superiorly, the vomer bone inferoposteriorly, the maxillary crest inferiorly, and the septal cartilage anteriorly.[25] The perpendicular plate of the ethmoid bone extends superiorly to the cribriform plate and continues as the crista galli. The vomer is continuous with the nasal crest of the maxillary and palatine bones inferiorly. The junction between the anterior septal cartilage and the vomer is called the chondrovomeral junction, where it appears grooved (Fig. 9.1A). Major variations of the septum include deviation (Fig. 9.1B), septal spur (Fig. 9.1C), and deformity of the chondrovomeral junction[29] (Fig. 9.1D).

Maxillary Sinus

The maxillary sinuses are the largest paranasal sinuses.[25] They are pyramid-shaped structures, with the base of the

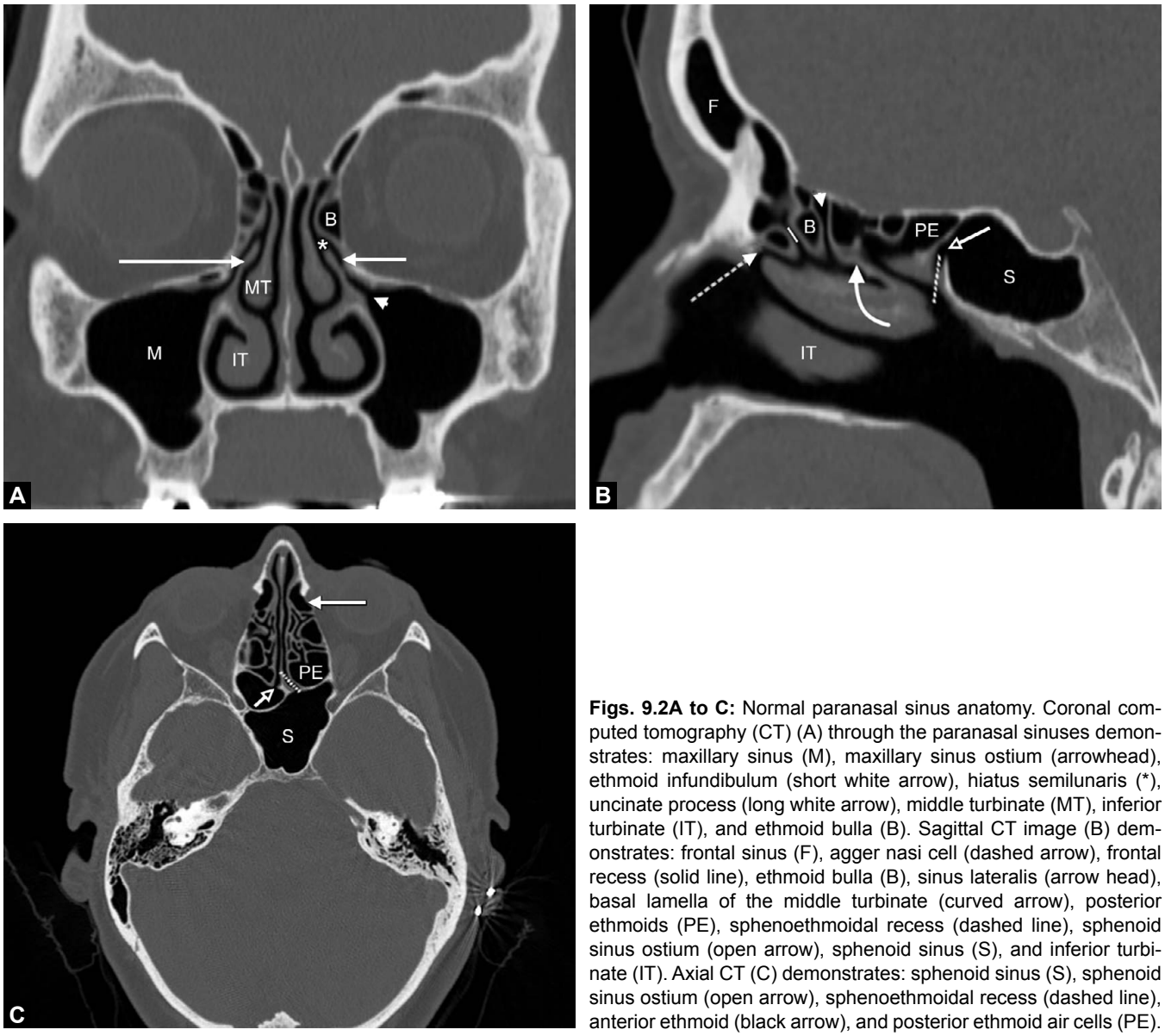


Figs. 9.1A to D: Normal chondrovomeral junction and septal variations. (A) The normal chondrovomeral junction with a grooved appearance (long arrow). (B) Septal deviation (short arrow). (C) Septal spur (short dashed arrow). (D) Chondrovomeral deformity (long arrow).

pyramid (medial wall) formed by the lateral nasal wall (Fig. 9.2A). The maxillary sinus is defined anteriorly by the anterior face of the maxilla, laterally by the zygomatic process, superiorly by the orbital floor, inferiorly by the alveolar process of the maxilla, and posteriorly by the posterior wall of the maxilla, separating it from the pterygomaxillary space. The infraorbital nerve courses along the roof of the maxillary sinus, exiting through the infraorbital foramen.

The maxillary sinus ostium is located in the superior, posteromedial aspect of the maxillary sinus wall, and physiologically clears into the posterior third of the ethmoid infundibulum (Fig. 9.2A). The posterior edge of the ostium is continuous with the lamina papyracea. The nasal fontanelles are regions in the lateral nasal wall just above the inferior turbinate attachment, containing no bone, composed only of mucosa and fibrous tissue. The anterior fontanelle is located anteroinferior to the uncinate process, and the posterior fontanelle is located superoposterior to the uncinate process. An accessory maxillary sinus ostium may be present in 10–20% of individuals (Fig. 9.3A), usually located in the posterior fontanelle.[30]

A common variation in the maxillary sinus is the infraorbital ethmoidal air cell, known as a Haller cell (Fig. 9.3B).



Figs. 9.2A to C: Normal paranasal sinus anatomy. Coronal computed tomography (CT) (A) through the paranasal sinuses demonstrates: maxillary sinus (M), maxillary sinus ostium (arrowhead), ethmoid infundibulum (short white arrow), hiatus semilunaris (*), uncinate process (long white arrow), middle turbinate (MT), inferior turbinate (IT), and ethmoid bulla (B). Sagittal CT image (B) demonstrates: frontal sinus (F), agger nasi cell (dashed arrow), frontal recess (solid line), ethmoid bulla (B), sinus lateralis (arrow head), basal lamella of the middle turbinate (curved arrow), posterior ethmoids (PE), sphenoethmoidal recess (dashed line), sphenoid sinus ostium (open arrow), sphenoid sinus (S), and inferior turbinate (IT). Axial CT (C) demonstrates: sphenoid sinus (S), sphenoid sinus ostium (open arrow), sphenoethmoidal recess (dashed line), anterior ethmoid (black arrow), and posterior ethmoid air cells (PE).

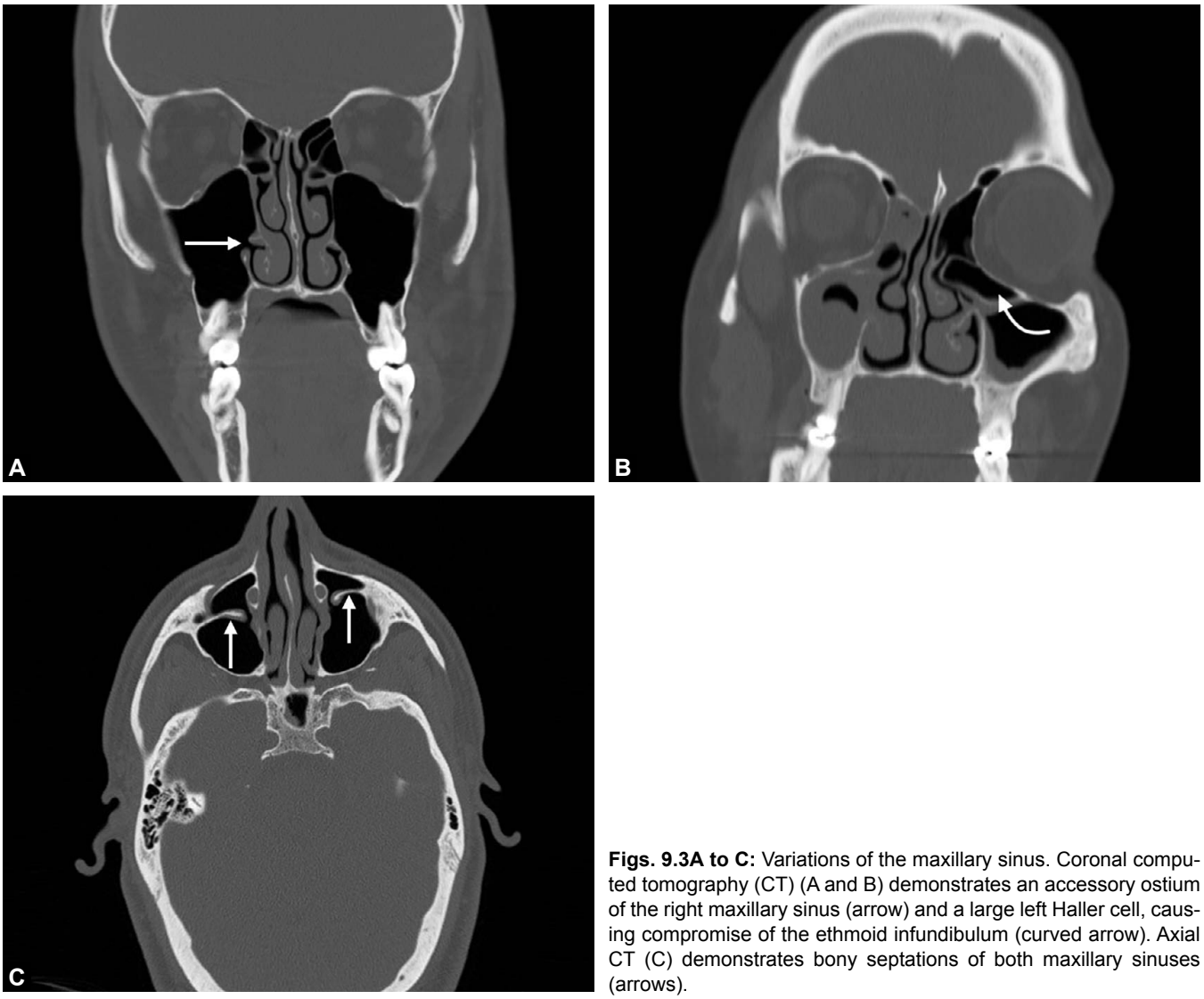
This is an ethmoid air cell incorporated into the roof of the maxillary sinus, located inferolateral to the ethmoid bulla. Its relationship to the ethmoid infundibulum and maxillary sinus ostium can predispose to obstruction. Other maxillary sinus variations include septations (Fig. 9.3C), hypoplasia, or atelectasis.

Ethmoid Sinus

Multiple air cells comprise the ethmoid sinus complexes, divided into anterior and posterior compartments by the basal lamella of the middle turbinate (Fig. 9.2B). The ethmoid air cells are bordered by the ethmoid roof superiorly, lamina papyracea (medial orbit wall) laterally, and the sphenoid sinus posteriorly. The medial border of the anterior ethmoid complex is formed by the middle turbinate; the superior turbinate forms the medial border of the posterior ethmoid complex.

Uncinate Process

The uncinate process of the ethmoid bone is the remnant of the descending portion of the first ethmoturbinal ridge, oriented in the parasagittal plane. The anterosuperior attachment of the uncinate process is variable and can insert on the lamina papyracea (Fig. 9.6A), the middle



Figs. 9.3A to C: Variations of the maxillary sinus. Coronal computed tomography (CT) (A and B) demonstrates an accessory ostium of the right maxillary sinus (arrow) and a large left Haller cell, causing compromise of the ethmoid infundibulum (curved arrow). Axial CT (C) demonstrates bony septations of both maxillary sinuses (arrows).

turbinate, or the skull base. The type of insertion affects the frontal sinus drainage pathway. Inferiorly, the uncinate process attaches to the ethmoid process of the inferior turbinate and the perpendicular process of the palatine bone. The superoposterior aspect of the uncinate process has a free margin (Fig. 9.2A). Variations in the uncinate process include pneumatization, hypoplasia, and medial or lateral deviation,[25] which may compromise the ostiomeatal complex.

Hiatus Semilunaris

The hiatus semilunaris is a two-dimensional cleft between the free posterior margin of the uncinate process and the anterior wall of the ethmoid bulla. Here, the ethmoid infundibulum communicates with the middle meatus (Fig. 9.2A). The hiatus semilunaris is also called the hiatus semilunaris inferior, distinct from the hiatus semilunaris superior.[31] The latter is a cleft between the ethmoid bulla and the middle turbinate, continuous with the retrobullar and suprabullar recesses.

Ethmoid Infundibulum

The ethmoid infundibulum is often referred to simply as the infundibulum due to its important pathophysiological role.[31,32] It should not be confused with two other infundibula in the paranasal sinuses, the maxillary and frontal infundibula, located within their respective sinuses funneling toward their respective ostia. The ethmoid

infundibulum is bordered anterolaterally by the lamina papyracea (Fig. 9.2), anteromedially by the uncinate process, and posteriorly by the ethmoid bulla.

Ethmoid Bulla

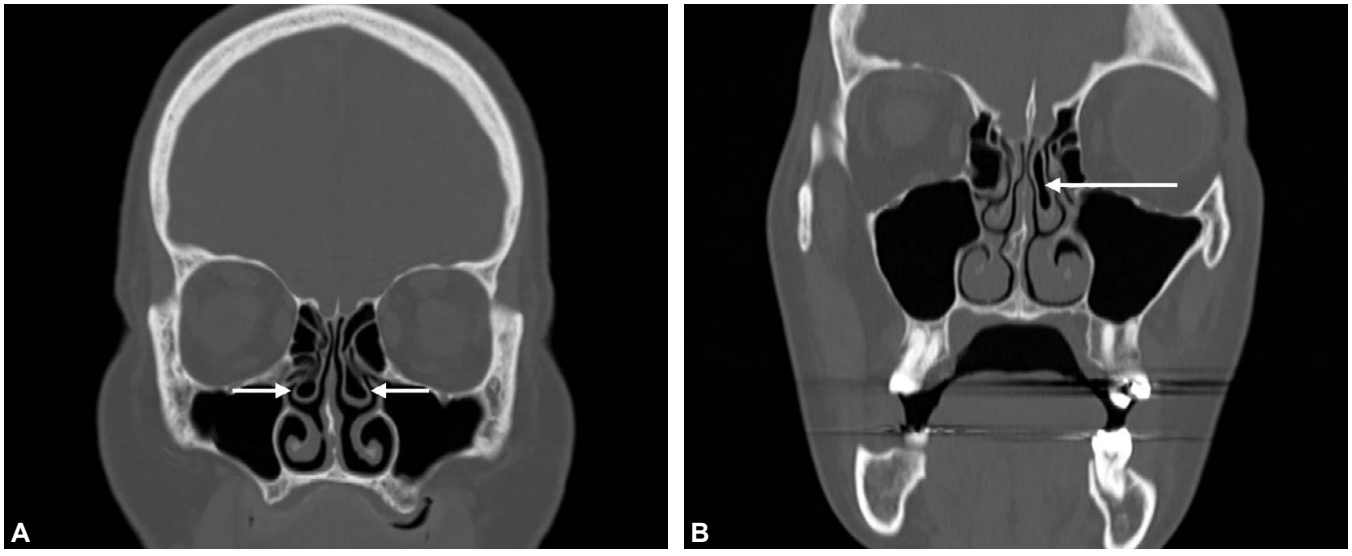
The ethmoid bulla is the largest air cell in the anterior ethmoid complex (Figs. 9.2A and B). It is formed as a result of pneumatization of the second ethmoid basal lamella. The ethmoid bulla forms the posterior wall of the frontal recess if it reaches the roof of the ethmoid. If it does not extend to the skull base, a suprabullar recess is present. The ostium of the ethmoid bulla is commonly located in the posterior wall. When enlarged, the ethmoid bulla may compromise the frontal recess and/or ethmoid infundibulum.

Suprabullar and Retrobullar Recess (Sinus Lateralis)

The space posterior to the ethmoid bulla and anterior to the basal lamella of the middle turbinate is called the retrobullar recess. If the ethmoid bulla lamella does not contact the basal lamella of the middle turbinate, the retrobullar recess may extend into the suprabullar recess. The suprabullar and retrobullar recesses are also called the sinus lateralis (Fig. 9.2B), bordered by the lamina papyracea laterally, and the ethmoid roof superiorly. Inferiorly, the sinus lateralis communicates with the middle meatus via the hiatus semilunaris superior.

Basal Lamella of the Middle Turbinate

The basal lamella of the middle turbinate is the most important lamella of the three turbinates, as it divides the anterior from posterior ethmoid air cells. The basal or ground lamella of the middle turbinate consists of three parts, in three different planes.[33] The anterior third is oriented sagittally and inserts vertically into the skull base at the lateral aspect of the cribriform plate. This is also called the vertical lamella, or the vertical portion of the middle turbinate basal lamella. The middle portion is oriented coronally and inserts laterally into the lamina papyracea, dividing the anterior and posterior ethmoid air cells (Fig. 9.2). The posterior portion is oriented in the axial plane and attaches to the lamina papyracea and/or the medial wall of the maxillary sinus. The posterior margin of the middle turbinate basal lamella inserts into the perpendicular plate of the palatine bone. The presence of an ethmoid cell within the middle turbinate is referred to as a concha bullosa (Fig. 9.4A). Although this is commonly pneumatized, it is important to understand that this is more than a pocket of air, but rather a true ethmoid cell. As such, it is lined by mucociliary mucosa that may affected by inflammatory changes, including edema, polypoid changes, mucopurulence, and opacification. The term interlamellar cell refers to pneumatization of the vertical lamella of the middle turbinate[31] (Fig. 9.4B). While concha bullosa is a common variation in healthy individuals, it can predispose to occlusion of the ostiomeatal unit (OMU) and contribute to inflammatory sinus disease.



Figs. 9.4A and B: Pneumatized middle turbinate. Coronal computed tomography (CT) (A and B) demonstrates bilateral concha bullosa (short arrows) and a left interlamellar cell (long arrow).

Basal Lamella of the Superior and Supreme Turbinate

Similar to the middle turbinate, the superior turbinate basal lamella also has a lateral attachment to the lateral nasal wall and a vertical attachment to the skull base. The superior turbinate forms the medial border of the posterior ethmoid air cells. The space between the superior turbinate (and supreme turbinate, if present) and nasal septum is the sphenoethmoidal recess. The posterior ethmoid cells physiologically clear into the superior meatus and supreme meatus (if present) before clearing into the sphenoethmoidal recess. The supreme turbinate is present in approximately 15% of the population.[34]

Fovea Ethmoidalis

The roof of the ethmoid air cells is called the fovea ethmoidalis, a portion of the frontal bone that extends medially from the orbital plate. The medial border of the fovea ethmoidalis is continuous with the lateral lamella of the cribriform plate of the ethmoid bone (Fig. 9.5). The ethmoid roof lies above the roof of the nasal cavity formed by the cribriform plate. The lateral lamella of the cribriform plate forms the lateral wall of the olfactory fossa. The olfactory fossa is bordered inferiorly by the cribriform plate and medially by the crista galli, an intracranial extension of the septal perpendicular plate of the ethmoid. The lateral lamella is the thinnest bone in the anterior skull base;[31,32,35] therefore, the larger the surface area of the lateral lamella, the greater the risk of surgical trauma.[31] A classification of the olfactory fossa based on the length of the lateral lamella of the cribriform plate in relationship to the ethmoid roof was proposed by Keros,[36] in which Type 1 is 1–3 mm in depth, Type 2 is 4–7-mm deep, and Type 3 is a depth of ≥ 8 mm (Figs. 9.5A to C).

Frontal Sinus and Frontal Recess

The frontal sinus has the most complex and variable drainage pathway of the paranasal sinuses.[33] Each frontal sinus narrows posteroinferiorly at the frontal infundibulum before draining into the frontal ostium, where it is most narrow. The frontal sinus drainage pathway, also called the frontal or frontoethmoidal recess, has variable borders. Its boundaries include the agger nasi air cell anteriorly and inferiorly, the ethmoid bulla posteriorly, the lamina papyracea laterally, and the lateral wall of the olfactory fossa (lateral lamella) and middle turbinate vertical lamella medially (Fig. 9.2).

The frontal recess opens into the middle meatus or ethmoid infundibulum, depending on the attachment of the anterior uncinate process. The anterior uncinate process most frequently attaches to the agger nasi cells and lamina papyracea and forms a terminal recess of the ethmoid infundibulum. As a result, the frontal sinus drainage pathway drains medial to the uncinate process and into the middle meatus directly (Fig. 9.6A). In this configuration, isolated obstruction of the ethmoid infundibulum does not result in frontal sinusitis. In contrast, if the uncinate process attaches anteriorly to the skull base without attachment to the agger nasi cells, the frontal sinus drains lateral to the uncinate process and directly into the ethmoid infundibulum (Fig. 9.6B). In this configuration, obstruction of the ethmoid infundibulum may predispose to frontal sinusitis.

Various accessory air cells around the frontal recess may affect the frontal sinus drainage pathway.[29,37] The frontal cell, or frontal ethmoidal air cell (Figs. 9.7A to C), is located superior to the agger nasi air cell. Frontal cells are further classified on the basis of their number and degree of extension into the frontal sinus.[38]

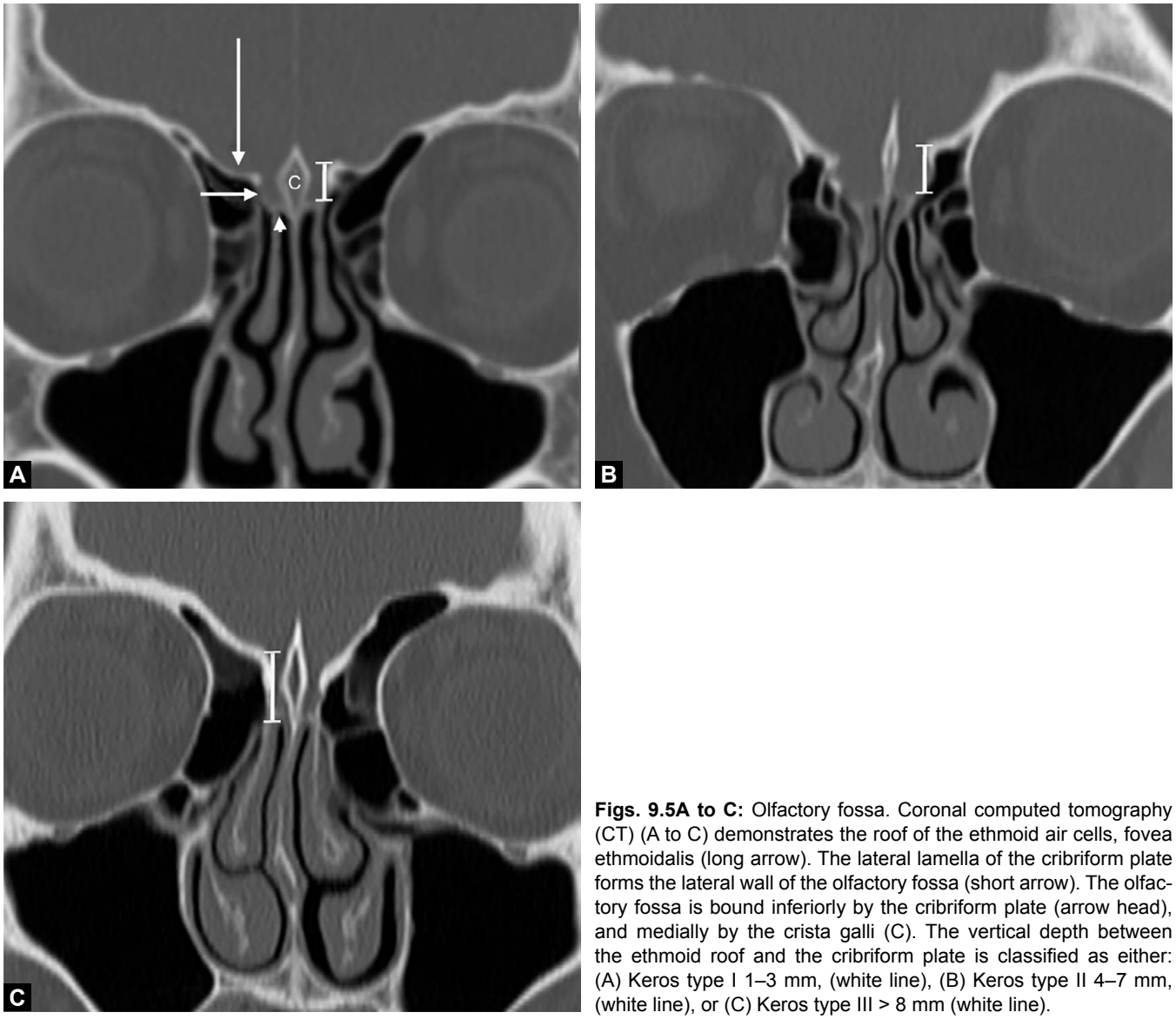
Variations involving the ethmoid bulla, agger nasi, and other accessory air cells, such as suprabullar cells and supraorbital ethmoid cells, influence the configuration of the frontal sinus drainage pathway.[29,33,37] A suprabullar air cell is immediately superior and anterior to the ethmoid bulla. A supraorbital ethmoid air cell results from lateral extension of the ethmoid sinus into the orbital plate of the frontal bone.

Ostiomeatal Unit

The ostiomeatal unit is not a distinct anatomic structure but rather a physiological region defined by multiple landmarks.[31] The OMU represents the final common pathway of mucociliary clearance from the maxillary sinus, anterior ethmoid air cells, and frontal sinus draining into the middle meatus. The relevant structures include the middle meatus, maxillary sinus ostium, ethmoid infundibulum, hiatus semilunaris, anterior ethmoid cells and their ostia, and the frontal recess (*see* Fig. 9.2).

Agger Nasi

Agger nasi (Latin, *nasal eminence*) refers to the superiormost remnant of the first ethmoturbinal ridge, immediately anterior and superior to the insertion of the middle turbinate. When pneumatized by an anterior ethmoid cell, it is called an agger nasi air cell (*see* Fig. 9.2). When enlarged, agger nasi cells may compromise the frontal recess.



Figs. 9.5A to C: Olfactory fossa. Coronal computed tomography (CT) (A to C) demonstrates the roof of the ethmoid air cells, fovea ethmoidalis (long arrow). The lateral lamella of the cribriform plate forms the lateral wall of the olfactory fossa (short arrow). The olfactory fossa is bound inferiorly by the cribriform plate (arrow head), and medially by the crista galli (C). The vertical depth between the ethmoid roof and the cribriform plate is classified as either: (A) Keros type I 1–3 mm, (white line), (B) Keros type II 4–7 mm, (white line), or (C) Keros type III > 8 mm (white line).

Posterior Ethmoid and Sphenoid Sinus

The sphenoethmoidal recess is the space bordered by the superior turbinate laterally, nasal septum medially, and the anterior surface of the sphenoid sinus posteriorly (*see* Fig. 9.2). It is the common drainage pathway for the posterior ethmoid and sphenoid sinuses before draining into the nasal cavity. The sphenoid sinus ostia physiologically clear anteriorly and directly into the sphenoethmoidal recess.

The sphenoid sinus is variable in pneumatization, paired and separated by a thin midline osseous septum. The sphenoid sinus may be hypoplastic (Fig. 9.8A), or form recesses by extension into the lesser or greater wings of the sphenoid, anterior clinoid process (Fig. 9.8B), pterygoid plates (Fig. 9.8C), or anteriorly into the nasal septum[29] (Fig. 9.8D).

If a posterior ethmoid air cell extends laterally and superiorly into the sphenoid sinus, it is referred to as a sphenoethmoidal (Onodi) cell (Figs. 9.9A to C). The anterior clinoid process may also become pneumatized by a sphenoethmoidal cell, complicating sinus surgery when locating the sphenoid sinus behind the posterior ethmoid complex, due to adjacent optic nerve and cavernous carotid artery. The vidian canal and foramen rotundum may also project into the sphenoid sinus (Fig. 9.8C).

Understanding paranasal sinus anatomy is critical for FESS. Identification of variant anatomy delineates structures that may impair normal drainage pathways, serve as a focus for occult disease, limit endoscopic access, or increase the risk of endoscopic procedures.

IMAGING OF SINONASAL DISEASE

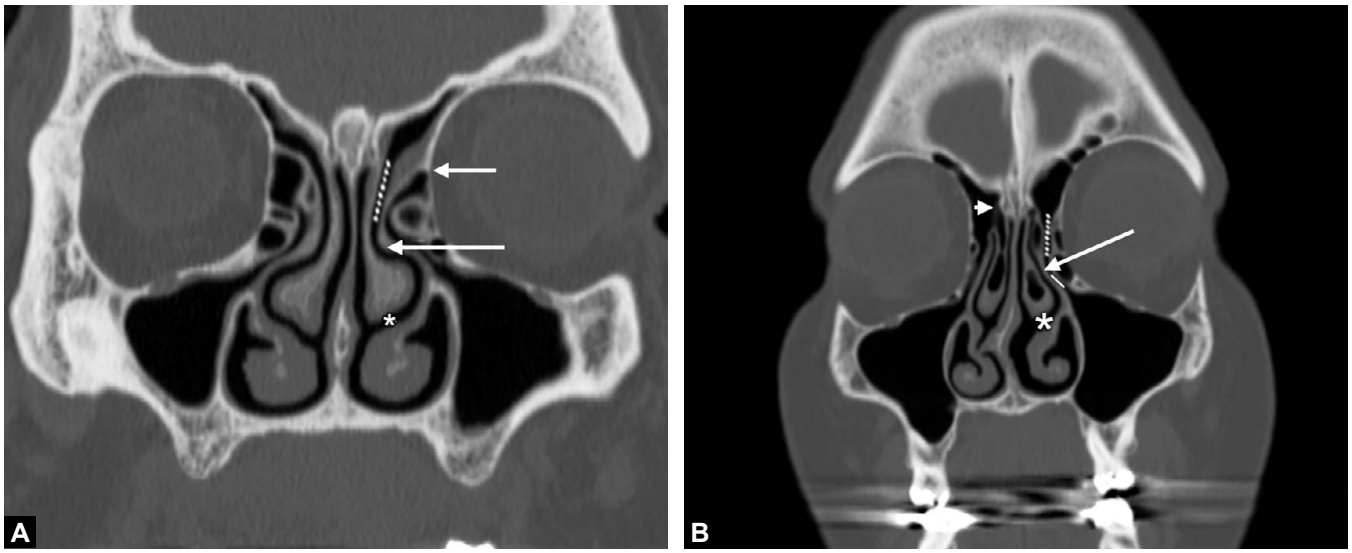
Modalities, Protocols, and Practice

A variety of imaging modalities are used to evaluate the paranasal sinuses. While specific imaging appearances of different disease processes are discussed in later sections, a general understanding of which study best addresses a given clinical question is helpful. Consideration should be given to the relative advantages and disadvantages of each modality, as well as the often-complimentary nature of different modalities in the workup of sinus pathology. As a guide to choosing the optimal examination for a given indication, the American College of Radiology has developed the ACR Appropriateness Criteria, freely available on the Internet (http://www.acr.org/Quality-Safety/Appropriateness-Criteria).[39]

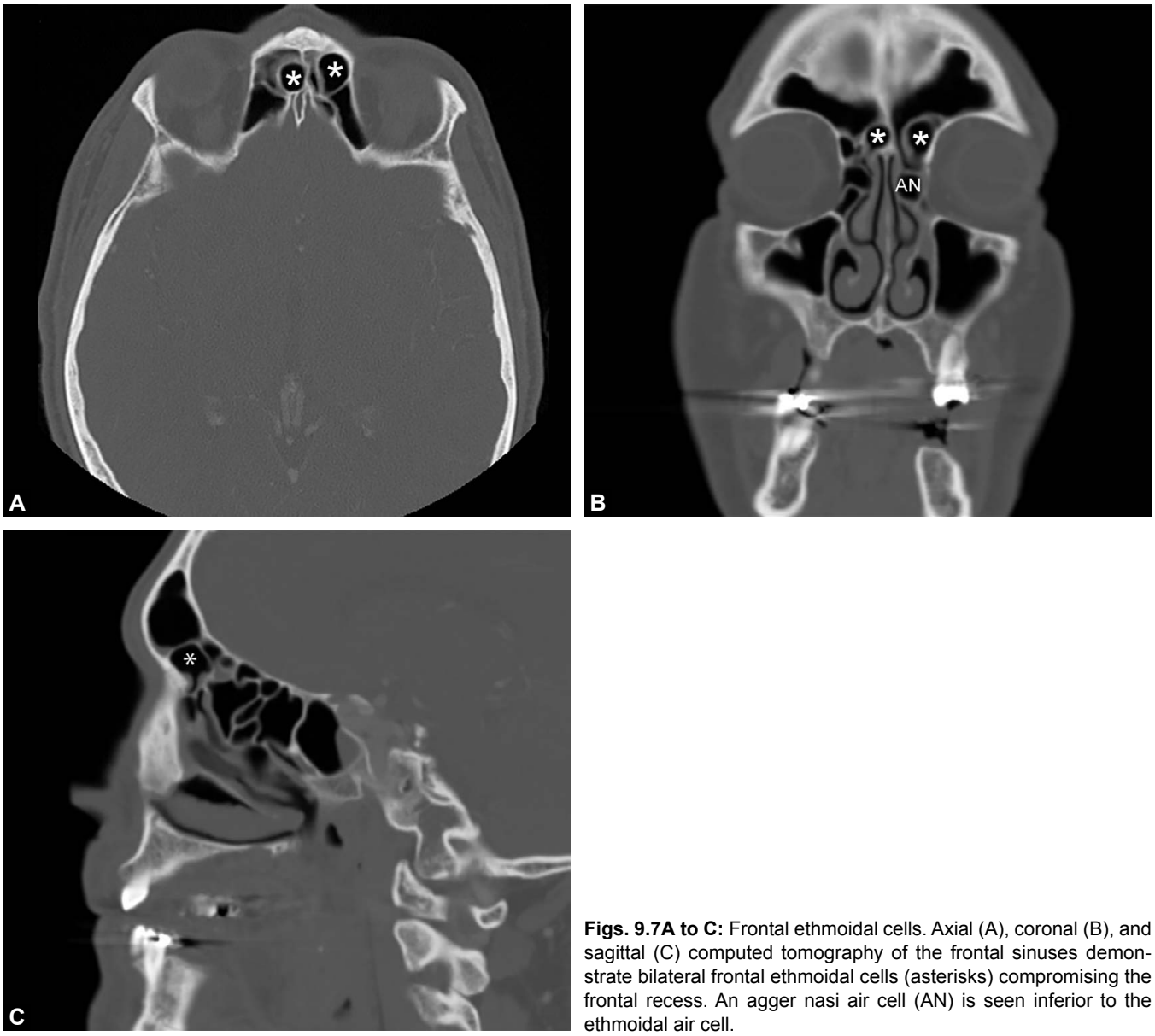
Conventional Radiography

Conventional radiography has been largely supplanted by cross-sectional modalities, in particular, CT. Since radiography may still be performed for the initial evaluation of sinus disease in the emergency department and primary care settings, general familiarity with the modality is helpful. The underlying imaging principle in radiography is that irradiated tissues attenuate X-ray photons differentially, according to their tissue-specific X-ray coefficient. This primarily depends upon density, with greater transmission of photons through low-density tissue and greater attenuation by high-density tissue. Applied to the paranasal sinuses, the difference between dense osseous sinus margins and normally aerated spaces yields clinically relevant tissue contrast, namely, white bone and black air. Lack of normal sinus aeration, whether due to fluid or abnormal tissue, results in full or partial opacification of the normally radiolucent space. When imaged tangentially, an air–fluid interface yields a characteristic fluid level or meniscus.

However, since radiography is a planar projection modality, the three-dimensional sinus structures are superimposed on a two-dimensional image. Thus, while radiography has the highest spatial resolution of all imaging modalities, the summation of overlying structures greatly limits contrast resolution, making these images more challenging to interpret. This has led to considerable inaccuracy compared with CT images.[40] However, compared with other modalities, advantages of radiography include low cost, low radiation dose, and wide availability. Nevertheless,



Figs. 9.6A and B: Variations of the anterior uncinate process. Coronal computed tomography (CT) images (A and B) demonstrate the uncinate process (long arrow) attaching to the lamina papyracea (short arrow). As a result, the frontal sinus drainage pathway (dashed line) drains medial to the uncinate process and directly into the middle meatus (asterisk). When the uncinate process attaches to the skull base (arrow head), the frontal recess (dashed line) drains lateral to the uncinate process (long arrow) and directly into the ethmoid infundibulum (solid line).



Figs. 9.7A to C: Frontal ethmoidal cells. Axial (A), coronal (B), and sagittal (C) computed tomography of the frontal sinuses demonstrate bilateral frontal ethmoidal cells (asterisks) compromising the frontal recess. An agger nasi air cell (AN) is seen inferior to the ethmoidal air cell.

an abnormal finding on radiography will commonly trigger further evaluation with CT or MR.[41]

A number of radiographic projections are utilized for sinus imaging, including Caldwell, Waters, lateral, and submentovertex views, obtained as a series. The Caldwell view, in a posteroanterior projection, shows the frontal and ethmoid sinuses to best advantage. The Waters view, a frontal projection with the chin more elevated, best demonstrates the maxillary sinuses; the frontal sinuses, anterior ethmoids, and anterior orbital rim are also visualized. The lateral view demonstrates the sphenoid sinuses and aids in visualization of the anterior and posterior walls of the frontal sinuses. The submentovertex view angles the X-ray beam through the skull base and vertex, providing the best view of the sphenoid sinuses.[42]

Computed Tomography

CT is the modality of choice for initial evaluation of sinonasal disease. Like radiography, CT imaging is based on the differential X-ray attenuation of various tissues. In CT, rotation of the X-ray beam around the patient and subsequent computer-based spatial reconstruction allows for tomographic slices, eliminating the superimposition of

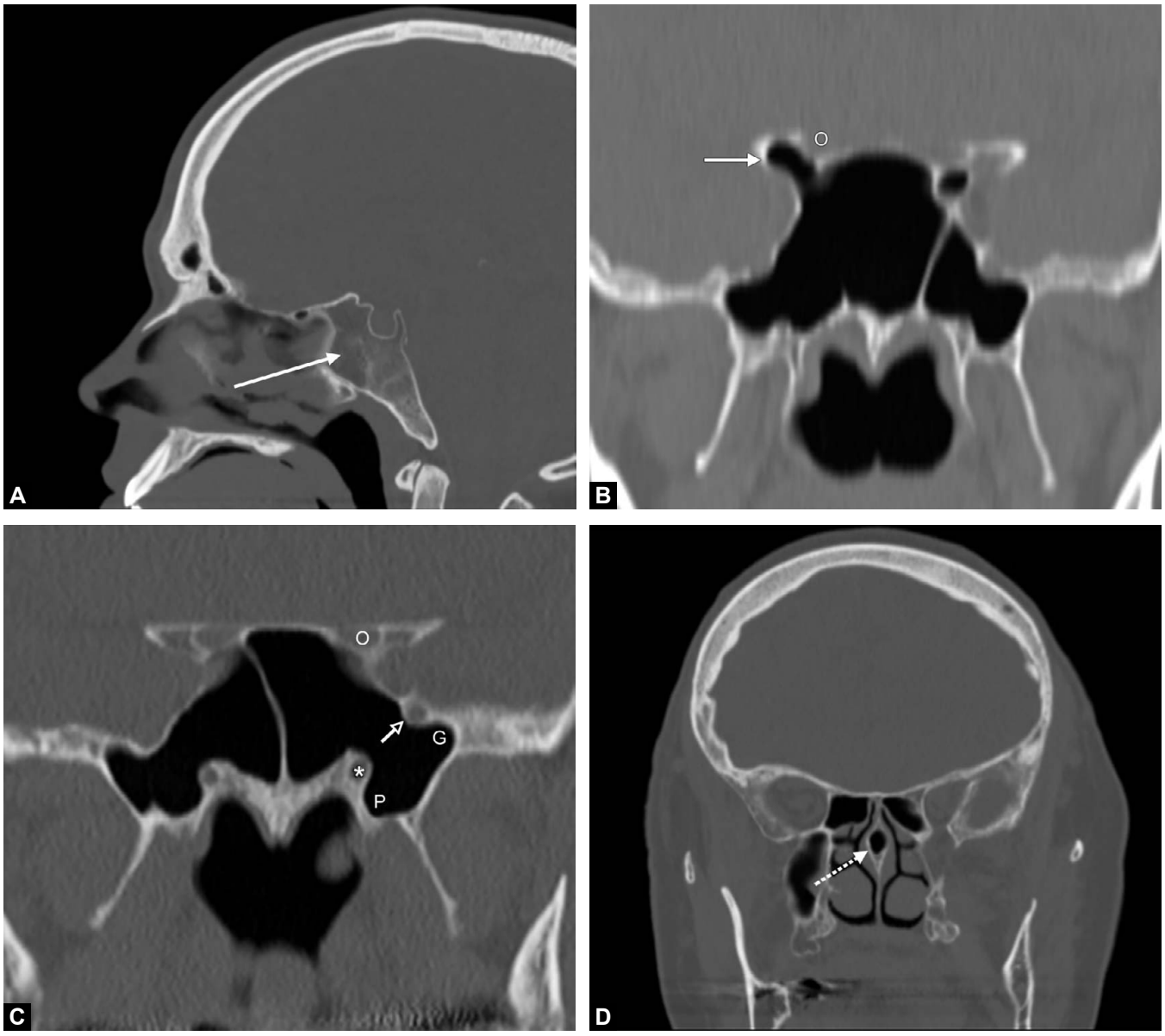
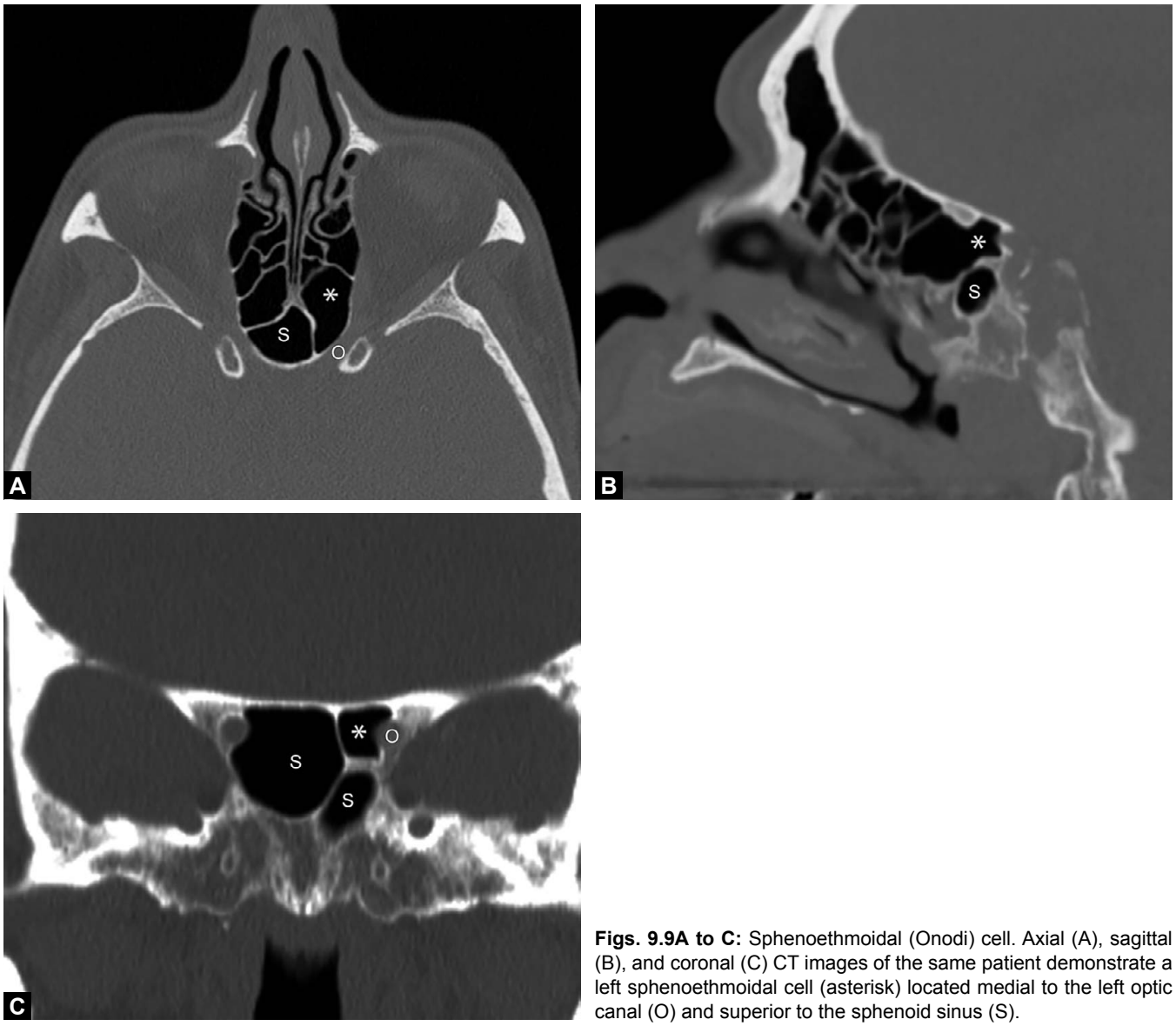


Fig. 9.8A to D: Variations of the sphenoid sinus. Sagittal computed tomography (CT) (A) demonstrates hypoplasia of sphenoid sinus (arrow). Coronal CT (B and C) demonstrates the lateral recesses of the lesser wing of the sphenoid with extension into the right anterior clinoid process (solid arrow), the optic canal (O), lateral recesses of the greater wing of the sphenoid (G) and pterygoid (P), vidian canal (asterisk), and foramen rotundum (open arrow). Coronal CT (D) demonstrates a midline sphenoid recess extending into the bony nasal septum (dashed arrow).

structures seen with radiography and accentuating contrast resolution. The majority of CT scanners in the United States utilize multiple, thinly collimated detectors (multidetector CT) allowing for rapid acquisition of images with high spatial resolution and permitting data reconstruction in multiple planes without additional radiation exposure. Coronal reformatted images optimize evaluation of the ostiomeatal complex, supplanting direct, coronal CT scanning. Postprocessing algorithms are typically applied to accentuate the sharp edges of bone or fine gradations in soft tissue density. The viewer selects image window and level (window refers to the range of densities assigned to the image and the level sets the center value for those densities). A narrow window highlights subtle differences in tissue attenuation; a wide window optimizes bone detail and interfaces between tissue and air.



Figs. 9.9A to C: Sphenoethmoidal (Onodi) cell. Axial (A), sagittal (B), and coronal (C) CT images of the same patient demonstrate a left sphenoethmoidal cell (asterisk) located medial to the left optic canal (O) and superior to the sphenoid sinus (S).

Intravenous contrast is not typically required for routine CT imaging of the sinuses. Evaluation of infectious complications such as subperiosteal abscess or epidural empyema and evaluation of local invasion or intracranial extension of malignancy are appropriate indications for contrast administration. However, in these settings, MRI is often preferred. Contrast-enhanced CT (CECT) is limited to situations where MRI is impractical, unavailable, or contraindicated.[43]

Compared with MRI, CT offers a number of advantages. It is widely available, less costly, and requires less time to perform. Particular to imaging the sinuses, CT offers superior bone detail. Compared to CT, air, cortical bone, calcification, and desiccated secretions appear dark on all MRI sequences and cannot be reliably differentiated.[43] Furthermore, CT may be safely performed on patients with ferromagnetic foreign bodies and non-MRI compatible implants.

The primary disadvantage of CT relative to MRI is ionizing radiation exposure. Radiation-induced cancer risk at low doses typically conferred by a single CT scan remains a controversial topic. However, current literature suggests a linear dose–risk relationship.[44] The potential risk in sinus imaging involves radiation exposure to the ocular lens causing cataract formation. The current cumulative dose threshold for cataractogenesis is 500 mGy.[45]

Reported dose estimates to the lens from sinus CT scanning range from 1.88 to 64 mGy; a more recent study utilizing helical multidetector scanning reports a dose estimate of 29.5 mGy.[46] Given these estimates, patients undergoing multiple scans remain well under threshold. Nevertheless, where imaging involving ionizing radiation is concerned, risk, benefits, and alternatives should be considered. Effort should be made to keep dose as low as reasonably achievable.

Magnetic Resonance Imaging

MRI of the sinuses serves as a complement, rather than an alternative, to CT. Unlike radiography and CT in which the interaction of X-ray photons and tissues generates a representation of anatomy according to tissue-specific attenuation coefficients, MRI utilizes radiofrequency-induced excitation and characterizes relaxation of hydrogen protons in the setting of a powerful static magnetic field. T1 and T2 represent tissue-specific time constants; changes in the interval between radiofrequency excitations (TR) and time from excitation to signal acquisition (TE) result in changes to the relative contribution of T1 and T2 to image contrast (T1 and T2 weighting). The image plane in MRI is not defined by the scanner geometry unlike CT; any spatial plane may be selected for direct data acquisition. Beyond this brief introduction, the physics of MRI and specific pulse sequences used in sinus imaging is beyond the scope of this discussion. An MRI examination of sinuses involves multiple pulse sequences or sets of images, in several planes. Unless contraindicated, gadolinium-based intravenous contrast is administered for sinus examinations.

The main diagnostic advantage of MRI relates to its superior soft tissue contrast resolution compared with CT. This is most apparent in assessing sinonasal tumors, infection, inflammation, or malignancy beyond the confines of the sinus, particularly intracranially. The absence of ionizing radiation makes MRI an attractive modality, particularly in children and patients requiring numerous follow-up studies.

Certain limitations of MRI necessitate correlation with CT imaging. In particular, fine bony detail and small calcifications are poorly seen on MRI, although bone marrow invasion is readily identified.[43] MRI studies can be quite lengthy; patient compliance is critical to image quality. Metallic dental or craniofacial hardware results in severe image distortion and may render images nondiagnostic. Finally, MRI is more expensive and less available than CT.

A major safety consideration with MRI relates to the interaction of the powerful static magnetic field with metallic objects. In patients with ferromagnetic foreign bodies or medical implants of uncertain MRI safety status, consultation with a radiologist prior to ordering the examination is essential to prevent potential harm and avoid patient inconvenience resulting from delayed or cancelled studies.

Patients on dialysis with severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m^2) may be at risk for developing nephrogenic systemic fibrosis after intravenous administration of gadolinium-based contrast media (GBCM). This condition mainly involves the skin and other organ systems. Symptoms may rapidly progress, and fatalities have been reported. Although institutional protocols vary, careful assessment of risks, benefits, and alternatives must precede GBCM administration. Severe allergic reactions to GBCM are extremely rare.[47]

Positron Emission Tomography

Whereas radiography, CT, and MRI primarily provide anatomical information, PET imaging demonstrates abnormal metabolic function. PET utilizes injected radioisotopes that emit positrons (β+ radiation). When a positron interacts with an electron, both particles are annihilated, releasing two high-energy photons in opposite directions. These photons are simultaneously incident on the PET detector ring, allowing for spatial localization. The most commonly used radiopharmaceutical in oncologic PET imaging is fluorodeoxyglucose (FDG)—the positron emitter fluorine-18 bound to a glucose analog. Compared with normal cells, malignant cells overexpress membrane glucose transporters and glycolytic enzymes, leading to increased FDG uptake and phosphorylation. FDG-6-phosphate cannot be further metabolized, and due to decreased phosphatase activity in tumor cells, it cannot escape back into the bloodstream. In this manner, FDG is preferentially concentrated in cells with increased glucose utilization, typical of many benign and malignant neoplasms.[20,41] As the initial radioisotope activity is known, and the amount of activity within a determined spatial region of interest can be measured, PET allows for semiquantitative analysis in the form of a standardized uptake value. Postacquisition fusion with a concomitantly performed MRI (PET/MRI), low dose CT (PET/CT), or separate diagnostic CT or MRI allows for improved spatial localization of abnormal FDG uptake and correlation with areas of concern on other imaging modalities.

Compared to PET imaging of other head and neck neoplasms, there is scant literature regarding its use for sinus tumors. In general practice, PET adds little information regarding the primary tumor and is not routinely performed prior to treatment. However, in a recent study, Ramakrishnan et al. demonstrated 94% sensitivity in detecting biopsy-proven sinus cancers. The detection of metastasis in 31% of these patients suggests a role in pretreatment planning.[48] Furthermore, PET may be of value for post-treatment surveillance, particularly in the exclusion of recurrent or metastatic disease. In one series, PET demonstrated 100% sensitivity, 40% specificity, 54% positive predictive value, and 100% negative predictive value in the surveillance of patients with previously treated skull base malignancies.[49]

Increased FDG concentration is not specific for malignancy. A variety of benign neoplasms, as well as non-neoplastic inflammatory and infectious processes demonstrate FDG avidity. Moreover, many normal tissues in the head and neck show increased FDG uptake; these include the lymphoid tissue of Waldeyer's ring, salivary glands, thyroid gland, active muscles, mucosa, and brown fat.[50] Other drawbacks of PET imaging include low spatial resolution (threshold tumor size of approximately 1 cm) and lack of FDG avidity in certain tumors; these factors contribute to false-negative studies.[51] PET imaging is also more time consuming, more expensive, and less available than CT. The radiation dose in PET is substantially higher than CT.

IMAGING OF BENIGN PARANASAL SINUS DISEASE

Inflammatory and Infectious Disease

Paranasal sinus inflammatory disease is the fourth most common diagnosis in outpatient visits, affecting >12.8% of the US population annually.[52] It poses an immense economic burden, accounting for substantial office visit expenditures, antibiotic prescriptions, lost work days, and missed school days. Major diagnostic criteria include nasal drainage, nasal congestion, facial pain or pressure, postnasal drip, and olfactory dysfunction. Minor diagnostic criteria include fever, cough, fatigue, dental pain, and ear fullness or pressure.[53] Most cases of uncomplicated acute and subacute sinusitis are diagnosed clinically and should not require imaging. Clinical judgment combined with history and physical examination usually makes the diagnosis. Nonenhanced CT (NECT) imaging is the modality of choice for evaluating recurrent acute sinusitis, chronic sinusitis with atypical symptoms, or presurgical evaluation of sinus anatomy. MRI is complementary for evaluation of aggressive sinus infection with ocular/intracranial complications, invasive fungal sinusitis (IFS) in immunocompromised patients, or evaluation of a sinonasal mass.[47] Sinusitis cannot be diagnosed solely by imaging; correlation should be made with clinical and endoscopic findings.

Radiography

Radiographic evaluation of the paranasal sinuses typically includes four views (Caldwell, Waters, submentovertex, and lateral). On plain films, the earliest sign of thickened sinus mucosa is a hazy or vaguely "clouded'" appearance of the sinus. Most often, this results from a combination of retained secretions and mucosal thickening. Although less costly and more widely available, radiographic evaluation is limited by the inability to accurately localize pathology, estimate degree of soft tissue changes, and assess sinus drainage pathways. Some authors advocate only the Waters view for radiographic evaluation, since >90% of sinusitis involves the maxillary sinus;[54,55] however, ethmoid and sphenoid sinus abnormalities are difficult to detect on this view.[56] Sensitivity and specificity for detection of inflammatory sinus disease is low compared with CT.

Computed Tomography

CT is the gold standard in sinus imaging, guiding management of sinusitis as it accurately depicts sinus anatomy, drainage pathways, soft tissue changes, bony detail, anatomic variations, and complications involving the orbit or intracranial structures.[57-59] With multidetector CT volume isometric imaging, it is possible to obtain axial images for reconstruction in coronal and sagittal planes. The dose of radiation in low-dose CT scanning of the paranasal sinuses is comparable with that of two plain film radiographs of the paranasal sinuses.[60] CT is the study of choice in patients with recurrent or chronic sinusitis undergoing FESS, providing a road map for surgical navigation. If complications are suspected, such as pre-septal or postseptal cellulitis, subperiosteal abscess, orbital abscess, cavernous sinus thrombosis (CST), osteomyelitis, subdural empyema, epidural or brain abscess, meningitis, brain infarction, or mycotic aneurysm, then CECT, to include the brain and sinuses, is indicated.[61]

Magnetic Resonance Imaging

MRI of the paranasal sinuses has several potential advantages. It differentiates mucosal thickening from sinus secretions, without exposure to ionizing radiation. MRI diagnoses complications of sinusitis extending to the cranium or orbits and is more sensitive than CECT in detecting intracranial complications such as meningeal enhancement and fluid collections.[62] In a study of adult and pediatric patients, MRI was found to be more accurate than CT and clinical examination in diagnosing meningitis (97% vs 87% and 82%, respectively).[62] However, MRI does not demonstrate bony detail of the sinus drainage pathways and is less sensitive for bony erosion.

Imaging and Clinical Correlation

In adults, good correlation exists between clinical presentation and significant mucosal disease on imaging. Occasionally, patients with symptoms of sinonasal inflammatory disease have normal CT and MRI. Conversely, asymptomatic patients may have mucosal disease on imaging studies. Furthermore, in patients with treated acute sinonasal inflammatory disease, clinical improvement may occur well ahead of resolution on imaging. Therefore, diagnosing sinus mucosal disease on imaging can be deceiving. The radiologist's role is to identify the sinuses involved, assess mucosal disease, and alert clinicians to disease complications.

Abnormal radiologic findings in sinusitis include air–fluid levels, mucosal thickening, complete sinus opacification, and sclerotic bone changes. Of these findings, complete sinus opacification is the most, and air–fluid level is the least common.

Acute and Chronic Sinusitis

Sinusitis is inflammation or infection involving the mucous membranes of the paranasal sinuses or underlying bone. The OMU is a common drainage pathway for the frontal, maxillary, and anterior ethmoid sinuses. This unit is composed of the maxillary ostium, infundibulum, uncinate process, hiatus semilunaris, ethmoid bulla, and middle meatus. OMU patency is critical for normal sinus drainage and ventilation.[63] Sinusitis arises from local mucosal inflammation due to allergens, viral infections, and air pollutants impairing mucociliary clearance and causing sinus ostia obstruction.[64] Sinus secretions pool and thicken, creating a nidus for superinfection.

Sinusitis is subdivided into acute, subacute, and chronic stages on the basis of symptom duration. Acute disease is sudden in onset, lasting up to 4 weeks; subacute sinusitis is a continuum of the natural progression of acute sinusitis, 4–12 weeks in duration; chronic sinus disease is defined as mucosal inflammation of the paranasal sinuses lasting 12 consecutive weeks.[57] The most distinguishing feature of acute sinusitis is the air–fluid level, whereas a sclerotic, thickened sinus wall more specifically characterizes chronic sinusitis. These imaging features may be helpful in determining disease chronicity; however, the terms acute, subacute, or chronic sinus disease should not be used by the radiologist without clinical correlation.

Air–Fluid Levels

An air–fluid level in a patient with acute symptoms of sinonasal infection generally correlates with the diagnosis of acute sinusitis (Fig. 9.10). However, some patients with acute sinusitis will not have air–fluid levels; the imaging appearance may be indistinguishable from subacute, chronic disease, or postoperative changes. An air–fluid level in the frontal sinus is most specific for acute bacterial sinusitis. Since intracranial complications readily occur, often within 48 hours, the clinician should be alerted to a frontal sinus air–fluid level.[65] These patients may require prompt, vigorous antibiotic treatment. Sphenoid sinus air–fluid levels may indicate the presence of acute sinusitis or nasal cavity obstruction. Ethmoid sinus air–fluid levels are rare even in trauma or acute infection.

Mucosal Thickening

Mucosal thickening is seen in both acute and chronic sinusitis. Mucosal enhancement characteristics help determine chronicity of inflammation. Actively infected and acutely edematous mucosa demonstrates a thin zone of mucosal enhancement with a variable zone of lower-attenuation, submucosal edema.[66] If the sinus is opacified, the CT appearance shows roughly concentric rings or zones consisting of an outer bony wall "ring," a water or mucoid attenuation (10 to 18 HU) submucosal ring, a thin infected mucosal enhancing ring, and entrapped mucoid secretions centrally.[67] Nonenhancing, thickened mucosa signifies chronic inflammation and/or fibrosis. The differential diagnosis of sinus mucosal thickening includes fungal sinusitis (mycetoma), which often coexists with chronic sinusitis.

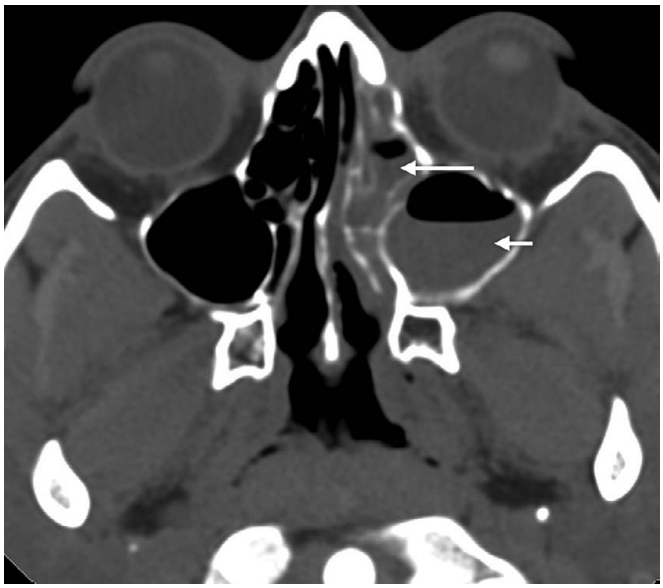


Fig. 9.10: Sinusitis. Axial computed tomographic image demonstrates opacification and air–fluid levels in the left maxillary sinus (short arrow) as well as an ethmoid air cell (long arrow). This pattern of sinus disease involves the middle meatus.
Courtesy: Dr William Gomes, Bronx, NY, USA.

Sinus Opacification

When sinonasal secretions become chronically obstructed, a number of predictable changes occur which alter protein concentration, free water, and viscosity. Normally, sinonasal secretions are composed of 95% water and 5% protein macromolecules, resulting in hypodensity on CT and hyperintensity on T2W MRI. With chronic obstruction however, virtually all of the free water is eliminated. The secretions become concentrated and inspissated with protein, resulting in hyperdensity on CT and hyperintensity on T1W and T2W MRI. A very high protein concentration can produce signal void on both T1W and T2W MRI with an appearance indistinguishable from a normal aerated sinus. Therefore, MRI may underestimate chronic sinus disease.[68,69]

Sclerosis

Sinus wall thickening and sclerosis is characteristic of chronic disease.[70] Up to one third of patients with acute sinusitis develop some evidence of chronic sinusitis.

Chronic disease can result in atrophic, sclerosing, or hypertrophic polypoid mucosa. Bony sinus walls surrounding a chronically infected sinus are thickened and sclerotic with reactive new bone formation. This nonspecific bony response can result from any chronic inflammatory process, regardless of etiology, due to increased local blood flow stimulating the periosteum. Care must be taken when reviewing a sinus CT with mucosal disease using narrow ("soft tissue") windows, as bone appears more dense and thick. Actual bone density and thickness are best evaluated on wide window ("bone") settings. Clinical context should indicate whether adjacent mucosal thickening in the sinus is due to acute or chronic disease.

Complications of Sinusitis

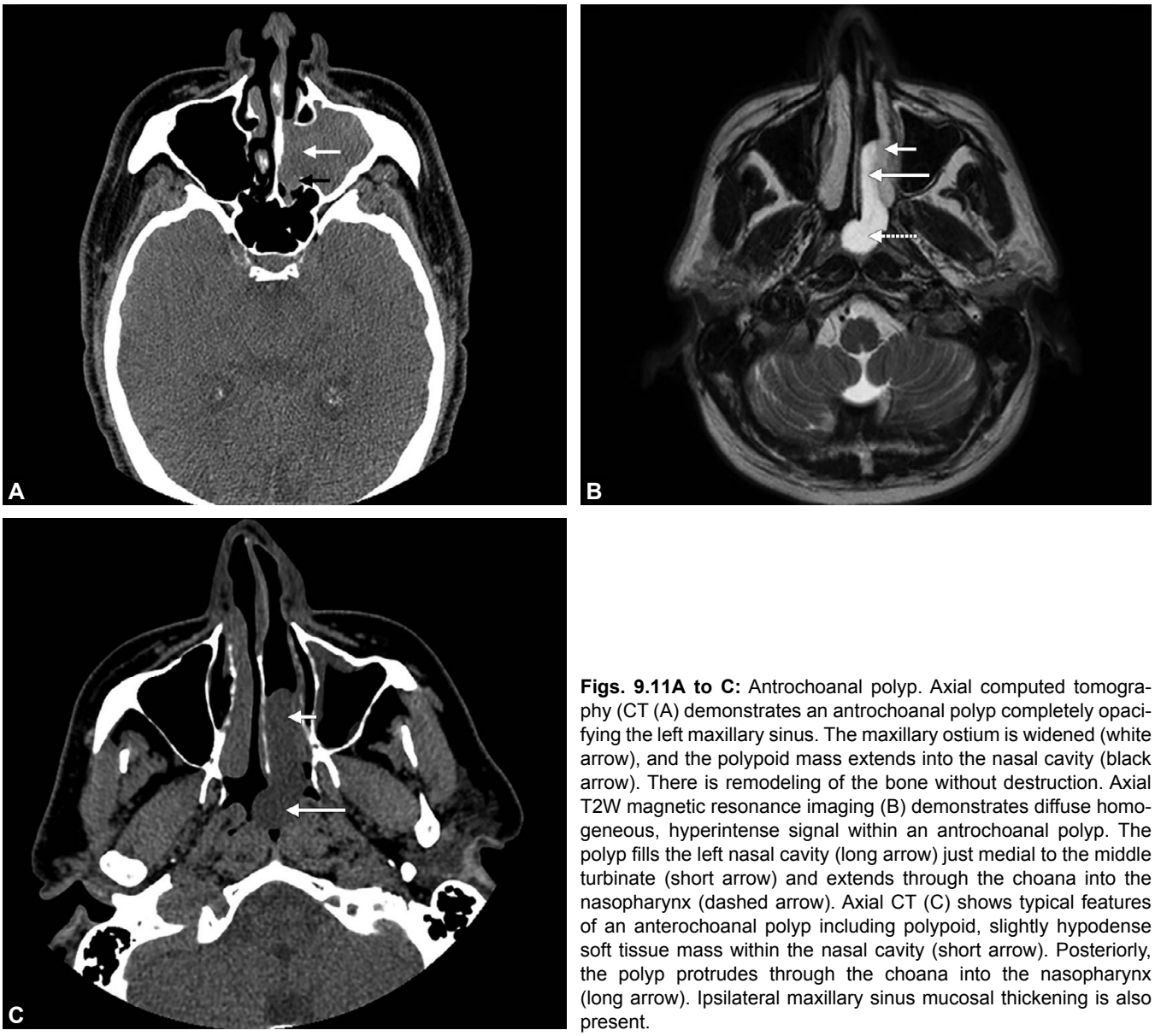
When assessing complications of sinusitis, CT excels in imaging subperiosteal abscess or orbital extension. MRI is necessary for assessing intracranial complications such as brain or epidural abscess, subdural empyema, or sinus thrombosis.

Retention Cysts

Mucous retention cysts result from chronic inflammatory sinus disease. Serous cysts are submucosal fluid collections and mucous cysts result from mucous gland obstruction. Radiographically, these subtypes are indistinguishable; both appear as dome-shaped radiopacities, convex to the floor of the maxillary sinus, without destruction, expansion, or thinning of sinus walls. Most retention cysts are asymptomatic and remain unchanged over time. On contrast MRI, the mucosa enhances with gadolinium, but the edematous submucosa does not, accounting for the characteristic appearance.

Polyposis

A polyp is a benign, rounded or pedunculated sinonasal soft tissue inflammatory change of sinonasal mucosa. Intrasinus polyps cannot be differentiated from retention cysts on plain films or cross-sectional imaging. The etiology of polyps is poorly understood, but it is likely related to repeated bouts of inflammation. Polyps have edematous and fibrous stages, and when chronic, can expand and erode bone. Polyposis is demonstrated on CT by enlargement of the sinus ostia, as these rounded or lobular masses expand within the nasal cavity. This commonly occurs at the ostia of the maxillary antrum, extending to the nasal choanal region, constituting the characteristic appearance of an "antral–choanal polyp" (Figs. 9.11A to C). Expanded sinuses, thinning of bony trabeculae, and erosive bone



Figs. 9.11A to C: Antrochoanal polyp. Axial computed tomography (CT (A) demonstrates an antrochoanal polyp completely opacifying the left maxillary sinus. The maxillary ostium is widened (white arrow), and the polypoid mass extends into the nasal cavity (black arrow). There is remodeling of the bone without destruction. Axial T2W magnetic resonance imaging (B) demonstrates diffuse homogeneous, hyperintense signal within an antrochoanal polyp. The polyp fills the left nasal cavity (long arrow) just medial to the middle turbinate (short arrow) and extends through the choana into the nasopharynx (dashed arrow). Axial CT (C) shows typical features of an anterochoanal polyp including polypoid, slightly hypodense soft tissue mass within the nasal cavity (short arrow). Posteriorly, the polyp protrudes through the choana into the nasopharynx (long arrow). Ipsilateral maxillary sinus mucosal thickening is also present.

changes at the skull base are additional features. Classically, polyps are hypodense on CT, hypointense on T1W and hyperintense on T2W MR imaging. Peripheral or solid enhancement may be seen. Specific CT and MRI findings do not distinguish polyps from neoplasms. Generally, polyps demonstrate heterogeneous MRI signal, whereas tumors appear more homogenous.[69]

Based on predominant histological elements, inflammatory sinonasal polyps are classified into five types: edematous, glandular, fibrous, cystic, and angiectatic or angiomatous nasal polyps (ANPs). ANPs are the rarest, characterized by extensive vascular proliferation and ectasia. They can grow rapidly, demonstrating aggressive clinical behavior simulating malignancy, and are easily confused with other benign entities including inverted papilloma (IP), juvenile angiofibroma, and hemangioma. CT features distinguishing ANPs from other etiologies include heterogeneous density, no or minimal peripheral enhancement, well-delineated contour, benign bone changes without soft tissue invasion, and absence of pterygopalatine fossa (PPF) or sphenoid sinus involvement.[71] ANPs typically demonstrate heterogeneous internal MRI signal, T2W hyperintensity with a peripheral hypointense rim, and strong nodular and patchy enhancement.

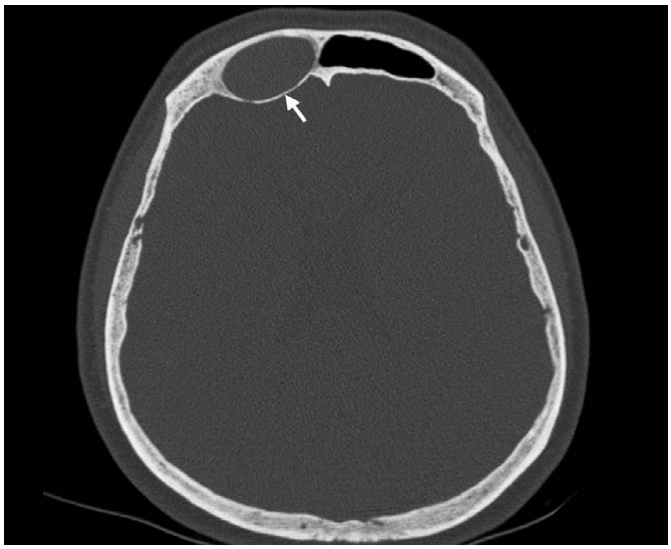
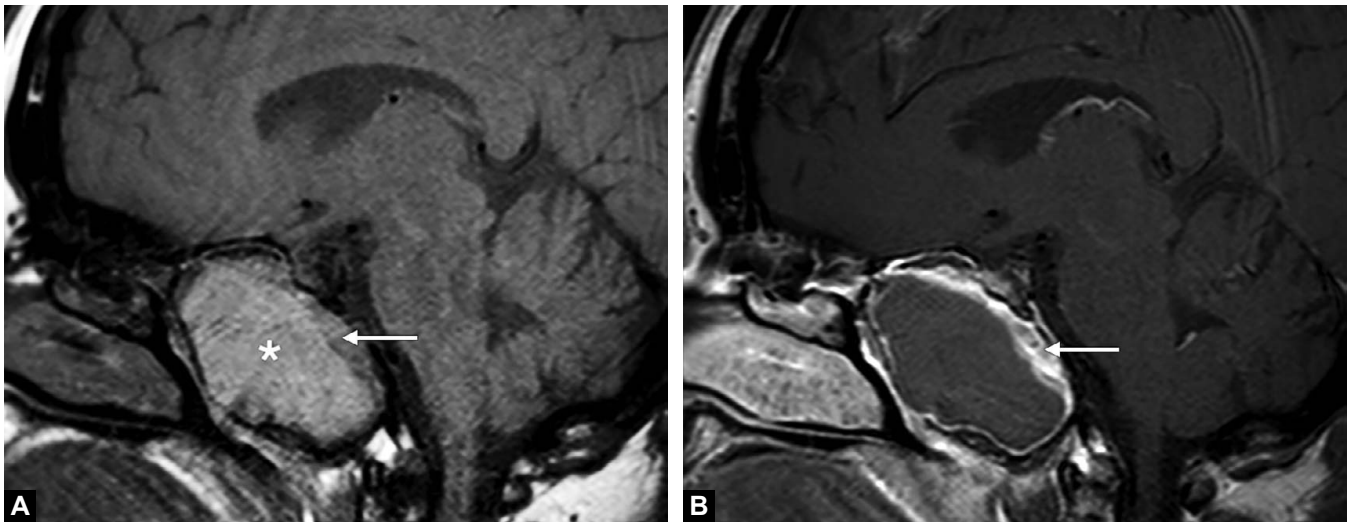


Fig. 9.12: Frontal sinus mucocele. Axial computed tomography demonstrates an opacified, expanded right frontal sinus with smooth bony remodeling (arrow).
Courtesy: Dr Jacques Romano, Bronx, NY, USA.



Figs. 9.13A and B: Sinonasal mucocele. Sagittal T1W magnetic resonance imaging (MRI) (A) shows a large mucocele in the sphenoid sinus (asterisk). The lesion is homogenously hyperintense, likely related to highly proteinaceous contents. Note the thickened sinus mucosa (arrow). Sagittal contrast enhanced T1W MRI (B) demonstrates a nonenhancing mass in the sphenoid sinus with peripheral rim enhancement (arrow).
Courtesy: Dr Jacques Romano, Bronx, NY, USA.

Progressive enhancement on dynamic, enhanced MRI may suggest the diagnosis.[72]

Mucoceles

Mucoceles present as airless, mucoid-filled, and expanded paranasal sinuses. They develop after obstruction of the sinus ostium, or rarely, after a distended mucous gland (retention cyst) fills the sinus.[73] They typically cause bony remodeling, without osseus destruction. Pathologically, mucoceles are expanding cysts lined by mucosa, with accumulated secretions and desquamation. Infected mucoceles are called mucopyoceles. On CT, an expanded, airless sinus filled with homogeneous mucoid attenuation secretions (10–18 HU) is diagnostic of a mucocele [74] (Fig. 9.12). If entrapped secretions are particularly viscid and proteinaceous, attenuation can increase to 20 to 45 HU, similar to that of muscle. Upon the administration of intravenous contrast, only a thin, uniform rim of mucosa should enhance[69] (Figs. 9.13A and B). By location, the frontal sinuses account for 60% of cases; ethmoid sinuses, 30%; and

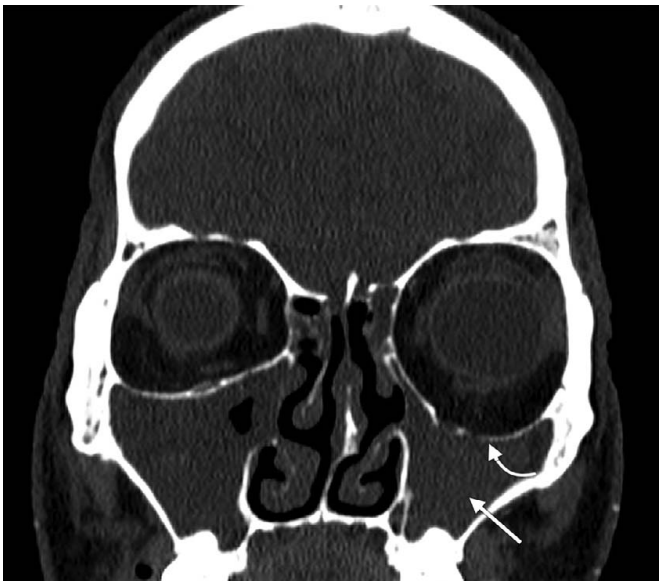


Fig. 9.14: Silent sinus syndrome. Coronal computed tomography (CT) shows an opacified left maxillary antrum with maxillary sinus volume loss (arrow). The orbital floor is inferiorly positioned (curved arrow) with secondary increase in orbital volume, resulting in enophthalmos.
Courtesy: Dr William Gomes, Bronx, NY, USA.

maxillary sinuses, 10%; the sphenoid sinus is only rarely involved. If the sinus is airless, filled with a mucoid density but not expanded, the diagnosis is that of an obstructed sinus, not a mucocele.[75]

Atelectatic Sinus

With chronic inflammation and/or poor ventilation, patients may develop atelectatic, shrunken sinuses. In these patients, stagnant mucus accumulating within the sinus elicits a low-grade inflammatory response, causing osteolysis of the sinus walls, which are pulled into the sinus by negative sinus pressure. Secondary, downward retraction of the orbital floor into the maxillary sinus results in the classically described unilateral enophthalmos. This constellation of findings is termed "silent sinus syndrome."[76] Hypoglobus (downward position of the globe within the orbit), malar depression, upper-lid retraction, and a deep upper orbital sulcus may be present.[77] Although the diagnosis of silent sinus syndrome is made clinically, it is confirmed radiologically, to exclude underlying orbital tumor or manifestation of trauma. On coronal CT images, there is occlusion of the maxillary infundibulum, due to lateral retraction of the uncinate process, which is opposed to the inferomedial orbital floor. Associated lateral retraction of medial sinus wall and middle turbinate can be seen with enlargement of middle meatus. The orbital floor, retracted into the maxillary sinus lumen, creates facial asymmetry[76] (Fig. 9.14).

Osteomyelitis

Osteomyelitis of the facial bones and paranasal sinuses is uncommon and usually associated with pain. The involved bone has a mottled, irregular appearance on plain films and CT. There may be sequestrum formation, reactive bony thickening, sclerosis, and ultimately, bony fragmentation. Intracranial and intraorbital complications are more common with acute sinusitis; osteomyelitis is more common with chronic sinusitis.[67]

Orbital Infection

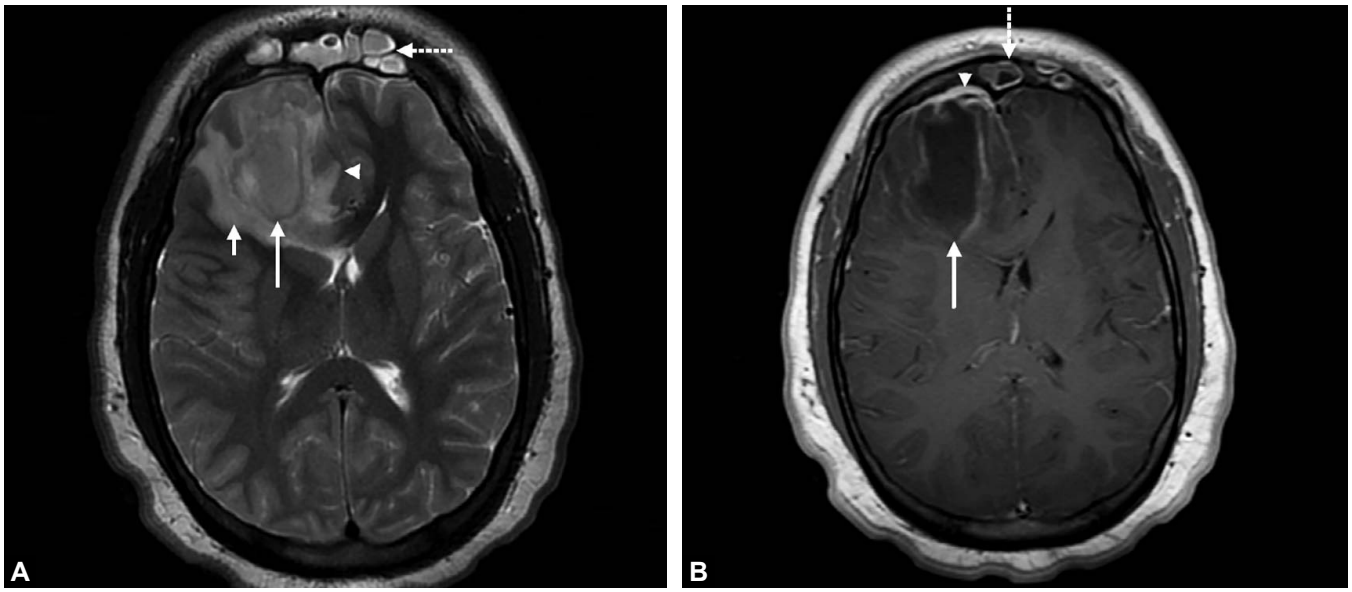
Approximately 3% of patients with paranasal sinusitis experience orbital or preseptal inflammatory disease.[75] These complications include edema of the eyelids, preseptal cellulitis, preseptal abscess, orbital cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus and/or superior ophthalmic venous thrombosis.[78] Ethmoid sinus disease is most predisposed to orbital extension, due to the thin lamina papyracea and absence of valves in posterior and anterior ethmoid veins. Sphenoid and maxillary sinusitis are the second most likely to spread to the orbits, followed by the frontal sinuses. Sphenoid sinusitis may also cause optic neuritis, via direct spread of infection, bony deficiency in the wall of the sinus, and vasculitis. An opacified sphenoid sinus in the context of decreased visual acuity and atypical headache suggests the diagnosis.

Intracranial Infection

Occasionally, sinusitis leads to intracranial complications, such as meningitis, epidural abscess, subdural abscess, cerebritis, and cerebral abscess. The propensity for frontal sinusitis to spread intracranially is due to the rich emissary venous network, Bechet's plexus, connecting the posterior sinus mucosa with the meninges[78] (Figs. 9.15A and B). A less common route is direct extension of osteomyelitis through bone. Clinical symptoms suggesting intracranial complications include Pott's puffy tumor, altered consciousness, seizures, hemiparesis, and cranial nerve palsy.

Central Venous Thrombosis

Cavernous sinus thrombosis/thrombophlebitis is a rare, potentially life-threatening complication of paranasal



Figs. 9.15A and B: Frontal sinusitis complicated by intracranial abscess. Axial T2W magnetic resonance imaging (MRI) (A) demonstrates a fluid–filled frontal sinus (dashed arrow) and an ovoid hyperintense mass in the right frontal lobe with marked vasogenic edema (short arrow). The hypointense signal of the capsule (long arrow) helps distinguish abscess from cystic neoplasm. Secondary mass effect results in sulcal effacement and mild midline shift (arrow head). Axial contrast-enhanced T1-weighted MRI (B) shows enhancing, thickened mucosa in the frontal sinuses (dashed arrow) with a small frontal extra-axial collection (arrow head). Note the ring-enhancing, hypointense abscess within the brain parenchyma (long arrow).
Courtesy: Dr Laurie Sanchez, Newark, NJ, USA.

sinusitis.[79] CST is most often associated with sphenoid or ethmoid disease and can spread via valveless venous networks or direct extension.[80] Signs and symptoms include fever, headache, ptosis, proptosis, chemosis, external ophthalmoplegia, and decreased corneal reflex. A high index of suspicion and emergent imaging are crucial to making an early, accurate diagnosis.[81]

CT findings of CST include enlargement and expansion of the cavernous sinus with lateral wall flattening or convexity rather than concavity, best visualized on coronal images. Multiple irregular or single, nonenhancing filling defects within the cavernous sinus suggest thrombi, which can be differentiated from intracavernous fat deposits by size (thrombi are usually >7 mm), density, and signal intensity.[79] Indirect signs of CST are related to venous obstruction, consisting of dilation of the superior ophthalmic vein, exophthalmos, soft tissue edema, and thrombi visualized in tributary veins and sinuses (superior ophthalmic vein and superior petrosal, inferior petrosal, and sigmoid sinuses).[82] MRI may be of greatest value in re-examining patients with nondiagnostic CT scans or further assessing complications, including extension of infection into adjacent meninges, pituitary gland, or brain.[83]

GRANULOMATOUS DISEASES OF THE NOSE AND PARANASAL SINUSES: IMAGING

Granulomatous diseases of the nose and paranasal sinuses may be categorized as infectious or noninfectious. The radiographic appearance of these diseases is similar to chronic rhinosinusitis, with findings such as sinus opacification, mucosal thickening, and obstruction of sinus outflow tracts. However, distinct radiographic characteristics, in combination with clinical suspicion, may persuade the clinician to consider alternative diagnoses. Histopathologic analysis of tissue specimens or laboratory confirmation is required for definitive diagnosis.

Infectious Granulomatous Diseases: Bacterial

Mycobacterium Tuberculae

Despite declining incidence in the United States in the past decade, multidrug resistant strains of *Mycobacterium tuberculae* have become a significant global health concern. The larynx, nasopharynx, oral cavity, salivary glands,

thyroid, and lymph nodes may be affected. In cases of suspected sinonasal involvement, imaging may be helpful in assessing extent of disease and confirming the diagnosis. Findings, typically nonspecific, may include mucosal thickening, soft tissue masses, and sinus opacification. CT delineates bony erosion; effusion, sclerosis, and coalescence in the mastoid may indicate tuberculous mastoiditis. On MRI, nodular soft tissue and mucosal thickening may be visualized in early stages. As disease progresses, soft tissue masses may erode bony structures including the sinus walls and skull base. Radiographic findings of orbital involvement include unilateral masses isolated to the choroid or filling the entire ocular space. Characteristic findings of tuberculous cervical lymphadenopathy with necrotic granuloma are peripherally enhancing structures with surrounding fat plane obliteration. Calcification in lymph nodes or in sinonasal lesions may suggest tuberculosis.[84,85]

Nontuberculous Mycobacterium

Sinonasal involvement with nontuberculous, or atypical, mycobacterial infections is extremely rare. Causative bacterial agents include *Mycobacterium avium-intracellulare, chelonae, marinum, fortuitum,* and *kansasii*. Each has its own unique set of risk factors; therefore, careful history is essential for diagnosis. Typically, Mycobacterium *avium-intracellulare* presents as an enlarging cervical lymph node in a pediatric patient. Imaging reveals asymmetric, heterogeneous nodes with occasional calcification or ring-enhancement. Surrounding fat stranding, typical of infectious lymphadenitis is generally absent, indicative of a "cold" lesion. These infections do not result in nasal disease.

Mycobacterium leprae, or leprosy, is a rare mycobacterial infection that may result in significant nasal deformity. Nasal mucosa plays an important role in transmission of the disease and is frequently affected. CT demonstrates mucosal thickening and soft tissue masses affecting one or more paranasal sinus. Ethmoid sinus mucosal thickening is the most common finding in paranasal sinus involvement by leprosy. Destruction of septal cartilage and inferior turbinates may also be visualized.[86] Findings are similar to chronic rhinosinusitis; therefore, diagnosis must be confirmed with tissue biopsy and culture.

Rhinoscleroma

Rhinoscleroma is a destructive granulomatous process that is rare in the United States but endemic in other countries such as Central and South America, Eastern Europe, and Egypt. The gram-negative bacillus, *Klebsiella rhinoscleromatis*, is the causative agent. Patients present with destructive lesions affecting the nose and nasal passages, rarely extending to the palate, nasopharynx, larynx, or orbit. Diagnosis is made by culture and histologic analysis of biopsied tissue. Long-term antibiotic therapy is required for eradication of this obstinate bacterium.

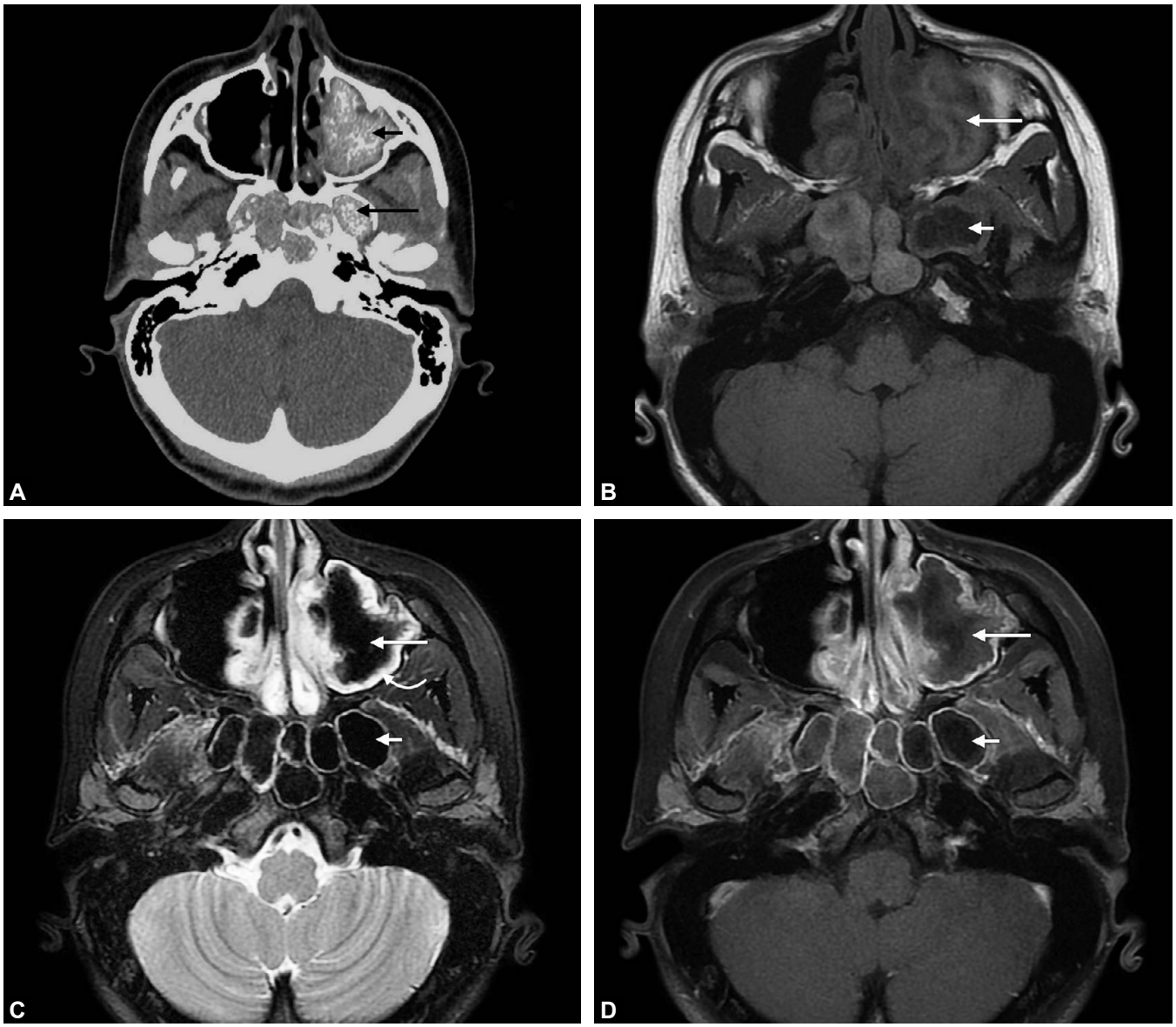
Imaging may be indicated to assess the extent of nasal and paranasal sinus involvement as well as treatment response. Lesions may originate from the sinuses or nasal cavity. On CT, patients may demonstrate inflammatory findings such as paranasal sinus mucosal thickening, bony and cartilaginous destruction, and well-defined homogenous masses that do not enhance with contrast. Bony destruction of the inferior turbinates, nasal septum, and medial wall of the maxillary sinus may be visualized. In addition to orbital invasion, PPF and intracranial extension has been reported.[87] The MRI appearance is similar to sinonasal tumors and fungal lesions. T2W images demonstrate homogenous, high signal intensity lesions compared with muscle and fat. On T1W images, lesions appear isointense to brain, or have high signal intensity due to elevated protein content.[88,89] Associated cervical lymphadenopathy may be visualized. In extensive disease, imaging may show involvement of the hard palate bone, tonsillar fossae, oropharynx, larynx, and trachea. MRI is useful for assessing the extent of invasion; CT is useful in assessing early bony changes.[87]

Infectious Granulomatous Diseases: Fungal

Numerous fungal organisms affect the nose and paranasal sinuses, including histoplasmosis, cryptococcosis, coccidioidomycosis, blastomycosis, aspergillosis, and mucormycosis. Transmission occurs via inhalation of spores. The clinical spectrum ranges from asymptomatic disease to life-threatening, progressive infection, especially in immunocompromised patients. IFS has three distinct forms, each with unique clinical characteristics.[90] Diagnosis is made by tissue analysis and visualization of the offending organism by special staining, but imaging is essential and may strongly suggest the diagnosis.

Noninvasive Fungal Sinusitis

Allergic fungal sinusitis: This is suspected in patients with atopy and chronic rhinosinusitis unresponsive to typical antibacterial therapy. Nasal polyposis is a characteristic



Figs. 9.16A to D: Allergic fungal sinusitis. Axial computed tomography (CT) (A) demonstrates mixed density material within the left maxillary sinus (short black arrow) and sphenoid sinus (long black arrow), consistent with fungal elements. Axial T1W magnetic resonance imaging (MRI) (B) shows mixed signal intensity material within the maxillary (long arrow) and sphenoid (short arrow) sinuses. T2W MRI (C) demonstrates markedly hypointense contents within the maxillary (long arrow), and sphenoid (short arrow) sinuses as well as reactive mucosal inflammation (curved arrow). Axial contrast-enhanced T1W fat-saturated MRI (D) shows enhancing mucosa at the periphery of the maxillary (long arrow) and sphenoid (short arrow) sinuses.

feature of this form of fungal sinusitis. A thick, "peanut butter"-like mucin, called allergic mucin, is identified during nasal endoscopy and endoscopic sinus surgery. Typical CT findings include one or more opacified sinus with high attenuation, clinically corresponding to thick collections of allergic mucin. These scattered opacities, described as a "starry sky" appearance, are the same density as calcium.[91] Allergic fungal sinus disease may result in heterogeneous soft tissue masses expanding the involved sinus, bony erosion or remodeling, and obstruction of sinus outflow tracts.[92] Thick, mycetomatous allergic mucin causes characteristic signal void on T1 and T2W MRI. Gadolinium-enhanced MRI demonstrates peripheral enhancement of these lesions (Figs. 9.16A to D). In severe disease, the skull base, orbit, and intracranial structures may become involved, best studied with MRI.[91]

Sinus mycetoma: Radiographic imaging is part of the diagnostic criteria for sinus mycetoma ("fungus balls"). Patients may be asymptomatic or have nasal obstructive symptoms. The mycetoma represents a matted collection of fungal hyphae within the sinus, most commonly caused by *Aspergillus fumigatus* or *flavus*. Radiographic findings are similar to allergic fungal sinusitis, but mycetomas do not typically extend into the nasal cavity or multiple sinuses. Three imaging findings are highly suggestive of sinus mycetoma: (1) heterogeneous opacification of a single sinus, (2) scattered radiodense material or microcalcifications, and (3) sclerosis of the surrounding bony wall. The maxillary sinus is most commonly involved, followed by the sphenoid sinus.[93] Additional imaging findings include mucoperiosteal thickening and nasal polyposis. CT is the imaging modality of choice, essential to surgical management, with a diagnostic sensitivity of 62% and specificity of 99%.[94] Scattered hypointensities on T1 and T2W MRI may represent areas of concentrated manganese, iron, and calcium in the mycetoma.[61] Fortunately, sinus mycetoma does not progress to invasive sinusitis and is managed surgically if symptomatic.

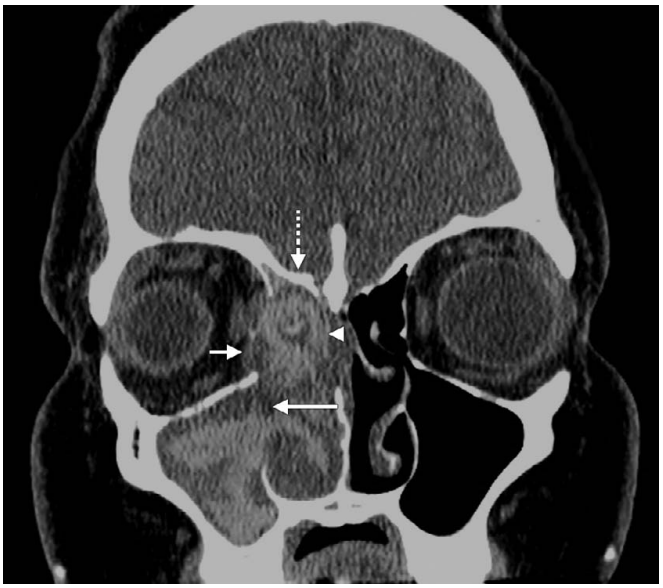


Fig. 9.17: Invasive fungal sinusitis. Coronal computed tomography (CT) demonstrates fungal sinusitis with mixed density material widening the right osteomeatal unit (long arrow), extension into the nasal cavity, and invasion of the ethmoid sinus (arrow head) and right orbit (short arrow). Thickening of the right fovea ethmoidalis (dashed arrow) is due to chronic inflammation.

Invasive Fungal Sinusitis

Fulminant IFS: It is caused by numerous fungi, including *Zygomycetes*, *Mucor*, and *Aspergillus*. IFS typically affects immunocompromised hosts such as patients with diabetes or neutropenia. Fungal hyphae invade tissues, bone, and vascular structures, resulting in vasculitis, thrombosis, and tissue necrosis. Emergency surgical management is indicated to debride infected tissues until healthy tissue is visualized. Without urgent therapy, rapidly progressive disease may be fatal within days. Pathology demonstrating vascular and tissue invasion provides the final diagnosis. Short follow-up, serial imaging after treatment is indicated to monitor disease recurrence.

Radiographic evidence of sinusitis must be demonstrated to meet the diagnostic criteria for IFS.[90] Facial swelling, mucosoperiosteal thickening, and soft-tissue masses within the sinuses and nasal cavity may be demonstrated on CT and MRI. Typically, sinus involvement is unilateral; bony erosion with intracranial and intraorbital extension may be visualized (Fig. 9.17). However, these findings may be absent or subtle in early stages; therefore, nasal endoscopy and biopsy are essential to the diagnosis.[95] Vascular involvement progresses rapidly, and CST, carotid invasion, and cerebral infarction may be identified on imaging. Leptomeningeal enhancement is an ominous sign, suggesting impending intracranial extension, a critical predictor of patient prognosis.[96] In addition to infarction, other intracranial MRI findings include ring-enhancing abscess and cerebritis. Intracranial granulomas appear hypointense on T1 and T2W MRI and enhance minimally with intravenous contrast administration. Orbital findings include proptosis and inflammatory changes of the orbital fat and extraocular muscles. Bony invasion is best studied with CT; MRI is superior in the assessment of intracranial and intraorbital disease extension.[97]

Granulomatous IFS: It is caused by *Aspergillus flavus*, commonly found in patients from Sudan and Southeast Asia. The characteristic pathologic finding is noncaseating granulomas. Surgical management and antifungal medications are essential to halt disease progression, which may involve critical structures such as the orbit and brain. Radiographic findings are similar to chronic IFS. In addition to findings of sinusitis, invasive soft tissue masses may be demonstrated, eroding bone and adjacent structures. The radiographic appearance may mimic malignant neoplasm; therefore, tissue diagnosis is essential.[98]

Chronic IFS: It follows a more indolent course than IFS, but clinical outcomes can be equally devastating if therapy is not initiated. Soft tissue masses of the paranasal sinuses may extend to involve the orbit, intracranial structures,

cavernous sinus, PPF, palate, and cribiform plate. The radiographic appearance may mimic a malignant process.[99] On CT bone window images, mottled sinus margins may be visualized. Mucosal thickening and sinus opacification may also be demonstrated. Normal fat planes surrounding the sinuses are obliterated when disease extends beyond the sinus. If disease extends intracranially, thrombosis, cerebritis, CST, and mycotic aneurysms may result. Aggressive therapy is required, as disease may progress and recurrence is common after treatment.[98]

Noninfectious Sinonasal Granulomatous Diseases

Autoimmune Diseases: Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare autoimmune process resulting in necrotizing granulomatous vasculitis primarily affecting medium-sized vessels. The classical clinical triad is upper airway, lung, and renal manifestations, but other organ systems may become involved. Diagnosis is made on tissue biopsy or by positive serological testing for antineutrophil cytoplasmic bodies. Treatment primarily involves immunosuppressive medication.

Sinonasal imaging is nonspecific in GPA but may be helpful in managing affected patients and suggesting diagnosis at an early stage. Typically, the appearance is similar to chronic rhinosinusitis. CT findings demonstrate neo-osteogenesis and inflammatory findings including mucosal thickening, sinus opacification, and mucocele formation. Punctate bony demineralization surrounding perforating vessels, mainly in the septum and sparing the ethmoid labyrinth is characteristic of a vasculitic process. In addition, periantral fat obliteration, septal perforation, and nodular-appearing mucosa are highly suggestive of the diagnosis.[100] MRI demonstrates non-specific inflammatory findings of the paranasal sinuses, with thickening of the paranasal sinus mucosa, evidenced by high-intensity lesions on T2W MRI occurring in most patients. Mucosal surface granulomas are visible as low-intensity lesions on T1 and T2W images.[101] The differential diagnosis of GPA includes nasal T or natural killer (NK) cell lymphomas, as these midline destructive lesions frequently demonstrate similar radiographic findings.[102]

Chest radiography, an essential study even in asymptomatic patients, may contribute to earlier diagnosis. Infiltrates, hilar adenopathy, cavitary lesions, and pleural opacity may be evident.[103]

Autoimmune Diseases: Churg–Strauss Syndrome

Churg–Strauss syndrome (CSS) is a rare disease notable for peripheral blood eosinophilia, systemic vasculitis, and asthma. Patients develop sinonasal manifestations in the majority of cases, with allergic rhinitis, and nasal polyposis. Diagnosis is based on a constellation of clinical and laboratory findings.[104] Prognosis is generally good and therapy involves corticosteroids; immunosuppressive chemotherapeutics are added in severe cases.

Radiographic studies of the nose and paranasal sinuses are frequently performed in patients with CSS, as paranasal sinus disease is a criterion for diagnosis. CT and MRI in CSS demonstrate inflammatory findings consistent with allergic rhinitis, chronic rhinosinusitis, and nasal polyposis. These findings are nonspecific, but imaging may aid in diagnosis. Rarely, orbital involvement manifests as orbital inflammatory pseudotumor, retinal artery occlusion, or optic neuropathy.[105,106]

Traumatic Causes of Sinonasal Granulomatous Disease

Cocaine-Induced Midline Destructive Lesions

Intranasal cocaine use has significant vasoconstrictive effects on mucosal surfaces and may result in tissue destruction. Severe cases resemble Wegener's granulomatosis and nasal T- or NK cell lymphomas. Diagnosis is made by careful history, physical examination, and diagnostic testing including biopsy of affected tissue to rule out similar appearing diseases. Sinonasal imaging reveals the extent of disease. In suspected cases, NECT consistently demonstrates septal perforation (Fig. 9.18). Bony and soft tissue destruction occurs, including erosion of inferior turbinates, the orbital walls, and hard palate. Destruction of the medial maxillary wall, lateral nasal wall, superior turbinates, and floor of the nasal cavity may also be visualized. MRI findings include inflammatory changes and abnormal signal within nasal or paranasal sinus mucosal surfaces. If cocaine abuse persists, destruction may progress to erode the entire palate and anterior skull base.[107]

Giant Cell Reparative Granuloma

Giant cell reparative granuloma (GCRG) is a benign, expansile, lesion believed to form as a result of post-traumatic intraosseus hemorrhage. These lesions frequently present in the mandible but can occur in the paranasal sinsuses

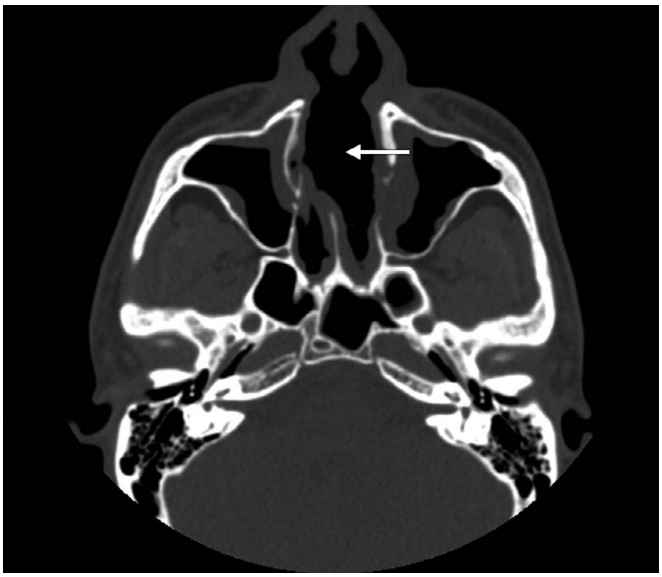


Fig. 9.18: Nasal septum perforation. Axial computed tomography demonstrates a mostly absent nasal septum (larrow) and inflammatory mucosal thickening of the maxillary sinuses in a patient with history of cocaine abuse.

and should be considered in the diagnosis of a sinonasal mass. Surgical resection or curettage is the primary treatment; radiation is performed in cases with difficult surgical access.

CT and MRI are essential tests in the evaluation of sinonasal masses. The radiographic appearance of GCRG is variable; lesions may be destructive or well-defined encapsulated masses. On CT, lesions are osteolytic and either homogenous or heterogenous expansile masses. On MRI, lesions appear isointense to muscle on T1W images and enhance after contrast administration. Fibrous septae and multicystic components may be visible on MRI, but lesions may also appear nonseptated and unilocular. CT is the preferred modality for surgical planning due to its superior definition of margins.[108-110]

Cholesterol Granuloma

Typically, cholesterol granulomas (CGs) are benign lesions in the temporal bone, but involvement of paranasal sinuses has been reported.[111-113] Symptoms result as the lesion expands. Trauma resulting in intraosseous hemorrhage is the presumed etiology, similar to GCRGs. Imaging is essential to diagnosis and management; CT findings may mimic chronic rhinosinusitis, with mucosal thickening and sinus opacification. Hypodense masses, osseous erosion, or sinus expansion with bony remodeling may occur. MRI differentiates these cystic lesions from mucoceles, which are also expansile lesions. Characteristically, CGs appear bright on T1W and T2W images. Hemosiderin deposition results in low signal intensity on MRI.[114] Diagnosis is confirmed by surgical resection or biopsy. While treatment is primarily surgical, serial imaging may be used to follow patients with asymptomatic or difficult to access lesions.

Neoplastic Causes of Sinonasal Granulomatous Disease

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH), commonly known as histiocytosis X, is a rare granulomatous disease and neoplastic process that affects the pediatric population. LCH is a multisystem disease, but head and neck manifestations occur in most patients. Head and neck imaging plays a limited role in management of these patients. Temporal bone involvement may be evidenced by granulation tissue in the external auditory canal or tympanic membrane perforation. Lesions of the mandible, oral ulcers, and cervical lymphadenopathy may also be visualized. Nose and paranasal sinus involvement is rare, but bony involvement of the maxilla may present with obstruction of the nasal passages and facial swelling. Lytic bony lesions without surrounding sclerosis may be demonstrated on CT. Lesions on MRI demonstrate contrast enhancement and are isointense to muscle on T2W imaging. There is a lack of surrounding peripheral edema.[115] If the diagnosis of LCH is suspected, a full skeletal survey should be performed as other bony structures may be involved.[116]

Rosai-Dorfman Disease

Rosai-Dorfman Disease, also known as sinus histiocytosis with massive lymphadenopathy, is a benign progressive process that affects children and adolescents. Patients usually present with painless, enlarging cervical lymphadenopathy. CT defines the extent of sinus involvement, which typically includes the maxillary and ethmoid sinuses, but extensive paranasal sinus inflammation may occur. The most common finding on imaging studies is enlarged cervical lymph nodes, followed by paranasal sinus involvement. Mass lesions, hypertrophy, and cystic changes may be visualized in the salivary glands. On CT and MRI, lesions enhance with contrast; they are isointense to muscle on T1W MRI and hypointense to muscle on T2W imaging.[117]

Idiopathic Causes of Sinonasal Granulomatous Disease

Sarcoidosis

Sarcoidosis is a well-described, multiorgan inflammatory disorder of unknown etiology. Classically, patients present with pulmonary disease; the nose and paranasal sinuses are occasionally affected. Imaging performed in cases of suspected sinonasal involvement demonstrates findings similar to chronic rhinosinusitis. CT demonstrates mucosal thickening or nodularity, sinus opacification, turbinate hypertrophy, osteosclerosis, and cartilage or bone destruction. Septal perforation may be present. On MRI, mucosal nodularity and inflammatory findings may be better visualized.[118] Other head and neck structures affected include the lacrimal glands, salivary glands, cervical lymph nodes, larynx, orbits, and cranial nerves (Fig. 9.19).

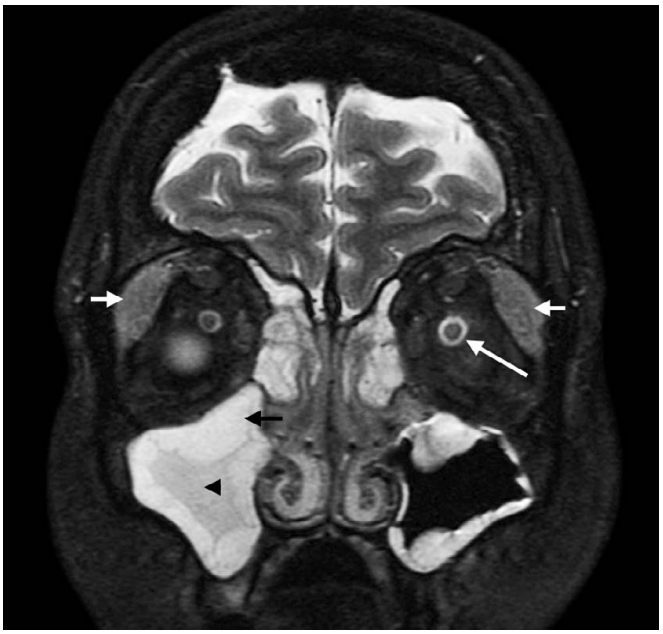


Fig. 9.19: Sinonasal sarcoid and optic neuritis. Coronal T2W magnetic resonance imaging shows right maxillary sinus mucosal thickening (black arrow) and fluid (black arrowhead). The left optic nerve is enlarged and edematous (long white arrow). Bilateral lacrimal gland involvement is noted (short white arrows) due to diffuse infiltration.
Courtesy: Dr Laurie Sanchez, Newark, NJ, USA.

CONGENITAL MIDLINE NASAL LESIONS

Congenital midline nasal lesions are rare, with an incidence of one in every 20,000 to 40,000 births, and male predominance.[119-123] These entities include nasal dermoids (NDs), gliomas, and encephaloceles. NDs are encountered most frequently.[119,120,122-124] The pathogenesis of these congenital malformations may involve the presence of ectopic neuroectoderm in the frontonasal region or lack of dural regression, persisting through the embryologic foramen cecum.[28,120,121,123]

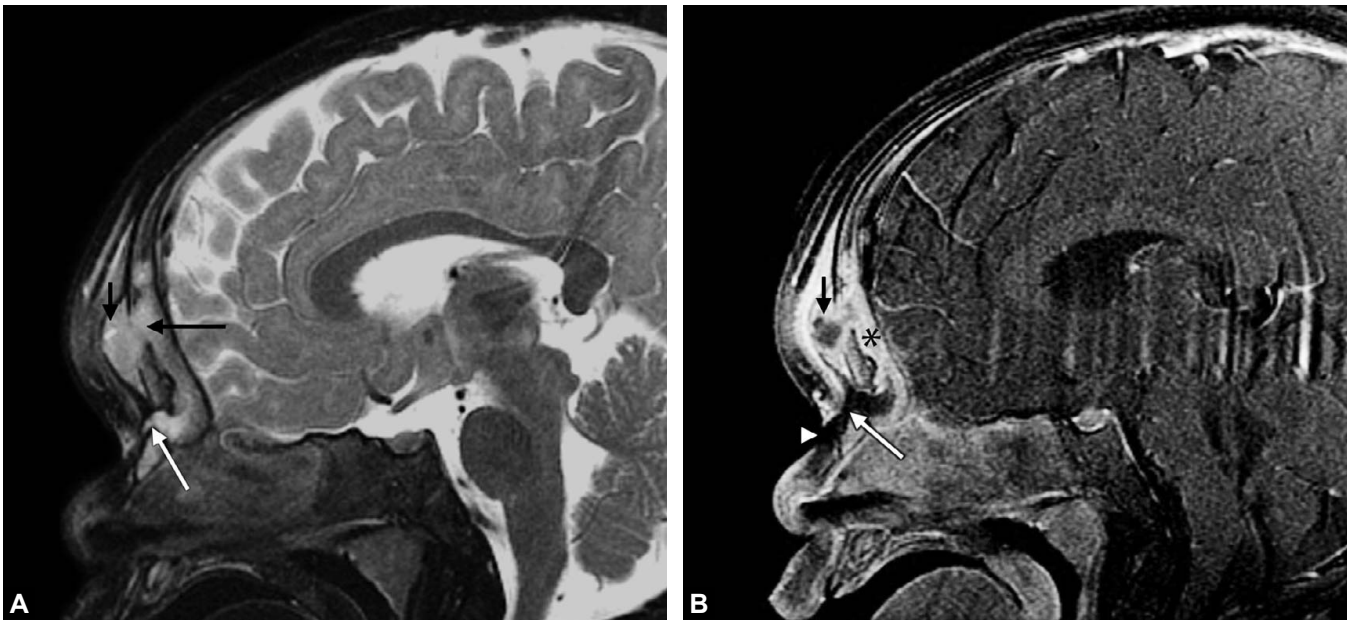
Nasal Dermoid

Nasal dermoids, or dermoid sinus cysts, account for 1–3% of all dermoid cysts, and 4–12% of cervicofacial dermoids.[119,120,122] NDs may present as discrete cystic masses, sinus tracts, pits, fenestrae or fistulas opening into the midline dorsum of the nose between the glabella and columella.[119,120,124,125] Approximately, 20% of cases demonstrate intracranial extension as dermoid or epidermoid cysts.[126]

Lesions are detected during infancy as noncompressible, nonpulsatile masses that do not transilluminate or enlarge with jugular venous compression (Furstenberg test).[120,123] NDs contain dermal appendages including hair and sebaceous glands, presenting as hair protruding through a punctum or sebaceous discharge from an ostium.[120,125]

Early treatment is recommended to avoid permanent anatomic deformity. Given the potential for intracranial involvement, it is important to consider surgical infectious complications including meningitis, cerebral abscess, CST, and periorbital cellulitis.[120] Complete surgical resection constitutes definitive treatment; high recurrence rates are reported in cases of incomplete resection.

CT and MRI are gold standard imaging modalities for preoperative evaluation of NDs,[124] delineating lesion extent and presence of intracranial components. CT evidence of intracranial extension includes a bifid crista galli, deformed cribiform plate, and enlargement of the foramen cecum.[120,124] Of note, ossification of the crista galli and cribiform plate is not present at birth; by 24 months of age, approximately 84% of the anterior skull base is ossified.[127] Once intracranial disease is suspected, MRI is recommended since false-positive CT results have been reported.[120,124] MRI findings include increased T2W fluid signal within the sinus tract and epidermoid or dermoid components. Decreased T1W signal is noted within the tract and epidermoid component; increased T1W signal is seen within dermoid components. Diffusion-weighted sequences demonstrate restriction within epidermoid



Figs. 9.20A and B: Dermal sinuses in a child. Sagittal T2W magnetic resonance imaging (MRI) (A) depicts fluid signal within a sinus tract extending through the anterior skull base to the skin at the nasal bridge (white arrow). Abnormal subgaleal edema (short black arrow) extends to involve the frontal bone (long black arrow). Sagittal contrast-enhanced, fat-saturated T1W MRI (B) shows low signal within the dermal sinus tract (white arrow) to the skin (white arrowhead). Contrast-enhanced imaging defines the subgaleal collection as an abscess (short black arrow) as well as demonstrating abnormally thickened, enhancing dura (asterisk).

components. Susceptibility artifact at the skull base may distort signal characteristics.[126] Sinus tracts provide pathways for infection; in such cases, contrast-enhanced T1W imaging is useful (Figs. 9.20A and B).

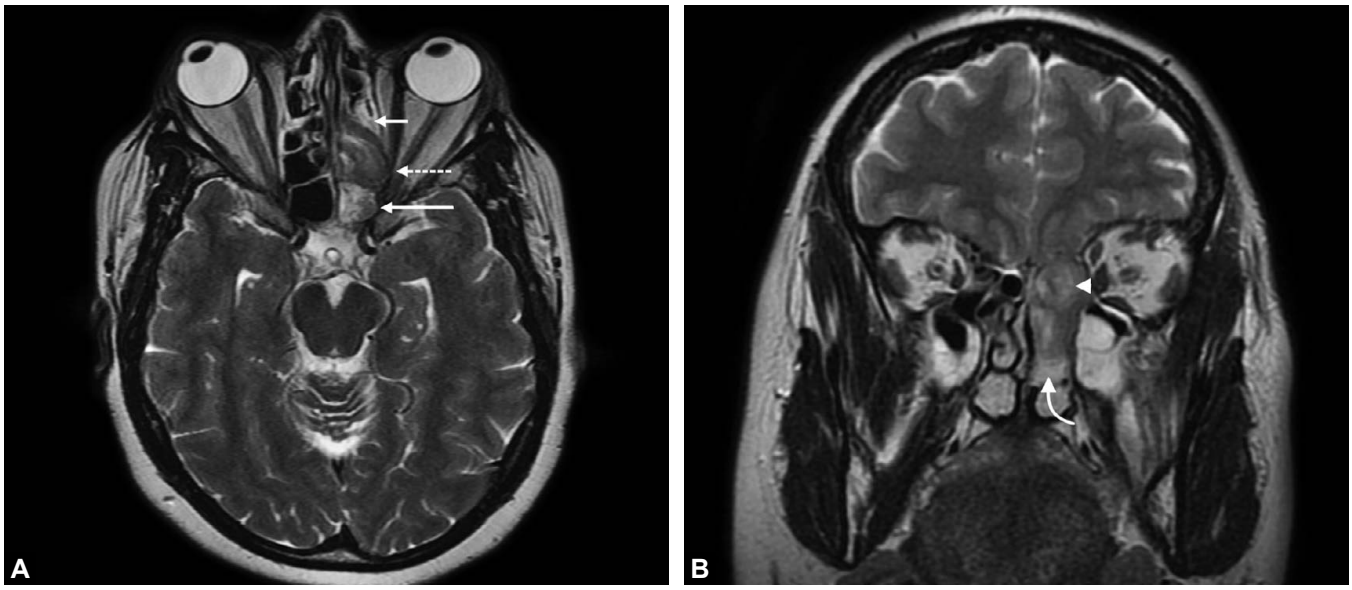
Encephalocele

Encephaloceles usually present in infancy as blue, compressible, pulsatile masses that transilluminate, enlarge with crying, valsalva, or jugular venous compression (Furstenberg test).[121,123] They commonly occur in the occipital region (approximately 75%)[121] and less commonly in the frontoethmoidal, parietal, and sphenoidal regions[128] (Figs. 9.21A and B). Hypertelorism and a broad nose are commonly associated craniofacial anomalies.[128] Treatment requires a combined intracranial/extracranial surgical approach. Potential postoperative complications include CSF rhinorrhea and infection.[121,123,129]

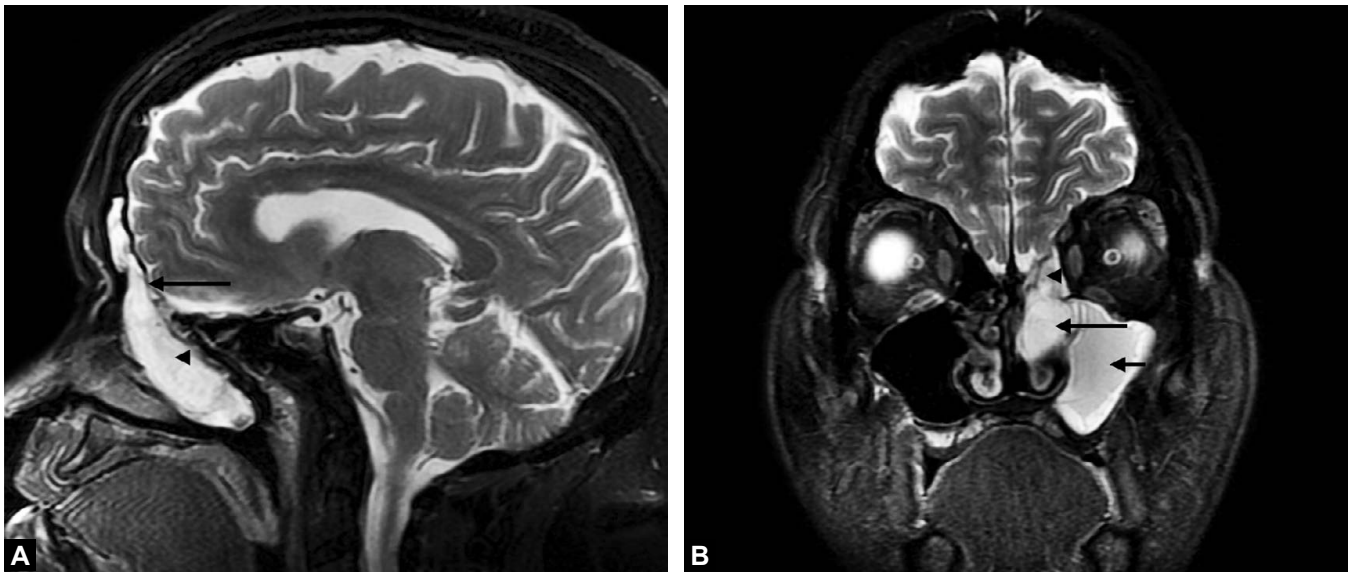
Frontoethmoidal cephaloceles are herniations of meninges, with or without brain parenchyma, through defects in the foramen cecum, lacrimal/frontal process of maxillary bone or an unobliterated fonticulus frontalis. They are classified on the basis of the tissue content: (1) meningoceles contain only meninges (Figs. 9.22A and B); (2) meningoencephaloceles contain meninges and neural tissue; (3) meningoencephalocystoceles contain meninges, neural tissue, and ventricular system tissue.[121] Unlike nasal glioma, an encephalocele contains T2W CSF signal surrounding the lesion, inferring a communication with the subarachnoid space. In the presence of gliosis, distinguishing ND from encephalocele may be difficult, due to altered T2W brain signal.[126]

Nasal Glioma

Nasal gliomas represent dysplastic neurogenic tissue within encephaloceles, sequestered from the brain and cranial vault early in gestation.[121,124] Sixty percent of NGs are extranasal, 30% are intranasal, and 10% have combined elements.[121,123,129] The presenting age of NGs is variable, dependant on location and associated clinical symptoms. NGs are solid, noncompressible, nonpulsatile masses that do not transilluminate or enlarge with jugular venous compression (Furstenberg test).[121,123,124] Intranasal NGs must be differentiated from nasal polyps since both present as solid intranasal lesions causing unilateral nasal cavity obstruction. Of note, 10–25% of NGs may demonstrate a fibrous stalk extending to the skull base with an underlying bony defect.[121,124,130] Surgical excision is the preferred treatment. At surgery, the cephalic end of



Figs. 9.21A and B: Meningoencephalocele. Axial and coronal (A and B) T2W magnetic resonance imaging demonstrate an inferior-frontal meningoencephalocele containing neural tissue extending through the left cribriform plate (arrowhead), causing lateral bowing of the left lamina papyracea and medial rectus muscle (dashed arrow). CSF within the distal portion of the meningeal sac is seen within the nasal cavity (curved arrow). Secondary obstruction of the adjacent sphenoid (long white arrow) and ethmoid air cells (short white arrow) is noted.



Figs. 9.22A and B: Paranasal sinus meningocele. Sagittal T2W magnetic resonance imaging (MRI) (A) shows a fluid–filled meningocele extending into the frontal sinus (long arrow) and nasal cavity (arrowhead). Coronal T2W MRI (B) demonstrates a cerebrospinal fluid filled mass herniating from the left anterior cranial fossa into the ethmoid sinus (arrowhead), nasal cavity (long arrow) and obstructing the maxillary sinus (short arrow).

the extracranial fibrous stalk should be analyzed histologically for the presence of neurogenic elements.[121,123] If present, additional intracranial surgical treatment is indicated, since tracking of infection along the fibrous stalk may result in meningitis.[126]

Choanal Atresia

Choanal atresia (CA) is a congenital disorder in which one or both nasal passages are obstructed. CA occurs in one of 5000 to 8000 births.[131-135] There is a 2:1 female to male

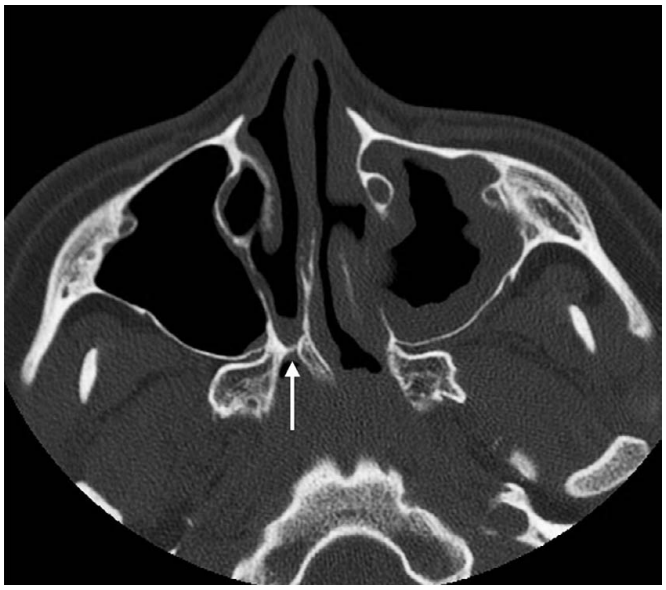


Fig. 9.23: Choanal atresia. Axial computed tomography demonstrates bony choanal atresia (arrow) resulting in an air–fluid level in the posterior right nasal cavity.
Courtesy: Dr Laurie Sanchez, Newark, NJ, USA.

incidence.[26,131,133,135-137] Unilateral CA is commonly found on the right side.[131,133] Up to 90% of CAs are bony and 10% are membranous; however, recent studies suggest that a mixed type is more common than either type alone.[134,136]

CA is diagnosed in the neonatal period since infants are obligate mouth breathers. Respiration becomes difficult during feeding, when the oral airway is closed. Bilateral CA is less common, presenting as cyanosis shortly after birth. The airway is initially protected with an oral airway followed by surgery. Prior to intervention, the infant instinctively mitigates respiratory distress by cyclical crying, favoring oral respiration.

The diagnosis of CA, made clinically by the inability to pass a nasogastric tube through the nasal cavity, is confirmed with imaging. After suctioning of the nasal passage to clear fluids and administering decongestant nose drops, CT is the imaging modality of choice, since it is rapid, noninvasive, and clearly delineates the anatomy in multiple planes.[132,133] CT does not require oral contrast and has supplanted nasopharyngograms, avoiding risk of aspiration.[138] The anatomic abnormalities demonstrated on CT include narrowing of the nasal chamber, bony, or membranous obstruction at the posterior choana, lateral impingement by the pterygoid plates, and an abnormally thickened vomer[134,138,139] (Fig. 9.23).

Thorough evaluation for other congenital anomalies should be pursued as CA is associated with achondroplasia, Crouzon syndrome, fetal alcohol syndrome, and CHARGE syndrome.[131,132,136,138,140]

Hypoplasia of the Paranasal Sinuses

Hypoplasia of the paranasal sinuses has been identified in numerous medical conditions. The most commonly associated congenital diseases include congenital sinus hypoplasia, hypothyroidism, Kartagener's syndrome (KS), fibrous dysplasia (FD), sickle cell disease, thalassemia, and Down syndrome (DS).

Congenital Paranasal Sinus Hypoplasia

Congenital hypoplasia (CH) of the paranasal sinuses is a rare condition, involving the frontal, maxillary, and seldomly, the sphenoid sinuses.[141-144] Awareness of CH is important since infection or neoplasm of the paranasal sinuses is commonly misdiagnosed.[143,144]

Hypoplasia of one or both frontal sinuses is more common than complete agenesis. Since the right and left frontal sinuses develop independently, asymmetry is common.[145,146] The incidence of bilateral absence of the frontal sinuses is 3–10%.[145,146]

The incidence of maxillary sinus hypoplasia (MSH) is approximately 10%.[141,147,148] MSH classification, proposed by Bolger et al., divides MSH into three distinct patterns (Types I–III) of increasing levels of severity.[149,150]

Sphenoid sinus hypoplasia and agenesis are extremely uncommon (*see* Fig. 9.8A). The degree of pneumatization of the sphenoid sinus is described by three categories: (1) conchal or fetal type, (2) presphenoid, and (3) postsphenoid (present in 90% of cases).[141,142] Complete agenesis of the sphenoid sinus has been reported in 1–1.5% of the population.[141,142]

Congenital Hypothyroidism

Congenital hypothyroidism is the most common childhood endocrine abnormality, with a prevalence of approximately 1 in 4000 births.[151-153] Hypothyroidism results in deficient secretion of thyroid hormone, thyroxin (T_4), which plays a critical role in mental and physical development, and bony maturation.

There are endemic, genetic, and sporadic types of congenital hypothyroidism. Endemic congenital hypothyroidism, the most common type of congenital hypothyroidism, is related to an iodine deficient diet.[154] Iodine is

essential to the production of thyroid hormones. Genetic and sporadic forms of congenital hypothyroidism result from abnormal thyroid gland development or function. Ectopic thyroid tissue, often at the tongue base (lingual thyroid), is suspected when the thyroid is hypoplastic.

Imaging findings of congenital hypothyroidism are related to delayed bony maturation, including hypoplasia of the nasal bones and decreased pneumatization and/or hypoplasia of the paranasal sinuses.[151,155]

Early diagnosis with prompt thyroid replacement therapy has nearly eradicated all types of congenital hypothyroidism within developed countries.[151]

Primary Ciliary Dyskinesia and Kartagener's Syndrome

Primary ciliary dyskinesia (PCD), also known as immotile ciliary syndrome, is a rare autosomal recessive disorder resulting in ciliary dysfunction. The abnormality is related to absence or dysfunction of the dynein arms, the bridges between adjacent ciliary filaments responsible for movement of cilia and flagella.[156,157] This syndrome affects the cilia lining the respiratory tract, sinuses, Eustachian tubes, middle ears, and fallopian tubes. Impairment of ciliary motility results in poor mucociliary clearance, leading to chronic infections such as chronic bronchitis, otitis, and sinusitis.[158]

KS, a related disorder, is a triad of situs inversus, bronchiectasis, and chronic sinusitis. The inheritance of KS, like PCD, is autosomal recessive. Diagnosis of this hereditary disease is made in early childhood.[159]

Patients with KS frequently demonstrate underpneumatization of the paranasal sinuses, including hypoplasia or aplasia of the frontal sinus, and incomplete development of the mastoid air cells.[158] Early conservative treatment of respiratory infections reduces the occurrence of severe bronchiectasis and hospital admissions.[158] With advanced pulmonary involvement, segmental lung resections or lobectomies are occasionally required. Despite recurrent respiratory tract infections, life expectancy in KS is normal.[158,159]

Hemolytic Anemia

Hemolytic anemia (HA) may be acquired or inherited. Two forms of inherited HA are sickle cell disease and thalassemia. The pathogenesis of these HAs relates to defects in hemoglobin production resulting in compensatory extramedullary hematopoiesis (EH).[160-163]

EH, commonly seen in the liver, spleen, and lymph nodes,[160,162] is rarely demonstrated within the paranasal sinuses. Most frequently, the maxillary and ethmoid sinuses are involved followed by the sphenoid sinus.[160,162] In these rare instances, CT or MRI of the paranasal sinuses exhibits expansion of the sinuses with soft tissue opacification, leading to decreased sinus volume and obliteration of airspaces.[160,161,163,164] Other radiographic findings include paranasal sinus underpneumatization, particularly the maxillary antra, and hypoplastic or absent sinuses.[165,166]

Clinically, patients with paranasal sinus EH present with nasal obstruction, headache, facial pain/pressure, and snoring.[160-162] Treatment decisions must balance the theoretical risk of removing a vital part of the patient's functioning hematopoietic tissue, with the benefit of alleviating the patient's clinical symptoms.[161]

Down Syndrome

Down syndrome, a genetic disorder caused by trisomy of chromosome 21, has an incidence of approximately 1 in 691 births, making it the most common genetic condition.[167] Advancements in medical and surgical treatment have increased life expectancy. Given the high prevalence of DS, and prolonged life expectancy, knowledge of associated comorbidities and treatment is important.

The characteristic midface hypoplasia in patients with DS results in a narrowed nasal cavity, contracted nasopharynx, and dysplastic paranasal sinuses. The paranasal sinuses in these patients may be aplastic (most commonly, the frontal sinus)[168] and/or hypoplastic. The frontal, maxillary, and sphenoid sinuses demonstrate underpneumatization.[168-172] These anatomic factors combined with an underlying immune dysfunction increase the incidence of rhinorrhea, nasal obstruction, and sinusitis.[173-176] Variant sinonasal anatomy predisposes to obstructive sleep apnea (OSA) in 45–79%.[177,178] Additional factors contributing to OSA include micrognathia, macroglossia, glossoptosis, adenoidal and palatine tonsillar hypertrophy, obesity, and muscular hypotonia.[169,177,178]

IMAGING SINONASAL NEOPLASMS

Overview: The Radiologist's Role

Symptoms of sinonasal tumor are often nonspecific, especially in the early stages of disease when timely intervention is critical. Symptoms include dull, often unilateral

facial pain, nasal discharge, epistaxis, and obstruction.[179] Because symptoms are nonspecific, imaging helps discern inflammatory from neoplastic etiologies.

Once the etiology of symptoms is known to be neoplastic, the radiologist helps the clinician prognosticate and formulate a treatment plan by assessing whether the tumor has benign or malignant imaging features, and determining the course and extent of tumor spread. Although endoscopy is useful in evaluating tumor spread, CT and/or MRI are necessary to assess involvement of deeper structures not easily accessed by endoscopy. Imaging plays an important role in the post-treatment follow-up and management of sinonasal neoplasms. CT, MRI, and PET scanning are used to evaluate treatment response and tumor recurrence.

Radiology versus Pathology

Radiologists and pathologists play complementary roles in the assessment of sinonasal tumors. On presurgical imaging, radiologists should describe whether the process is inflammatory or neoplastic, aggressive or benign, tumor extent and routes of spread, and the presence of bony destruction or orbital invasion.

Radiologists are not expected to distinguish among types of sinonasal malignancies, since many have similar radiographic characteristics.[180] A pathologist's input is required for establishing diagnosis.

Differentiating between Tumor and Inflammation

The most accurate imaging modality for differentiating tumor from inflammation is T2W MRI. In one study, 95% of sinonasal tumors demonstrated intermediate signal on T2W MRI, whereas 100% of sinonasal inflammatory conditions demonstrated high T2W signal. Two notable exceptions to this "rule" are minor salivary gland tumors and neuromas.[180]

Direct tumor spread superiorly, through the cribriform plate or orbital floor, may cause dural thickening in the anterior cranial fossa. A diagnostic quandary arises as inflammation can also cause mild dural thickening, usually < 5 mm in thickness.[181] Tumor spread to the anterior cranial fossa has grave prognostic implications; therefore, frozen section histology is recommended to diagnose tumor versus inflammation.[179]

Patterns of Tumor Spread

Direct Extension

Direct tumor extension traversing the cribriform plate or orbital floor to infiltrate the anterior cranial fossa is well visualized on T1W postcontrast, fat-suppressed sequences.[181] Direct tumor extension may also occur in the inferior and inferolateral directions, resulting in tumor involvement of the hard palate and buccal space, respectively.

Perineural Spread

Spread of sinonasal neoplasms often involves the PPF. Once tumor reaches the PPF, it gains easy passage to the orbit, nasopharynx, nasal cavity, oral cavity, cavernous sinus, sphenoid sinus, and middle cranial fossa.

Understanding the anatomy of the PPF and adjacent structures is critical to appreciating the pathways by which paranasal sinus pathology spreads. The superior aspect of the frontal sinus borders, the anterior margin of the anterior cranial fossa. The cribiform plate borders the superior nasal cavity, and the fovea ethmoidalis forms the superior aspect of the ethmoid sinus. The sphenoid sinuses are defined superiorly by the planum sphenoidale and posteriorly by the tuberculum sellae. The posterior aspect of the sphenoid sinus is defined by the clivus, which, in turn, serves as a boundary for the posterior cranial fossa. Posterior and lateral to the sphenoid sinus are the cavernous venous sinuses. The foramen rotundum lies along the anterior and medial margin of the greater wing of the sphenoid skull base, also referred to as the middle cranial fossa. The cavernous segment of the internal carotid artery abuts the posterolateral aspect of the sphenoid sinus. Of particular importance, the PPF lies anterior and lateral to the sphenoid sinuses, posterior to the maxillary sinuses and lateral to the posterior ethmoid sinuses. Direct invasion can also occur through any of these structures, leading to intracranial extension of pathology.

The nerves commonly associated with perineural spread (PNS) from the sinuses are the second division of the trigeminal nerve (CNV), and the greater superficial petrosal branch of the facial nerve (CNVII). The PPF is the "hub" for many perineural pathways. One of the main retrograde routes for PNS from the PPF is via the maxillary (V2) branch of the trigeminal nerve into the cavernous sinus, Meckel's cave and ultimately, the brainstem.[182] The V2 branch gives rise to the superior alveolar nerve

supplying sensory innervation to the maxillary sinus, and the palatine nerves innervating the hard and soft palate. A second important pathway of PNS is via the vidian nerve, which becomes the greater superficial petrosal nerve, receiving innervation from the geniculate ganglion of CNVII. The vidian nerve provides parasympathetic innervation to the sphenoid sinus, maxillary sinus, and nasal cavity. The geniculate ganglion provides direct innervation to the ethmoid sinuses. Any neoplasm along these neural pathways may retrogradely spread intracranially or anterogradely spread toward the periphery. For example, tumor reaching Meckel's cave retrogradely may descend along the mandibular (V3) branch of the trigeminal nerve through foramen ovale and to the masticator space. In addition, the close proximity of the greater superficial petrosal nerve to Meckel's cave may lead to adjacent spread and subsequent involvement of trigeminal pathways.[183]

Several findings suggest perineural tumor spread on MR imaging. Enhancement of the nerve may be seen on postcontrast MRI. However, enhancement may also be due to inflammation. Intense enhancement within the PPF, cavernous sinus or Meckel's cave is highly suspicious for PNS of disease. On routine precontrast T1 imaging, fat planes at the extracranial opening of neural foramina are frequently effaced in the presence of tumor, a marker for tumor extension.[184] While T1W images without fat suppression may be helpful in defining tumor involvement within the fat planes, susceptibility artifact at the skull base is notorious for obscuring underlying pathology.[185] Of note, postsurgical changes may alter MRI signal and confound disease recurrence. For example, once the PPF is surgically manipulated, it may demonstrate intense enhancement with loss of normal T1W fat signal indefinitely.[186]

PNS is an important finding for the radiologist to appreciate. The diagnosis of PNS is infrequently made on clinical grounds alone; up to 40% of patients with PNS have no symptoms.[183] When present, PNS places certain diagnoses higher in the differential, in particular, adenoid cystic carcinoma (ACC). Finally, the presence of PNS is a negative prognostic factor due to low success of curative resection.

Orbital Invasion: Implications for Treatment Planning and Prognosis

Orbital invasion, demonstrated on MRI by loss of the normal, curvilinear low-signal periosteum lining the orbit, has critical implications for both treatment planning and prognosis. If extensive, orbital invasion may require orbital exenteration. Orbital extension is a major factor in determining outcome and survival of sinonasal tumor patients.[187] In one retrospective study, the 5-year cure rate for patients with orbital involvement was 17%, with a 10-year survival rate of 2%[187] (Fig. 9.17).

Bone Destruction in Tumor Imaging

Bone destruction is an important finding in tumor imaging. In addition to loss of normal fat signal in the PPF, pterygoid bone destruction bordering the PPF can serve as categorical evidence of PPF involvement. Bone destruction of the cribriform plate may indicate direct tumor extension into the anterior cranial fossa. Destruction of the osseous margins of the skull-base neural foramina, seen best on CT, alerts the radiologist to the presence of perineural tumor spread.

Bone destruction may be associated with poor prognosis. In one study, all patients with pterygoid erosion died within 5-year despite treatment with radical surgery and radiotherapy.[187]

Cerebrospinal Fluid Leaks

CSF leaks may occur in patients with sinonasal neoplasm either as a direct consequence of tumor invading the skull base or iatrogenically, following treatment. Patients can develop CSF leaks after receiving radiotherapy, due to radiation-induced necrosis of the bony skull base or tumor shrinkage, leaving skull base defects exposed. Imaging modalities including CT cisternography (with contrast administered into the CSF via lumbar puncture), mutliplanar T2W MRI sequences, and radionuclide cisternography are useful in localizing CSF leaks and guiding surgical repair.[188]

Carotid Blowout

Carotid blowout is a rare, post-treatment complication in 3–4% of head and neck cancers. Factors increasing the risk of carotid blowout include prior radiotherapy, flap necrosis, wound infection, mucocutaneous fistula formation, and tumor recurrence. Carotid blowout can occur as a rare complication of CT-guided radiofrequency ablation of inoperable head and neck cancers, especially when electrodes are placed close to the carotid artery during ablation.[189] Because of the potential mortality of this complication, radiologists should be vigilant in monitoring findings of "threatened" carotid blowout, such as an

exposed carotid artery surrounded by air, presence of a mucocutaneous fistula, arterial wall irregularity, or pseudoaneurysm. These findings are best seen on CECT and MRI of the neck, CTA of the neck, or catheter angiography. Neurointerventional radiology procedures, including internal carotid artery embolization (carotid takedown) and placement of covered endovascular stents, are gaining popularity as less invasive alternatives to surgery.[190]

Benign Neoplasms

Inverted Papilloma

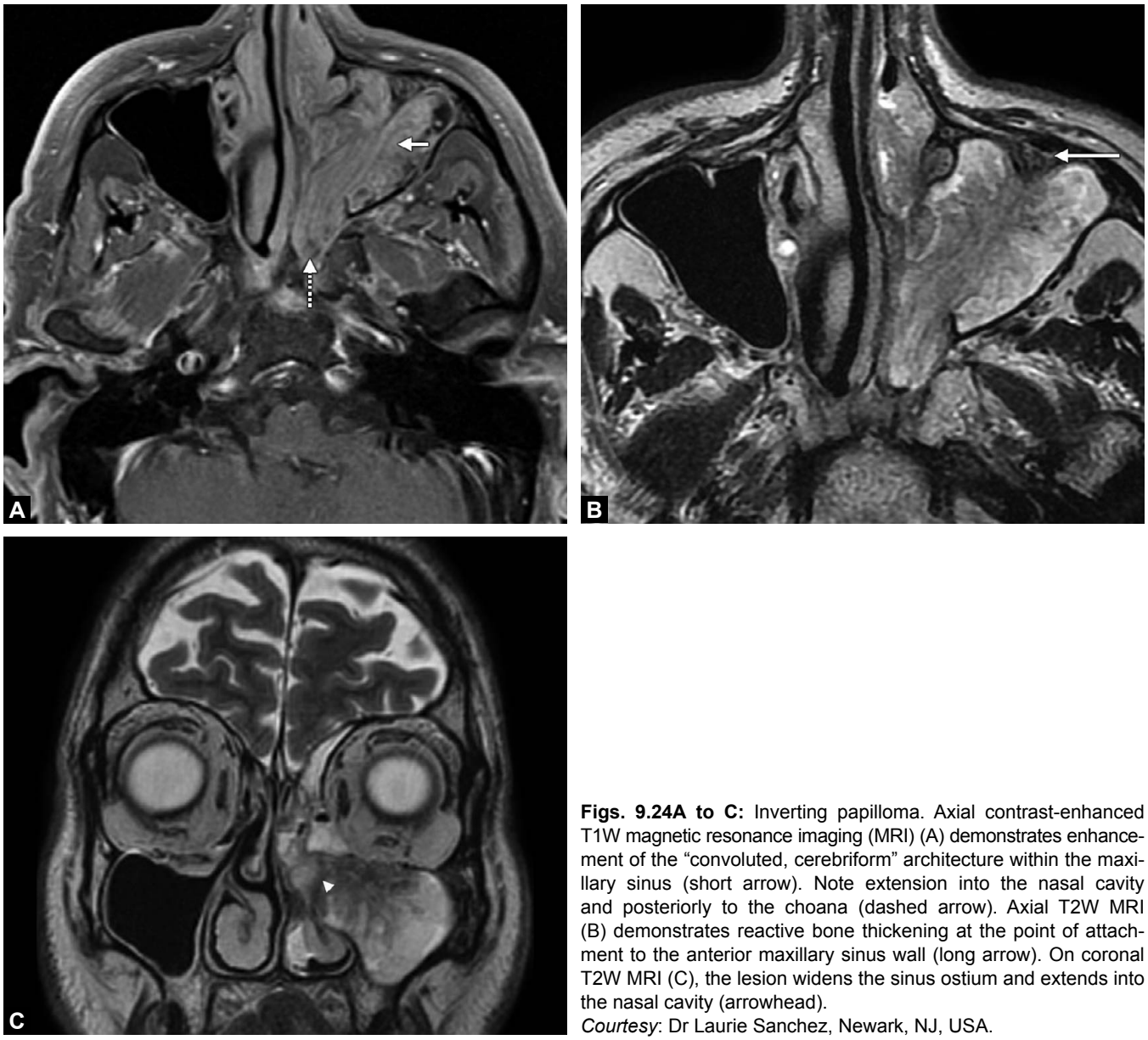
Inverted papilloma is a rare, benign epithelial tumor named for the characteristic pathologic appearance of an intact epithelium involuting into the underlying stroma. Although benign, IPs are locally aggressive and harbor synchronous or metachronous squamous cell carcinoma (SCC) in 3–24% of patients.[191,192] IPs commonly originate from the lateral nasal wall in the region of the middle meatus, near the middle turbinate, with extension to adjacent maxillary and ethmoid sinuses. Frontal and sphenoid sinus extension has been described. The imaging appearance of IPs is nonspecific on CT, as soft tissue density masses with heterogeneous enhancement. Identifying focal hyperostosis at the site of attachment may be seen on CT and MRI. IPs are described as having a "cerebriform pattern" on MRI due to convoluted, hypercellular epithelium, and edematous underlying stroma, which appear hyperintense on T2W sequences. Mild enhancement may be noted[193] (Figs. 9.24A to C). Intracranial extension is rare but documented, even in the absence of coexisting SCC. Common points of intracranial spread are the cribriform plate, fovea ethmoidalis, and orbits.[194]

Juvenile Nasal Angiofibroma

Juvenile nasal angiofibroma (JNA) is a benign, nonencapsulated, slow growing, locally aggressive vascular tumor occurring almost exclusively in male adolescents. Patients present with unilateral nasal obstruction and recurrent epistaxis. Despite benign histology, JNA can be associated with potentially life-threatening complications, including epistaxis or intracranial extension. Imaging assessment includes CECT, contrast-enhanced MRI, and catheter angiography. JNA is a well-defined, intensely enhancing soft tissue mass, originating in the nasal cavity, centered on the sphenopalatine foramen, with sharp, lobulated margins and "finger-like" extensions into multiple adjacent compartments via the PPF in up to 90% of cases.[195] MRI demonstrates flow-related signal void typical of lesion vascularity. T1W and T2W signal is often intermediate and heterogeneous. On MRI, the vessels are often too small to be evaluated by MR angiography. Catheter angiography is diagnostic, demonstrating a hypervascular mass in its typical location. Preoperative embolization reduces intraoperative blood loss. JNAs demonstrate characteristic submucosal spread and early invasion of bone at the pterygoid root and greater wing of the sphenoid bone. Bone invasion manifests as avidly enhancing soft tissue on CT or postcontrast fat-saturated T1W images, distinct from the adjacent fatty marrow signal. From the PPF, JNAs can extend medially into the nasal cavity with associated enlargement/erosion of the sphenopalatine foramen; anteriorly, with characteristic bowing of the maxillary sinus wall; laterally via the pterygomaxillary fissure; superiorly toward the orbital apex via the inferior orbital fissure; and into the middle cranial fossa via foramen rotundum or the vidian canal in 5-20% of cases. Sphenoid, maxillary, and ethmoid involvement is seen in 60%, 43%, and 35%, respectively. Intracranial extension is more likely through "finger-like" projections through foramina rather than frank bony destruction (Figs. 9.25A to D). JNAs have a high rate of persistence/recurrence; follow-up imaging is imperative; CECT or MRI accurately identifies avidly enhancing residual.[196]

Benign Fibro-osseous Lesions

Benign fibro-osseous tumors account for a heterogeneous group of bony and fibrous lesions affecting the paranasal sinuses, including osteoma, ossifying fibroma, and FD. Osteoma, the most frequent benign tumor nasal and paranasal sinus tumor, is frequently an incidental finding. If symptomatic, presentation includes frontal headache in the third to fourth decade with slight male predominance. Eighty percent of osteomas are found in the frontal sinuses with the remaining 20% in maxillary and ethmoid sinuses. Osteomas appear as dense, homogenous, well-circumscribed lesions on CT[197] (Fig. 9.26). For surgery of symptomatic lesions, multiplanar CT reconstructions identify the precise site and origin relative to sinus anatomy. Osteomas progress slowly but may spread intracranially, resulting in a pneumatocele, CSF leak, brain abscess, or subdural empyema. Osteomas demonstrate hypointense

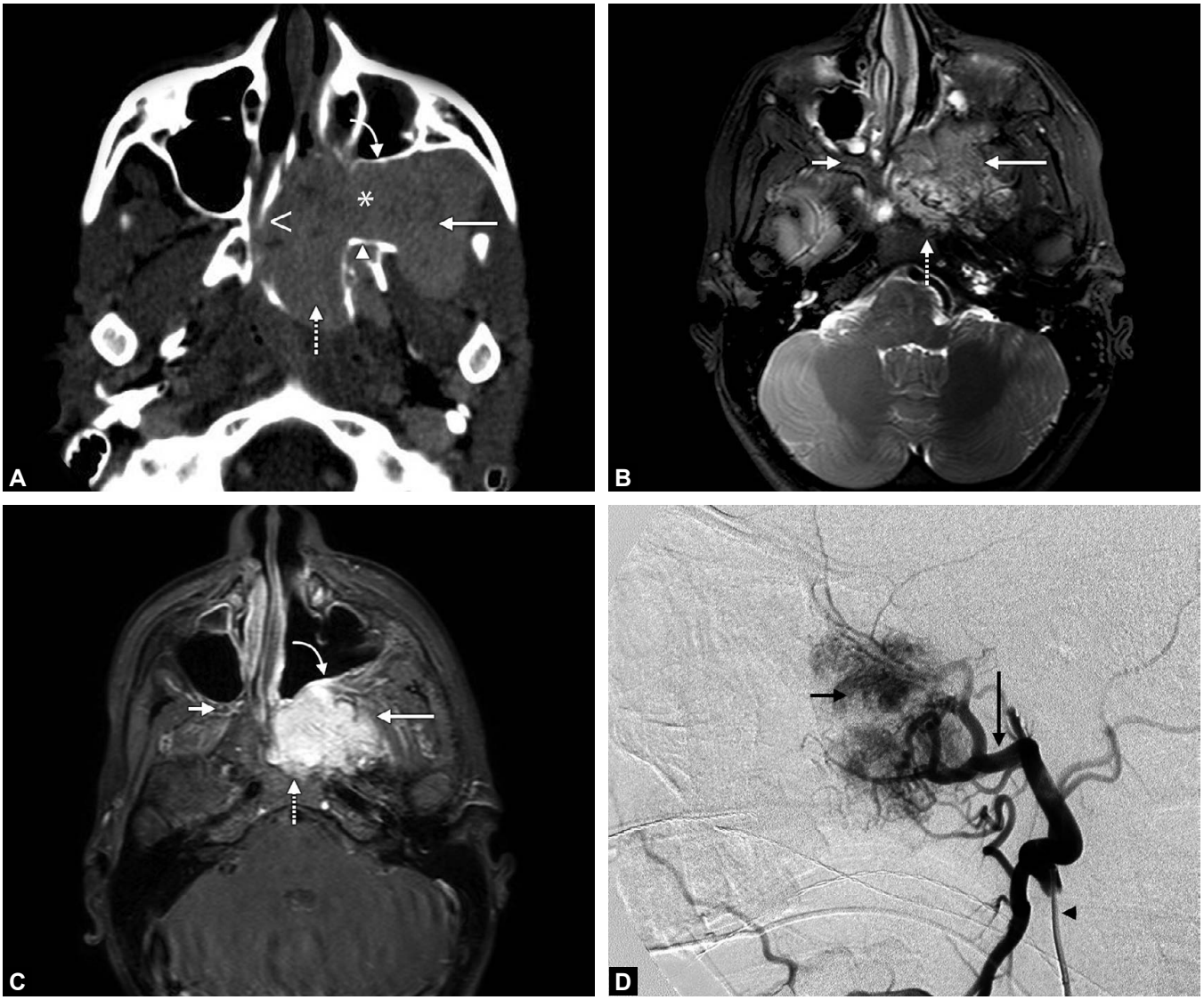


Figs. 9.24A to C: Inverting papilloma. Axial contrast-enhanced T1W magnetic resonance imaging (MRI) (A) demonstrates enhancement of the "convoluted, cerebriform" architecture within the maxillary sinus (short arrow). Note extension into the nasal cavity and posteriorly to the choana (dashed arrow). Axial T2W MRI (B) demonstrates reactive bone thickening at the point of attachment to the anterior maxillary sinus wall (long arrow). On coronal T2W MRI (C), the lesion widens the sinus ostium and extends into the nasal cavity (arrowhead).
Courtesy: Dr Laurie Sanchez, Newark, NJ, USA.

signal on T1W and T2W images, and no enhancement on postcontrast T1W images; however, intracranial involvement will likely demonstrate enhancement.[126]

In FD, medullary bone is replaced by fibrous tissue, resulting in the classic "ground glass" CT appearance (Figs. 9.27A and B). FD presents in the first or second decade; three classic forms are described. Monostotic FD is most common (80% of cases), with head and neck structures involved in 20%, most commonly the mandible and maxilla.[198] Polyostotic FD occurs in 20% of cases and affects sites throughout the body. McCune-Albright is a rare condition consisting of polyostotic FD, precocious puberty, and skin pigmentation.

Ossifying fibroma is a benign tumor composed of fibrous tissue, bone, and calcification with a predilection for the mandible; it also affects the maxilla, ethmoid sinus, and nasal cavity. Ossifying fibromas occur with 5:1 female to male incidence.[199] On CT, ossifying fibromas are expansile, well-demarcated lesions, difficult to distinguish from FD (Fig. 9.28).



Figs. 9.25A to D: Juvenile nasopharyngeal angiofibroma (JNA). Axial computed tomography (A) shows typical features of a JNA widening the pterygopalatine fossa (asterisk), displacing the posterior wall of the maxillary sinus (curved arrow) and pterygoid plate (solid arrowhead). The mass extends medially, displacing the nasal septum (open arrowhead), laterally into the left masticator space (long white arrow), and posteriorly into the nasopharynx through the choana (dashed arrow). Axial T2W fat-saturated magnetic resonance imaging (MRI) (B) shows dark, serpiginous vascular flow-related signal voids within the tumor (long arrow). The tumor invades the sphenoid sinus and clivus (dashed arrow). Note the normal appearance of the contralateral pterygopalatine fossa (short arrow). T2-weighted imaging distinguishes tumor from mucosal thickening and secretions. Axial contrast-enhanced T1W fat-saturated MRI (C) demonstrates avid enhancement of tumor extending into the nasopharynx (dashed white arrow) and infratemporal fossa (long arrow). Note the normal appearance of the contralateral pterygopalatine fossa (short arrow). The posterior wall of the left maxillary sinus is displaced anteriorly (curved arrow). Digital subtraction angiography in the lateral projection (D) with a catheter injection of the external carotid artery (arrow head) shows early vascular blush of the JNA (short arrow) supplied by branches of the internal maxillary artery (long arrow).

Malignant Neoplasms

Squamous Cell Carcinoma

Malignant sinonasal tumors are rare, comprising <1% of all malignancies and 3% of those involving the head and neck. SCC is the most common, representing 27.8–92% of sinonasal cancers,[200] occurring in the sixth and seventh decades with a 2:1 male to female ratio. An association with nickel exposure has been reported; SCC occurs in up to 10% of cases of IP (either synchronous or metachronous). Alcohol and tobacco are much less associated with sinonasal SCC than with SCC of the aerodigestive

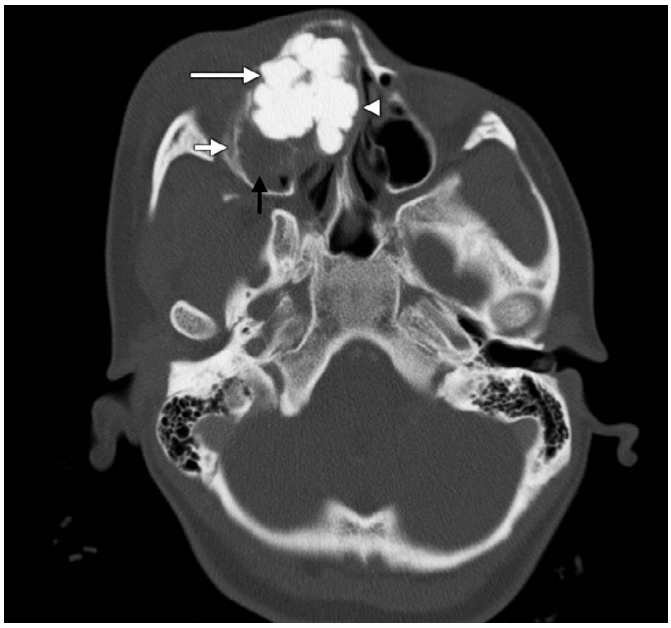
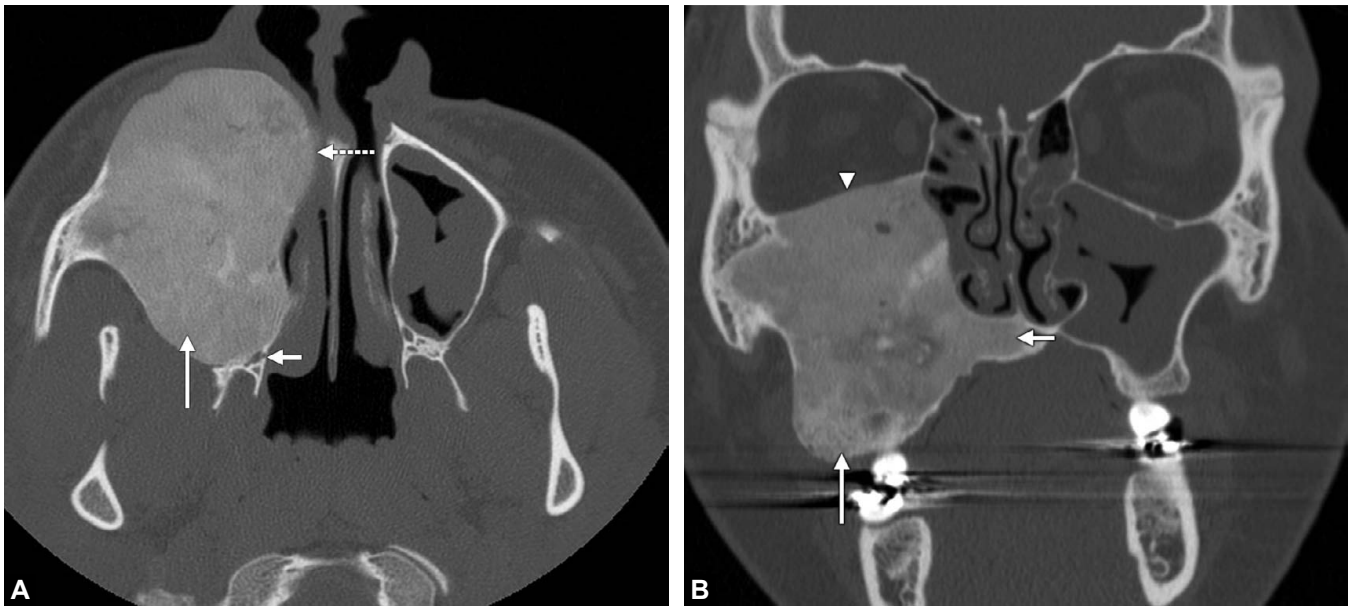


Fig. 9.26: Sinonasal osteoma. Axial computed tomography demonstrates the classic appearance of an "ivory" osteoma (long arrow). The maxillary sinus is secondarily expanded, with reactive wall thickening (short white arrow) and obstructed secretions (black arrow). Note the extension of the mass into the nasal cavity with deviation of the nasal septum (arrow head).
Courtesy: Dr Jacques Romano, Bronx, NY, USA.



Figs. 9.27A and B: Fibrous dysplasia. Axial computed tomography (CT) (A) demonstrates the typical "ground-glass" feature of fibrous dysplasia (long arrow) resulting in facial asymmetry. The lesion bulges into the nasal cavity (dashed arrow). Note posterior deviation of the pterygoid strut and compromise of the greater and lesser palatine foramina (short arrow). Coronal CT (B) demonstrates an expansile, ground-glass lesion involving the right maxilla, with elevation of the orbital floor (arrowhead), and extension into the hard palate (short arrow) and alveolar ridge (long arrow).
Courtesy: Dr Laurie Sanchez, Newark, NJ, USA.

tract.[201] The maxillary sinus is commonly affected, followed by the ethmoid sinus; sphenoid or frontal sinus involvement is extremely rare. Sinonasal malignancies are typically asymptomatic early on, presenting when tumors extend beyond the bony sinuses, making it difficult to determine the site of origin (Fig. 9.29). Nodal metastasis carries a poorer prognosis.

Optimal imaging workup of malignant sinonasal tumors involves both multiplanar CT and MRI with and without contrast. MRI better differentiates disease from

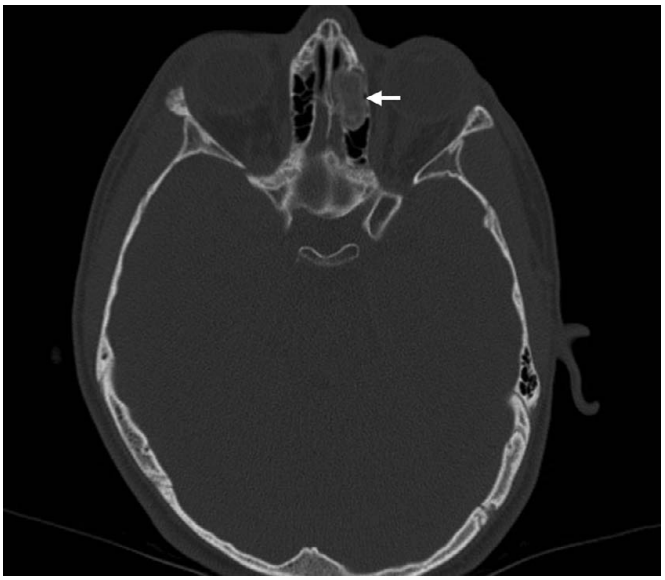


Fig. 9.28: Sinonasal ossifying fibroma. Axial computed tomography shows an ossifying fibroma of the left ethmoid sinus (arrow). A thin "eggshell" calcific rim surrounds a fibrous center.

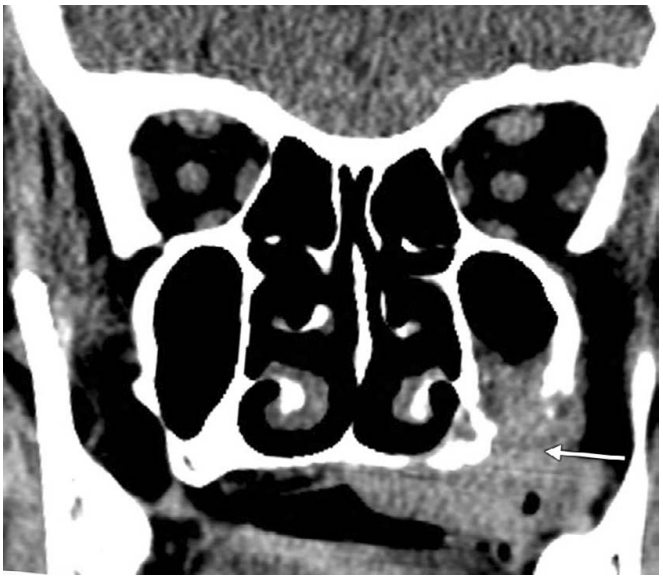


Fig. 9.29: Maxillary sinus squamous cell carcinoma. Coronal soft tissue computed tomography shows an irregular mass at the floor of the left maxillary sinus with bone destruction (white arrow). *Courtesy*: Dr Jacques Romano, Bronx, NY, USA.

secretions and surrounding tissues; CT is indispensable for demonstrating bone destruction (Figs. 9.30A to C). Imaging characteristics of SCC are nonspecific with intermediate signal demonstrated on T2W images. PNS of tumor occurs frequently.[202]

Nonepithelial Sinonasal Malignancies

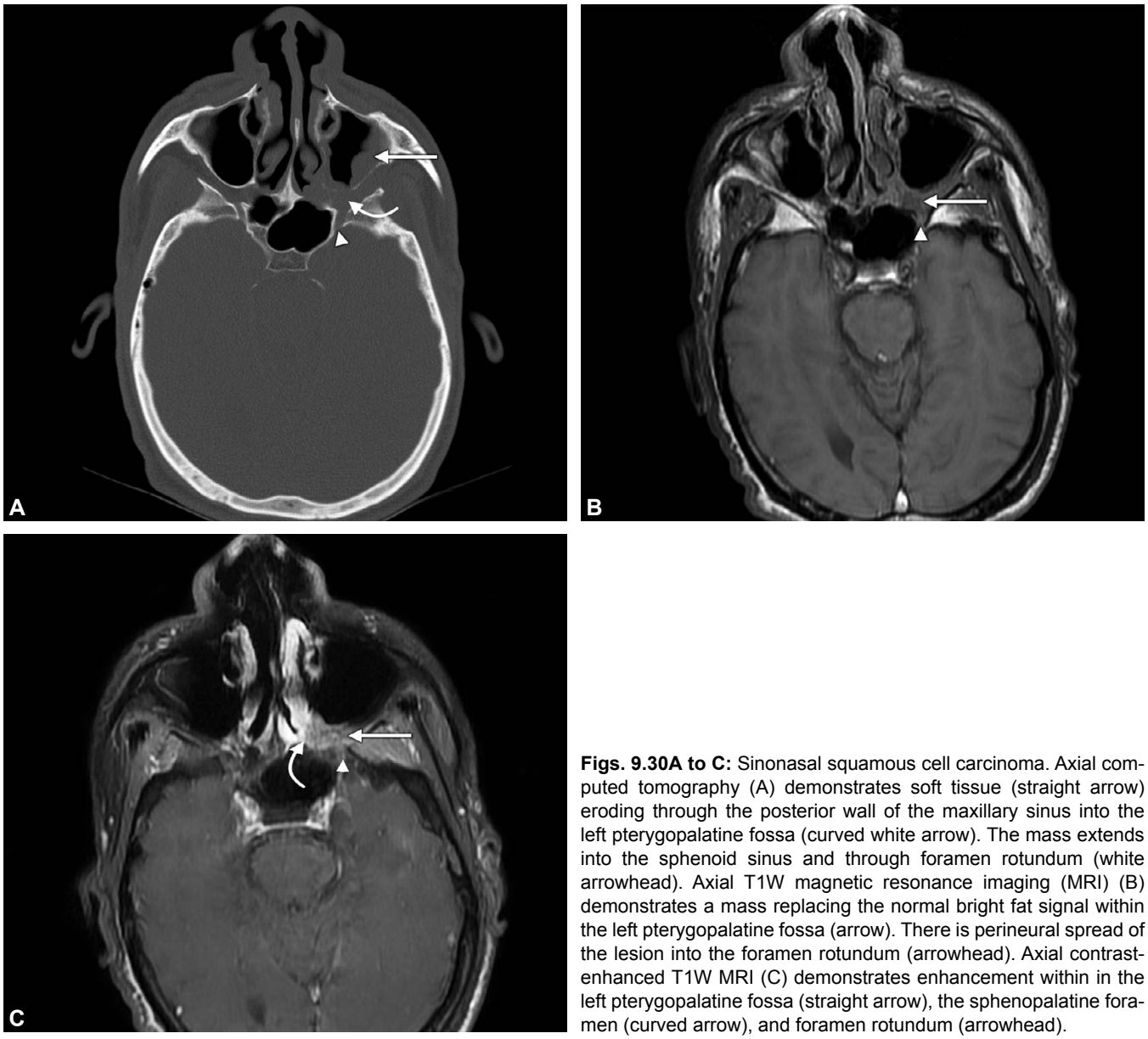
Nonepithelial malignant sinonasal tumors, including adenocarcinoma and salivary gland type tumors, comprise 10–20% of sinonasal malignancies. Adenocarcinoma is divided into intestinal-type adenocarcinoma (ITAC), histologically resembling gastrointestinal tumors, and non-ITAC (NITAC). ITAC is associated with exposure to wood and leather dust, likely accounting for its male predominance, typically presenting in the sixth and seventh decades. The nasal cavity and ethmoid sinus are common sites for occupational-related tumors.[203] NITAC are divided into low-grade tumors, occurring mostly in the ethmoid sinuses, with an indolent course; high-grade tumors occur primarily in the maxillary sinus, with an aggressive course. Imaging features of adenocarcinoma are nonspecific, resembling SCC. However, anterior extension, involving the glabella and posterior extension to the sphenoethmoidal recess and nasopharynx suggest ITAC.

The paranasal sinuses harbor minor salivary and salivary gland tumors such as ACC, adenocarcinoma not otherwise specified (AdNOS), pleomorphic adenoma, and mucoepidermoid tumors, rare sinonasal malignancies. ACC is the most common of these, most frequently affecting the maxillary antrum followed by the nasal cavity. The affected age range is broad, with peak incidence in the fifth decade. ACC grows slowly but local recurrence occurs commonly (75–90%). Imaging characteristics of ACC include a locally aggressive tumor, early submucosal spread, and subperiosteal bone invasion. PNS is a hallmark of ACC.[204] Signal characteristics are nonspecific, with intermediate to high-T2W signal intensity. It can be difficult to differentiate low-grade tumors from inflammatory disease.

AdNOS and mucoepidermoid carcinoma typically affect the maxillary sinus and nasal cavity. PNS and perivascular invasion are common with AdNOS. Mucoepidermoid carcinoma has a tendency for regional and distant metastasis as well as local recurrence. Pleomorphic adenomas are rare, typically arise from the nasal septum, spherical in configuration, and remodel bone.

Nasal Lymphoma

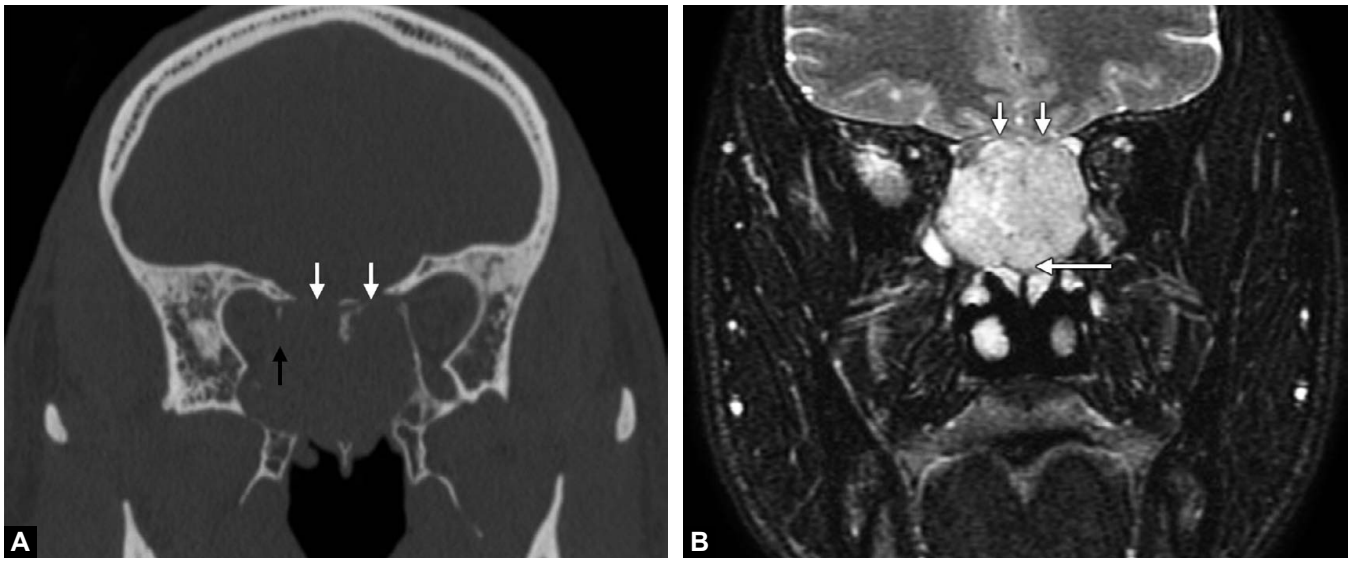
Lesions formally categorized as "idiopathic midline destructive diseases" have been identified as nasal T-cell and NK cell lymphoma. These rare diseases are progressive, disfiguring, and despite systemic therapy, outcomes are poor. Beyond biopsy, surgery plays little role in management.



Figs. 9.30A to C: Sinonasal squamous cell carcinoma. Axial computed tomography (A) demonstrates soft tissue (straight arrow) eroding through the posterior wall of the maxillary sinus into the left pterygopalatine fossa (curved white arrow). The mass extends into the sphenoid sinus and through foramen rotundum (white arrowhead). Axial T1W magnetic resonance imaging (MRI) (B) demonstrates a mass replacing the normal bright fat signal within the left pterygopalatine fossa (arrow). There is perineural spread of the lesion into the foramen rotundum (arrowhead). Axial contrast-enhanced T1W MRI (C) demonstrates enhancement within in the left pterygopalatine fossa (straight arrow), the sphenopalatine foramen (curved arrow), and foramen rotundum (arrowhead).

Radiographic findings mimic cocaine-induced midline destructive disease or Wegener's granulomatosis. However, specific features may suggest the diagnosis. In addition to destruction of the septum and obliteration of the nasal passages, the hard palate and orbital walls may be eroded. Erosion of bone by expansile mass suggests the diagnosis on CT. Lesions commonly originate in the maxillary sinus, obliterating the sinus or nasal passages with mucosal thickening and periantral soft tissue infiltration. Mucosal thickening may also occur in benign sinus disease; T2W MRI distinguishes tumor from benign mucosal thickening. Lymphoma has relatively low-T2W signal intensity[182] and may appear heterogeneous, with calcifications and hemorrhage.[205]

Sinonasal lymphoma is most commonly non-Hodgkin's lymphoma, a component of disseminated aggressive disease. B-cell lymphoma appears as a large soft tissue mass with bony remodeling or bony erosion; T-cell lymphoma features bony destruction disproportionate to the size of the mass, similar to Wegener's granulomatosis. Signal intensity is intermediate on all MRI sequences; contrast enhancement varies.



Figs. 9.31A and B: Esthesioneuroblastoma. Coronal computed tomography (A) shows a mass occupying the upper nasal cavity and ethmoid sinuses. The lesion extends through the cribriform plates of the anterior skull base (white arrows). Destruction and lateral displacement of the lamina papyracea is noted (black arrow). Coronal T2W magnetic resonance imaging (B) demonstrates extension of the tumor intracranially, eroding the cribriform plates (short white arrows) and invading the midline nasal cavity (long white arrow).

Neuroectodermal Tumors

Olfactory neuroblastoma (ONB) or esthesioneuroblastoma is a neuroectodermal tumor originating from neural crest cells in the olfactory mucosa. ONB accounts for 5% of sinonasal malignancies, affecting a wide age range from children to the elderly, with bimodal peaks in the second and sixth decades. Imaging features of ONB are nonspecific, with intermediate signal intensity on T1W and mild hyperintensity on T2W images (Fig. 9.31B). Enhancement is variable; peripheral areas of cystic degeneration are specific but seen in a minority of cases. The diagnosis of ONB is suggested by tumor location, especially early, when the presence of soft tissue in the olfactory cleft is the earliest imaging sign.[206] Low-grade ONB tend to be expansile; bony erosion can also be seen on CT (Fig. 9.31A). Direct spread to the ipsilateral maxillary and ethmoid sinus is common. Sphenoid sinus involvement is rare. Nodal metastasis occurs in 23% of patients.

Primary sinonasal malignant melanoma accounts for < 2.5% of malignant melanoma. These tumors arise in the nasal cavity, frequently in the nasal septum, followed by the lateral nasal wall. Imaging appearance does not correlate with biological activity, and well-defined lesions may be clinically aggressive.[207] The presence of hemorrhage and melanin confer high T1W and T2W signal characteristics, but nonspecific intermediate signal intensity can also be seen. Mild to moderate contrast enhancement is typical; PNS can be seen.

Malignant Bony and Cartilaginous Tumors

Chondrosarcomas are uncommon malignancies of cartilage commonly affecting the pelvis and long bones; however, 5–10% occur in the head and neck.[208] Chondrosarcomas are divided into three histological grades, each specific to biological activity and aggressiveness. Sinonasal chondrosarcomas are commonly found at the nasal septum and demonstrate a typical pattern of superior extension to the skull base along the perpendicular plate of the ethmoid and inferiorly to the palate. CT is particularly useful in diagnosis due to the presence of calcified matrix. Stippled, chondroid matrix is common in chondrosarcomas, with low-T1W and high-T2W signal intensity on MRI. Calcification demonstrates low signal on all MRI sequences. Contrast enhancement is homogenous or heterogeneous.

Osteosarcoma, a malignant tumor of bone, often occurs in long bones; 4–14% occur in the head and heck, typically in the jaw.[209] Sinonasal involvement can be primary or by direct extension. The incidence of head and neck osteosarcoma peaks during the third decade, unlike long bone osteosarcoma, which occurs in younger patients. Risk factors for osteosarcoma include radiotherapy, Paget's disease, and FD; osteosarcoma is associated with Maffucci,

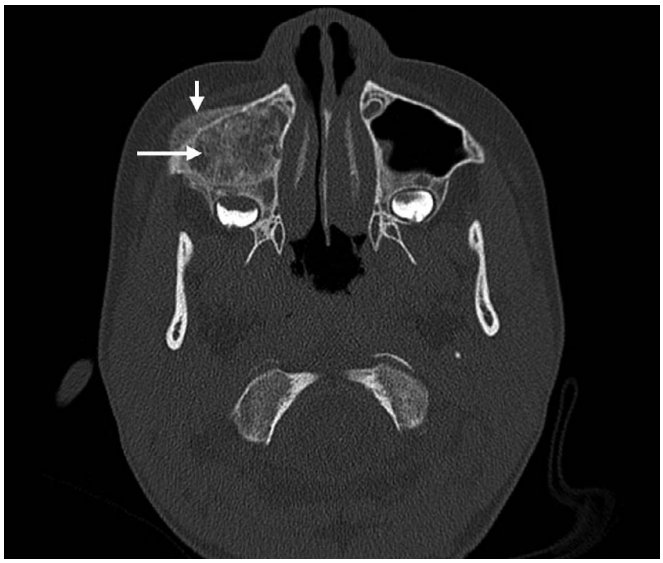


Fig. 9.32: Maxillary sinus osteosarcoma. Axial computed tomography demonstrates soft tissue mass with osteoid matrix filling the right maxillary sinus (long arrow). Periosteal reaction is noted along the anterior maxillary sinus wall (short arrow).

Ollier, and Li-Fraumeni syndromes. The CT appearance of osteosarcoma is a soft tissue mass causing bony destruction with internal areas of osteoid matrix (Fig. 9.32). Aggressive forms of periosteal reaction, including a sunburst pattern are characteristic but not always seen. MRI signal characteristics depend on degree of mineral content but are typically low on T1W and intermediate on T2W images. MRI depicts the intramedullary and extraosseus extension of tumor. Osteosarcoma enhances with contrast, less avidly than chondrosarcoma.

Other Neoplasms

Sinonasal undifferentiated carcinoma is a poorly differentiated tumor with neuroendocrine features. This is a rare tumor, with nonspecific imaging features similar to SCC, poor prognosis, and frequent local and regional metastases.

INVADING THE SKULL BASE FROM BELOW

The skull base and intracranial compartment are frequent sites for extension of sinus pathology. The anatomical structures lying between the nasal sinuses and the skull base provide numerous pathways by which infectious, inflammatory, or neoplastic pathology can spread intracranially. Commonly, involvement of the skull base results from direct invasion of pathology from the sinuses.[182] In many instances, only a thin segment of bone and dura mater separate the sinuses from intracranial structures. Other mechanisms, such as PNS, contribute to intracranial extension of disease (Figs. 9.33A to C), as described earlier.

When interpreting images, it is important to remember that tumors originating outside the sinuses, as well as hematogenous metastases, may simultaneously involve the sinuses and intracranial compartment. Discrimination between different points of origin may be challenging from an imaging perspective, particularly once several structures are involved.

Once the skull base and brain parenchyma are involved, CT or MRI findings may establish a differential diagnosis but cannot predict histology. CT is preferred for detecting calcification and bony changes. Imaging of the sinonasal cavities requires thinner slices than those used for brain imaging. Sections of ≤1.25 mm are particularly useful in detecting skull base invasion.[182] MRI is more helpful in evaluating complex sinus pathology. In particular, MRI is superior to CT in determining and defining intracranial extension of pathology, tumor margins, cerebritis, encephalocele, or abscess formation. Leptomeningeal enhancement may be an early sign of intracranial invasion, and MR may detect subtle disease, in the initial stages.[97]

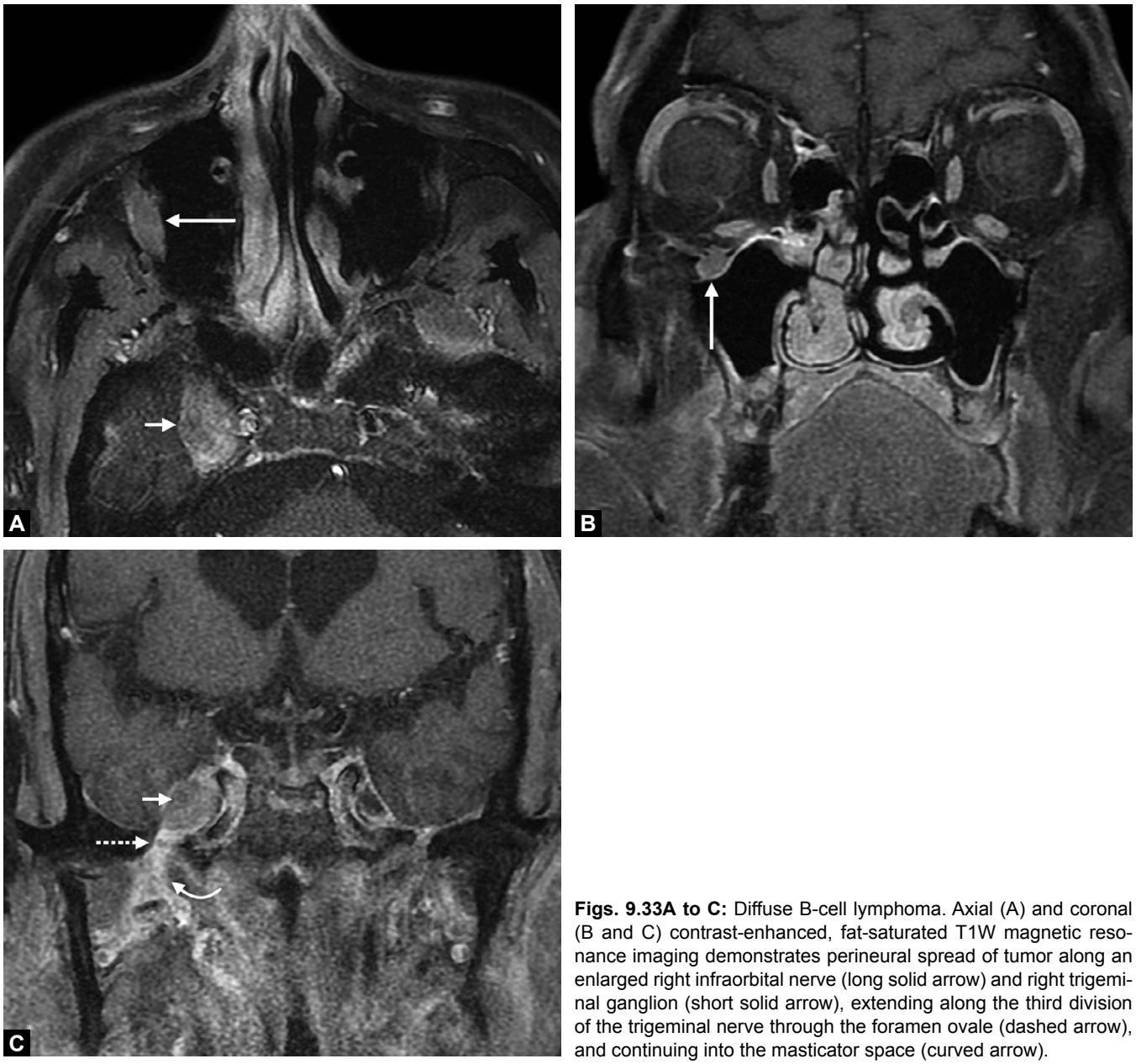
Infectious and Inflammatory Invasion

Sinus inflammation or infection may extend intracranially. Sinus infections most likely to do so include acute and chronic forms of bacterial and fungal sinusitis. In the setting of acute bacterial sinusitis, the frontal sinus is most likely to spread intracranially, followed by sphenoid, ethmoid, and maxillary sinuses.[182] Proposed pathways of invasion are sinus emissary veins in communication with meninges; therefore, bony destruction may not be present in such cases.[182] As discussed previously, leptomeningeal enhancement on MRI represents an early sign of intracranial extension.

The sequelae of inflammation may also result in intracranial pathology. Chronic inflammation may result in mucoceles, retention cysts, and polyps, well described previously.

Benign Sinus Tumors Involving the Skull Base

JNA, IP, paranasal sinus osteomas comprise the differential diagnosis of benign sinus tumors involving the skull base. They are described earlier and are listed here for completeness.



Figs. 9.33A to C: Diffuse B-cell lymphoma. Axial (A) and coronal (B and C) contrast-enhanced, fat-saturated T1W magnetic resonance imaging demonstrates perineural spread of tumor along an enlarged right infraorbital nerve (long solid arrow) and right trigeminal ganglion (short solid arrow), extending along the third division of the trigeminal nerve through the foramen ovale (dashed arrow), and continuing into the masticator space (curved arrow).

Malignant Tumors Invading the Skull Base

Primary sinus malignant neoplasms are uncommon but may involve the skull base. These neoplasms include SCC, adenocarcinoma, esthesioneuroblastoma, ACC, melanoma, non-Hodgkin's lymphoma, plasmacytoma, and sarcomas, such as osteosarcoma and rhabdomyosarcoma, as previously described.

Secondary Extension of Tumor Originating Outside the Sinuses

It is important to remember that direct invasion of malignant tumors originating from outside the sinuses may extend simultaneously into both the sinuses and the skull base and involve multiple structures. Some of the more common neoplasms with direct local invasion include: nasopharyngeal carcinoma, meningioma, hemangioma,

bone-related tumors, pituitary adenoma, neurogenic tumors, chordoma, and plasmacytoma. The most common skull base metastases include lung, kidney, breast, and prostate cancers, which may involve the paranasal sinuses. Metastasis to the paranasal sinuses is rare; case reports suggest renal cell carcinoma as the most frequent primary tumor.[182]

Nasopharyngeal carcinoma typically invades skull base through a midline approach, growing preferentially in a superior direction from the nasopharynx[210] to erode the sphenoid sinus. From this point, extension into foramen lacerum and the petroclival synchondrosis may occur. From there, tumor can reach the cavernous sinus, middle cranial fossa, or posterior fossa. Alternatively, lateral tumor extension may involve the foramen ovale, providing a perineural route into the middle cranial fossa.

METASTATIC PARANASAL SINUS DISEASE

Lymphatic drainage from the paranasal sinuses and nasal cavity occurs both anteriorly and posteriorly. The anterior pathway drains via lymphatic channels en route to the facial, parotid, or submandibular groups, which drain to the superior cervical nodal chain, primarily level II. Contributors to the anterior pathway include the anterior ethmoid sinus, frontal sinus, lateral portion of maxillary antrum, and anterior half of the nasal cavity/nose. The posterior lymphatic channels head toward a plexus anterior to the torus tubarius, continuing posteriorly to the retropharyngeal nodes, and then inferiorly to the posterior and superior deep cervical nodes. Contributors to the posterior pathway include the posterior ethmoid sinus, main portion of the maxillary sinuses, and the posterior half of the nose and nasopharynx.[182,211]

Lymphatic metastasis is an important mechanism of spread for sinonasal carcinoma, given the wide network of lymphatic channels in this region.[212] Features of metastatic nodal disease, including nodal enlargement, extracapsular spread, and necrosis are well described.[213] Central necrosis is considered a reliable criterion for metastatic nodal disease, with an MRI appearance of central high signal intensity on T2W images, and low signal intensity on T1W images, with or without rim enhancement. Although less reliable, size criteria for nodal enlargement include the shortest axial diameter of 5 mm for lateral retropharyngeal nodes or shortest axial diameter of 10 mm for cervical nodes. A group of three or more borderline nodes is also deemed suspicious for metastatic nodal disease.[213]

Extracapsular spread is identified in the presence of ill-defined nodal margins, fat stranding, or infiltration into the adjacent soft tissues.[214] Identification of metastatic nodal disease plays a vital role in staging, treatment planning, and postoperative monitoring. Regional lymph node metastasis is the single most important prognostic factor for SCC of the head and neck. The American Joint Committee on Cancer (AJCC) provides the following staging criteria for head and neck cancer (excluding nasopharynx): N0, no regional node metastasis; N1, a single ipsilateral metastatic lymph node of ≤3 cm; N2, a single ipsilateral metastatic node of >3 cm but <6 cm, or multiple ipsilateral, contralateral, or bilateral metastatic nodes of <3 cm; and N3, metastasis in a lymph node >6 cm.[215] While CT is superior to MRI in regional metastatic lymph node assessment, 18F-fluorodeoxyglucose PET (FDG PET)/CT has been shown to have increased sensitivity compared with CECT alone.[16]

SCC accounts for approximately 80% of sinonasal malignancy with a 15% incidence of nodal metastasis at presentation. Primary sinonasal malignant melanoma, a rare entity, may have lymph node metastasis in up to 40% of cases at presentation. Lymph node involvement is also common in sinonasal rhabdomyosarcoma, lymphoma, and ACC.[179]

Distant Metastasis

The occurrence and location of distant metastases varies among sinonasal malignancies as well as the initial T and N tumor staging. AJCC staging for distant metastasis includes MX, where distant metastasis cannot be assessed; M0, no distant metastasis; and M1, in which distant metastases are present.[215] Distant metastases may necessitate additional therapeutic measures, but if the patient's clinical prognosis is poor due to upstaging of disease, palliation may be more appropriate.

Synchronous tumors are seen in approximately 15% of SCC with approximately 60% of secondary tumors identified in the lungs, gastrointestinal tract, and breasts. Sinonasal ACC has a 25% occurrence of metastasis overall and a 50% occurrence for maxillary antral ACC, primarily to the brain, lungs, and bone. Metastases to the brain, spine, and pelvis have been reported in sinonasal undifferentiated carcinoma and sinonasal neuroendocrine carcinoma. Melanoma has been reported to metastasize to the lung, adrenal glands, liver, brain, skin, and lymph nodes.[43,179]

Tumor Recurrence versus Treatment Changes

Treatment for sinonasal cancer including surgery, radiation therapy, and chemotherapy creates a daunting array of tissue changes complicating the diagnosis of recurrent or residual tumor. For example, asymmetric soft tissue bulk from surgical neck dissection, flap reconstruction, and postradiation fibrosis may cause false-positive imaging interpretation of tumor. Post-treatment fibrosis occurs within the first few months but may develop years later. A stable post-treatment appearance may not be achieved until 12–18 months after therapy.[216] While reports have stated that CT is useful for the detection of early tumor recurrence,[217] CT is unreliable in distinguishing recurrent tumor from post-treatment fibrosis.[218] By comparison, MRI, with its multiplanar imaging capability and superior contrast resolution, differentiates recurrent tumor from muscle and clearly visualizes vascular anatomy.[217] High signal intensity on T2W MRI differentiates recurrent tumor from mature scar or late radiation fibrosis. Such fibrosis is mainly collagenous, hypocellular scar tissue characterized by low signal intensity on T2W images.[218] However, early fibrosis, which is hypercellular with associated edema, shows high T2W signal intensity, similar to recurrent tumor. Differentiation of early fibrosis from tumor using contrast-enhanced T1W images can be difficult; several studies describe variable enhancement in early fibrosis.[218] PET/CT has differentiated recurrent disease from radiation and surgical changes, as cancer cells retain more FDG for longer periods of time than normal tissues.[219]

Role of FDG PET

FDG PET is effective in the diagnosis of many different cancers, including SCC of the head and neck. The combination of PET and CT provides anatomic and metabolic information, increasing the accuracy and confidence level of the radiologist (Fig. 9.34). PET/CT is also superior in the detection of regional lymph node and distant metastases, compared with conventional imaging modalities; in detecting primary tumor, it is not superior to CT. Of note, FDG PET/CT has a high negative predictive value, such that a negative scan excludes disease. Given its ability to detect, differentiate, and exclude recurrent or residual tumor, FDG PET/CT is used for monitoring treatment response, restaging, and surveillance. There has been interest in PET/CT for radiotherapy planning because it provides improved tumor definition, sparing normal tissues, minimizing adverse effects. Measures of FDG PET standard uptake value and tumor metabolic rate also predict the aggressiveness of the tumor.[214]

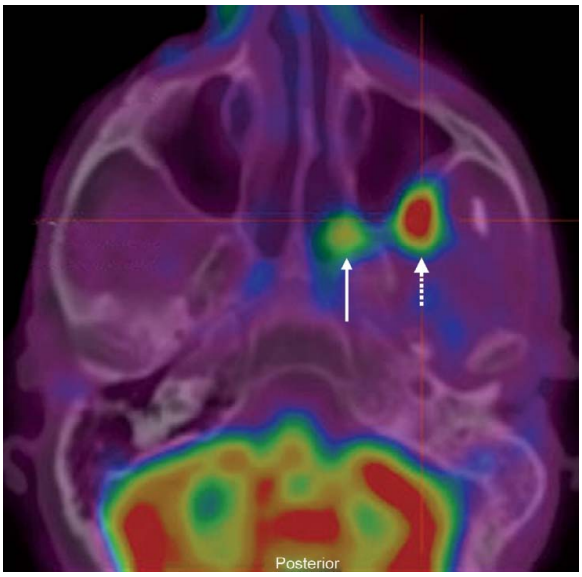


Fig. 9.34: Sinonasal squamous cell carcinoma. Axial fluorodeoxyglucose (FDG) positron emission tomography/computed tomography fusion image shows intense FDG uptake corresponding to the left pterygopalatine fossa (dashed arrow), extending to the posterior nasal cavity along the sphenopalatine foramen (solid arrow). This study corresponds to the same patient imaged in Figure. 9.29.

Debate exists over the best timing for the first surveillance study after treatment. Early scanning may demonstrate false-positive results, with postoperative or postradiation inflammatory changes mimicking residual tumor. False-negative results are also seen with early scanning as a few stunned, yet viable tumor cells may not be detected. Therefore, initial surveillance should not be performed for at least 2 months after therapy. Both length and intervals of surveillance are debated.[16]

Complications of Treatment

Radiation Therapy Necrosis

While the goal of radiotherapy is to affect tumor, surrounding tissues are also subject to its adverse effects. Within weeks of radiotherapy, an acute inflammatory reaction occurs in deep tissues, yielding interstitial edema and subsequent fibrosis. Albeit rare, tissue necrosis is a complication of radiotherapy in the head and neck, occurring months to years after completion of treatment. Risk factors for tissue necrosis include high radiation doses and large

radiation fields. Necrosis involving bone, cartilage, local vasculature, and brain parenchyma may occur.[220]

Severe edema and radionecrosis of the larynx occurs in approximately 1% of patients undergoing head and neck radiation therapy. Although laryngeal necrosis peaks within 12 months after radiotherapy, it has been reported 30 years after treatment. The imaging appearance of laryngeal edema and necrosis include laryngeal soft tissue swelling, destruction of cartilage or bone, and sclerotic appearing cartilage with fragmentation. Abscess and fistula formation in the paralaryngeal fat or strap muscles are additional complications. Necrosis involving the arytenoid and thyroid cartilages as well as progressive cricoid cartilage sclerosis may also be seen.[216,220]

After head and neck irradiation, the mandible is most frequently affected by osteoradionecrosis. Imaging appearances of mandibular osteonecrosis include cortical interruption, loss of spongiosa trabeculation, pathological fractures, sequestra formation, soft tissue thickening, and fistula formation. The skull base may be affected, with a 3% incidence of osteoradionecrosis after radiation therapy for nasopharyngeal carcinoma; specifically, the sphenoid bone and the atlantoaxial articulation are commonly affected. Imaging features include a mottled appearance of the skull base on CT, with mixed T2 signal changes and heterogeneous enhancement on MRI. These changes may progress to bony defects and sequestra formation as well as CSF leaks and gas in the soft tissues. Other potential complications include internal carotid artery pseudoaneurysm and rupture, blindness, and meningitis.[216]

Brain parenchyma may be included in radiation fields extending to the skull base. For example, inferior and medial temporal lobe damage may occur after radiotherapy for nasopharyngeal carcinoma, and frontal lobe injury may follow irradiation of esthesioneuroblastoma. Post-radiation brain parenchymal injury occurs in different stages, identified as acute, early delayed, and late delayed. The late-delayed reaction presents beyond 6 months, often seen after 2 years. These changes are irreversible and progressive. On MRI, the affected area initially demonstrates low T1 and high T2 signal predominantly affecting white matter. Variable postcontrast MRI enhancement ranges from small, enhancing nodules to necrotic, rim enhancing lesions. Areas of hemorrhage on gradient-echo T2W sequences and restricted diffusion on diffusion-weighted Imaging may be seen. These imaging appearances overlap with those of tumor recurrence, thus complicating differentiation of tumor recurrence from postradiation change.[216]

Cranial Neuropathy

Brainstem and cervical spinal cord damage has a reported incidence of 2–3% after radiotherapy for head and neck cancer, most commonly after radiotherapy for nasopharyngeal carcinoma. However, with improved shielding and intensity-modulated radiation therapy, this is declining. Radiation-induced transverse myelitis is an irreversible process, related to multiple factors, including field size, fraction size, and total radiation dose. Postradiation spinal cord changes are well demonstrated on MRI and include cord edema, hyperintense T2W signal intensity and hypointense T1W signal intensity, with possible contrast enhancement in acute and subacute phases. In the chronic phase, spinal cord atrophy may be the only finding. Trigeminal, spinal accessory, and hypoglossal nerve damage has also been reported secondary to radiotherapy, with denervation sequelae demonstrated by muscle edema in the acute and subacute phases, and atrophic changes in the chronic phase. In the acute and subacute phases, muscle edema is demonstrated by T1 and T2 prolongation. Hyperintense signal on both T1 and T2W images represents progressive fatty infiltration in the chronic phase, with associated hemiatrophy.[216]

Radiation-Induced Neoplasms

The development of secondary neoplasms is another complication of radiotherapy. Postradiation sarcomas have been described after successful treatment of nasopharyngeal carcinoma, ACC, soft palate SCC, tonsillar SCC, and primary sarcoma of the head and neck. The risk of postradiation sarcoma increases with higher radiotherapy dose in combination with chemotherapy. Radiation-induced SCC tends to affect the temporal bone and external auditory canal, with a mean occurrence of 13 years postradiotherapy. Postradiation lymphoma and meningiomas have also been reported. The latency for radiation-induced tumors is quite variable, with reported latency ranging from a few months to 65 years.[216]

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CHAPTER

10 Measuring Quality of Life and Outcomes in Rhinology

David M Poetker, Timothy L Smith

INTRODUCTION

Endoscopic sinus surgery (ESS) is one of the most commonly performed procedures, with >250,000 outpatient surgeries done annually in the United States.[1] Sinus surgery has seen significant changes over the past 40 years with the advent of "functional" surgery and the dawn of the endoscopic era. Despite these advances, only within the last two decades have surgeons attempted to demonstrate patient improvement after sinus surgery. These patient-reported outcomes have become the current method of measuring improvement after various interventions, including sinus surgery.

This chapter will review the role of quality of life (QOL) and outcome measurements in patients with rhinologic disease. We will discuss the various instruments available, how each is used, the data supporting their use, and the ideal time each is used.

NEED FOR INSTRUMENTS

Why do we need QOL or outcome instruments? They are needed for many different reasons, all revolving around quantifying the improvement in a patient's symptoms after surgery. Sinus surgery frequently involves multiple sinuses and currently offers relatively high reimbursement through relative value units assigned to the procedures. Given the frequency of these surgeries, sinus surgery can be a very expensive proposition for a third party payer. With healthcare costs rising dramatically, insurers want to invest in procedures with the highest rates of return, measured by decreased downstream costs. They want data to prove that sinus surgery not only makes people feel better, but also decreases their needs for expensive medicines, office visits, and costly interventions such as computed tomographic (CT) scans and nasal endoscopy.

Sinus surgery may be costly for patients as well. In addition to their individual deductable and copay, they will also miss work after the procedure, experience pain associated with surgery, and must accept the risks of performing surgery such as vision damage and cerebrospinal fluid leak. Patients want to know what type of improvement they are likely to achieve by undergoing surgery. They want to know that the benefits of surgery will outweigh the short-term costs, discomfort, and risks of the procedure.

Existing objective measures are known to correlate poorly with patient's symptoms. Specifically, CT scans have been shown to correlate quite poorly with patient's symptoms.[2] In addition, nasal endoscopy has been shown to have a poor inter-rater reliability when it comes to findings.[3] The gold standard for comparisons has been a randomized, controlled trial; however, using this type of study would require patients to be randomized into a control group. Control groups for surgical interventions would include a sham surgery, which not only is unethical, but would also be difficult to recruit sufficient patients to achieve statistical significance.

We are left with using patient-reported symptoms as a way to measure impact on one's life as well as changes in those symptoms due to various interventions. Many different tools exist, and these tools, or instruments, have been tailored to address the symptoms associated with the disease in question.

The tools measure the "health burden" of a disease process using the model of health status and are created according to the outline from the Institute for Medical Rehabilitation and Research. Health status is determined by a patient's physical impairments, functional limitations, disabilities, and social limitations. Both patients and physicians can describe one's health status, which differs from one's QOL. A patient's QOL is more personal than the health status and can only be described by that individual.[4] Although QOL can be impacted by multiple issues, QOL can be narrowed to only include the component that is determined primarily by the persons' health and is thus referred to as the health-related QOL (HRQOL).[5] The ideal QOL instrument needs to reflect important aspects of the disease process, be responsive to the effects of treatment, and accurately reflect the impact of disease on patient's HRQOL. Several important factors go into the validation and utilization of the instruments.

PSYCHOMETRIC CHARACTERISTICS OF QOL INSTRUMENTS

Instruments used to measure QOL are validated through several psychometric tests including validity, reliability, and responsiveness. The ease of use is also important when considering which specific instruments to use. Table 10.1 lists the various chronic rhinosinusitis (CRS) disease-specific QOL instruments, specifics of the instruments themselves, and their psychometric data.

Validity

Validity is the degree to which an instrument measures what it is supposed to measure. Validity is broken down into several subcategories.

Content-related validity measures the appropriateness and redundancy of items and scales of the instrument. An instrument has content validity if factors not related to the purpose of the measurement do not influence the score. Content-related validity is usually assessed by having experts and/or patients with the target condition review the instruments for the breadth of coverage.

Criterion-related validity measures how well the instrument relates to the gold standard. This can be quite difficult to measure if criteria are not widely accepted. Due to the lack of widely accepted criteria, criterion-related validity is rarely tested. Concurrent and predictive validity are two forms of criterion-related validity.

Construct-related validity is the degree to which the score changes as the condition worsens. This is often correlated with the general health measures of the instrument. Construct-related validity can be divided into convergent validity and discriminant validity.

Convergent validity is confirmed if the instrument correlates with another instrument that measures the same concept. This is measured by the Spearman's rank correlation test with like disease instruments, whereas a Pearson's correlation is used to measure correlation with general health instruments. Correlations range from 0.4 to 0.8; if the correlation is >0.8, the two instruments are considered too similar and the tested instrument does not add to the evaluative process.

Discriminant validity measures the instruments' ability to distinguish between disease-affected patients and those without the disease process. It is measured by an independent t test, and a statistically significant difference ($p < 0.05$) confirms distinct groups of patients. If the measurement goal is evaluation over time, the discriminant validity is not applicable.[4,6-9]

Reliability

Reliability reflects the way individual items on the instrument relate to each other, suggesting the instrument is free from random error and has homogeneity of the items. It is measured by internal consistency and test–retest reliability. Internal consistency measures whether several items proposed to measure the same general concept produce similar results. It is measured by Cronbach's alpha and a score ≥ 0.7 is considered reliable. Test–retest reliability tests the stability of the instrument over time, looking for any substantial variation in the scores when taken on two separate occasions. Test–retest reliability uses the scores from the two administrations and is calculated with a t test and a Pearson or Spearman's correlation coefficient or using the intraclass correlation coefficient. The values from these calculations range from -1 to 1, with 1 signifying a perfectly positive association. A correlation coefficient of ≥ 0.70 is considered adequate reliability.[4,6,8,9]

Responsiveness

Responsiveness is the instruments' sensitivity to change over time. This change can reflect confounding variables such as external factors altering a patient's perception of the disorder (also referred to as external responsiveness), or changes due to treatments (internal responsiveness).

Table 10.1: Rhinologic HRQOL instruments

					Ease of use	*Reliability*		*Validity*			*Responsiveness*			
QOL instrument	*Subscales*	*Items*	*Score range*	*High score =*	*Completion time (minute)*	*Cronbach's alpha*	*Test–retest*	*Discriminant*	*Convergent*	*Concurrent*	*p Value*	*SRM*	*MCID*	*References*
RSDI	3	30	0–120	Disease	<5	0.95	0.60–0.92	$p < 0.01$	NR	NR	NR	NR	≥10.4	22
CSS	2	6	0–100	Health	<5	0.73	0.86	NR	0.36–0.46	NR	NR	0.82	≥9.75	18
RQLQ	7	28	0–6	Disease[1]	5–15	0.92	0.86	NR	0.31–0.59[2]	NR	0.037	0.76	0.49[3]	12
RQLQ(S)	7	28	0–6	Disease	5–15	0.93	0.97	NR	0.69	NR	<0.005	0.75	0.48	13
Mini-RQLQ	5	14	0–6	Disease	5	0.90	0.93	NR	0.73	NR	<0.001	0.83	0.70	14
N-RQLQ	4	16	0–6	Disease	5	NR	0.87	NR	0.38–0.55	NR	NR	0.93	NR	15
Rhin-QOLQ	6	24	0–7	Disease	5–10	NR	NR	NR	0.77	NR	0.0001	NR	NR	16
ROQ	4	26	0–130	Disease	5	0.8–0.92	NR	NR	NR	NR	<0.0002	NR	0.875*	17
RSOM 31	7	31	0–155	Disease	15–20	0.95	NR	>0.05[4]	0.29–0.50[5]	NR	<0.0001	NR	≥1.0	19
SNOT-20	-	20	0–100	Disease	5–10	0.9	0.9	<0.0001	NR	<0.002	0.04	0.4	>0.8	4
SNOT-16	-	16	0–48	Disease	<5	0.89	NR	<0.001	0.23–0.64[6]	NR	NR	0.69	NR	21
SNOT-22	-	22	0–110	Disease	<5	0.91	0.93	<0.0001	NR	<0.0001	<0.0001	0.81	≥8.9	20
RhinoQOL	3	17	0–100	Health	5–10	0.89[7]	0.57–0.67	NR	0.51–0.61[8]	NR	<0.01	1.9–2.4	NR	32
SN-5	-	5	0–7	Disease	<5	0.62	0.71	NR	0.14–0.62	NR	NR	0.74	NR[9]	31
SOQ	5	26	0–130	Disease	5–10	0.84	NR	NR	NR	NR	<0.001	NR	≥11.5*	33
RSI	5[10]	23	0–100	Disease	5–10	0.80	NR	NR	NR	NR	NR	1.25	NR	23-26
RSUI	5	10	0–1	Health	5–10	0.94	0.4	$p < 0.05$	0.35	NR	NR	NR	≥0.115*	27
SNAQ	-	11	0–80	Disease	<5	NR	NR	NR	0.79[11]	NR	NR	1.08[12]	NR	30
NOSE	-	5	0–100	Disease	<5	0.785	0.702	<0.001	0.21-0.76[13]	NR	NR	1.66	9.75*	28
AOS	4	7	0–100	Disease	<5	0.73	0.52–0.95	NR	0.43	NR	NR	0.54	NR	29
MSSUI	-	5	0–1	Health	>5	NR	NR	NR	−0.58	NR	NR	1.17	0.03	34

AOS, Allergy Outcomes Survey; CSS, Chronic Sinusitis Survey; MCID, Mean clinically important difference; MSSUI, Major Symptoms Score Utility Index; NOSE, Nasal Obstruction Symptom Evaluation; NR, not reported; QOL, quality of life; RhinoQOL, Rhinosinusitis Quality of Life; Rhin-QOLQ, Rhinitis Quality-of-Life Questionnaire; ROQ, Rhinitis Outcomes Questionnaire; RQLQ, Rhinoconjunctivitis Quality-of-Life Questionnaire (S) – Standardized; RSDI, Rhinosinusitis Disability Index; RSI, Rhinosinusitis Symptom Inventory; RSUI, Rhinitis Symptom Utility Index; RSOM, Rhinosinusitis Outcome Measure; SNAQ, Sinonasal Assessment Questionnaire; SNOT, Sinonasal Outcomes Test, 20, 22, and 16 item; SOQ, Sinusitis Outcomes Questionnaire.

[1] In 6 of the 7 subscales, higher numbers signify more burden from the disease process. In emotional subscale, higher numbers mean less burden.

[2] All RQLQ instruments were compared with a nasal diary score.

[3] Per the published report by the developers of the RQLQ. Additional data analysis has shown a ≥ 0.68 change is needed to detect a moderate change (Ref. 40).

[4] The authors compared a rhinosinusitis population versus an audiology population and found they were not statistically similar.

[5] Four of the 8 SF-36 subscales showed correlations of >0.40.

[6] Six of the 8 SF-36 subscales showed correlations of >0.40.

[7] Psychometric testing reported by subscale. Data presented here represent the impact scale. Frequency and bothersomeness subscales had Cronbach's alpha of 0.68 and 0.57, respectively.

[8] RhinoQOL was compared with the CSS.

[9] MCID evaluated but not statistically significant due to limited sample size.

[10] The RSI has three subscales with a total symptom subscale and a medical resource subscale.

[11] Described as the "correlation factor" in the original report of the SNAQ, comparing the SNOT-20 with the SNAQ-11. Methods not described adequately in report (Ref. 30).

[12] Defined in the text as the "change in the SNAQ-11 as compared with the standard deviation." Presumably, they are calculating the SRM as the mean change in the score divided by the standard deviation.

[13] Of the five questions, Spearman's coefficient was >0.4 suggestion good correlation with a like disease instrument, in this case a visual analog scale.

*MCID was calculated as half of the standard deviation of the baseline QOL value for the given population (Ref. 10).

Many different statistics can be used for responsiveness and a statistically significant change proves responsiveness of the instrument. Responsiveness is commonly measured by the standardized response mean (SRM), which is defined as the mean change score divided by its standard deviation, and is often referred to as effect size. An SRM of < 0.2 is insensitive to change, > 0.5 is moderately sensitive to change, and > 0.8 is highly sensitive to change.[6-9]

Ease of Use

Ease of use is not a typical psychometric characteristic, but it is very important when considering the practicability of the instrument. If too long for the patients to complete, they will be less likely to complete, but if too complex for the researcher to calculate, the instrument will be less favorable as well.

MINIMAL CLINICALLY SIGNIFICANT DIFFERENCE

One difficulty encountered with QOL instruments is determining the minimal change in symptoms following an intervention that represents a relevant, perceptible, or meaningful change to the patient. This minimal change is referred to as the "minimally clinical important difference" (MCID). This issue has been addressed and validated using statistical constructs, and in general terms, changes in scores become clinically meaningful when they approximate half of the standard deviation of the baseline score for that population.[10]

CRS DISEASE-SPECIFIC QOL INSTRUMENTS

There exist two main categories for HRQOL instruments, generic and specific. Generic instruments are applicable to patients in all health states. Specific instruments are only applicable to a specific group of patients, such as an age group, a specific function such as pain, or a specific disease process.[5] The advantage of a generic instrument is that the burden of illness can be compared across different disease processes. For example, the health burden in patients with rhinosinusitis can be compared with the health burden of patients with asthma, chronic pain, or arthritis. The disadvantage of generic instruments is that they lack depth in any one disease process, so they are frequently unresponsive to changes that may be small, but quite significant to the patient. Disease-specific instruments ask the patients about the impairments most important to them and focus on specific problems, making them more sensitive to detect clinically important changes.[5]

An example of a commonly used, generic instrument is the Short Form-36 (SF-36). First published in 1992 by Ware and Sherbourne, it is a 36-item survey with eight health concepts including limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health; limitations in usual role activities because of emotional problems; vitality; and general health perceptions. It is designed to be self-administered in patients over the age of 14 years. Scores range from 0 to 100 for each area with higher scores indicating a better QOL. The SF-36 has been well validated and used in thousands of studies and publications.[8,11]

There also exist many disease-specific QOL instruments for rhinologic diseases. We will review the most commonly used instruments here.

Rhinoconjunctivitis Quality-of-Life Questionnaire

The Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ) was published in 1991, and although not disease specific for CRS, it has been very well validated for identification and disease progression in patients with allergic rhinoconjunctivitis. It has 28 questions divided into seven categories, including sleep problems, activity limitations, nose or eye symptoms, non-nose or eye symptoms, practical problems, and emotional function. Interestingly, the patient identifies three activities important to that individual patient in which they are limited by the rhinoconjunctivitis. A subsequent instrument, the Standardized RQLQ or RQLQ(S) has three generic activities (home/work, social, and outdoor activities) on which the patients are to base their symptoms. It has been criticized for poor ease of use and has been inappropriately used to measure CRS symptoms.[8,9,12,13] The Mini-RQLQ has 14 items and 5 subscales. It is also scored 0–6 with higher scores signifying more disease. This instrument has also shown high validity in psychometric testing.[14] A further modification of the RQLQ is the Nocturnal RQLQ (NRQLQ), which was designed to measure QOL in patients with nocturnal allergic rhinitis. This too has good validity in psychometric testing.[15] The RQLQ was further modified to only include symptoms or rhinitis by removing the four questions that dealt with eye symptoms. The Rhinitis Quality-of-Life Questionnaire was reported in 1993. They did limited psychometric analysis but found good responsiveness and convergent validity.[16]

Rhinitis Outcomes Questionnaire

The Rhinitis Outcomes Questionnaire (ROQ) was introduced as an easy-to-use instrument for private practices to track treatment outcomes. It measures 26 items on a 0–5 point scale with higher scores signifying more significant disease burden. It has been shown to have good reliability and responsiveness. It has been used to measure symptoms associated with mold exposure as well as response to immunotherapy.[17]

Chronic Sinusitis Survey

Gliklich and Metson published the Chronic Sinusitis Survey (CSS) in 1995 as a duration-based monitor that generates an overall sinusitis symptoms score and two subscales, symptoms, and medication use. It was designed for CRS and has high reliability, validity, responsiveness, and ease of use. It has also correlated well with general health surveys. It has six questions addressing pain or pressure, nasal congestion, and rhinorrhea or postnasal drip symptoms as well as medication usage, all over the past 8 weeks. Scores range from 0 to 100, the lower the score, the lower level of functioning, or poorer QOL due to disease burden. The two big advantages of the CSS are that it is very brief, taking 2–3 minutes to complete and it captures data on recent drug use.[6,18]

Rhinosinusitis Outcome Measure

The Rhinosinusitis Outcome Measure (RSOM 31), also published in 1995, is a 31-question, seven-subscale survey including nasal, eye, sleep, ear and general symptoms, practical problems, and emotional consequences. Although the RSOM 31 demonstrates good validity and responsiveness, the instrument is reportedly difficult to complete and score.[8,9,19] This has subsequently been modified into the various Sinonasal Outcome Tests.

SNOT-20

The 20-Item Sinonasal Outcome Test (SNOT-20) was introduced as a modified version of the RSOM-31, developed and validated by Piccirillo et al. Eleven items were removed from the RSOM-31 due to redundancy and results of psychometric testing, which demonstrated a lack of contribution of these elements. The 20 questions are scored from 0 to 5 with higher scores indicating a greater rhinosinusitis-related health burden across various domains including physical problems, functional limitations, and emotional consequences. In addition, the patients are asked to indicate the five items that are most important to them and that they expect to improve with treatment. The SNOT-20 was intended primarily to measure the effectiveness of treatment by calculating the difference between SNOT-20 scores before and after treatment. The psychometric testing demonstrated an overall Cronbach's alpha of 0.90, suggesting good internal consistency. The test–retest demonstrated a high degree of correlation. The discriminant and concurrent validity were both found to be statistically significant. The sensitivity to change was 0.4 at both 6 and 12 months, suggestion that the SNOT-20 is moderately sensitive to change.[4]

SNOT-22

The SNOT-22 is a slight modification of the SNOT-20. It was initially reported and used by the Royal College of Surgeons of England in 2000; however, full psychometric testing was not fully performed until published by Hopkins et al. in 2009.[20] The main criticism of the SNOT-20 was the lack of items relating to nasal blockage and sense of smell and taste. The SNOT-22 added items on each of these attempts to improve the content validity. The SNOT-22 also removes the importance rating to simplify the scoring. It is similar to the Rhinosinusitis Disability Index (RSDI) in that it captures physical, functional, and emotional data. It does not, however, capture recent drug use data. The SNOT-22 was very thoroughly validated. The Cronbach's alpha score was 0.91, with a test–retest reliability coefficient of 0.93, both demonstrating high internal consistency. The SNOT-22 discriminated between healthy controls and CRS patients and stratified subgroups of CRS patients. The MCID was found to be 8.9 points.[20]

SNOT-16

The SNOT-16 is a further modification of the SNOT-20, including 16 items that attempt to quantify patient's symptoms and social/emotional consequences of their disease. Like all SNOT instruments, the higher the score, the greater the rhinosinusitis-related health burden. Psychometric testing of the SNOT-16 was published in 1999 out of the University of Washington. They reported a Cronbach's alpha of 0.89 demonstrating good internal consistency. It also reportedly demonstrated excellent discriminant validity and correlated well with the SF-36. The SRM was 0.69, indicating moderate sensitivity to change. Despite the validation, the SNOT-16 did not gain widespread acceptance.[21]

Rhinosinusitis Disability Index

The RSDI was published in 1997 by Benninger and Senior.[22] The RSDI measures rhinologic-related health via 30 questions, with three subscales, physical, functional and emotional. The questions are written in the first person in efforts to allow the patient to individualize the impact of their disease process. Capturing data on the functional and emotional subscales in CRS patients is a unique advantage of the RSDI. Scores range from 0 (lowest level of disease impact) to 120 (highest level of disease impact). It has been demonstrated to have excellent test–retest reliability, good internal consistency, content- and construct-related validity with good general health correlation. The time burden for completion has been reported as approximately 5 minutes.[6,22]

Rhinosinusitis Symptom Inventory

The Rhinosinusitis Symptom Inventory has been used for both sinus surgery and nasal surgery such as turbinate reduction for over a decade. It consists of rating the severity of 12 different symptoms using a 6-point Likert scale over the prior 12 weeks. There are an additional 11 questions regarding medication use, work missed, doctors visits, and impact on functioning. The published data have demonstrated a Cronbach's alpha of 0.8, demonstrating good internal consistency and reliability and an SRM of 1.25, demonstrating very good responsiveness.[23-26]

Rhinitis Symptom Utility Index

The Center for Health Outcome Research developed and first published The Rhinitis Symptoms Utility Index in 1998. It is a 10-item questionnaire that includes frequency and severity of rhinitis symptoms (stuffy nose, runny nose, sneezing, itchy eyes, nose and throat) over the past 14 days, graded on a 4-point Likert scale. The instrument showed an excellent Cronbach's alpha of 0.94, but a relatively poor test–retest reliability, felt to be due to the inherent fluctuation of rhinitis symptoms. The instrument is rhinitis-, not sinusitis-specific and as such, the Rhinitis Symptoms Utility Index is not widely used in CRS outcome studies.[27]

Nasal Obstruction Symptom Evaluation Scale

The Nasal Obstruction Symptom Evaluation Scale was commissioned and developed through the American Academy of Otolaryngology—Head and Neck Surgery Foundation. It was designed and developed to provide a validated HRQOL instrument for nasal obstruction. In its final form, it is a five-item instrument with a Likert scale ranging from 0 to 4 with 0 being "Not a problem" and 4 being "severe problem". The scaled total score ranges from 0 to 100, the higher the score, the increased burden on health. Psychometric testing demonstrated a Cronbach's alpha for the final scale was 0.785 with a test–retest coefficient of 0.702, both demonstrating good reliability. The SRM was 1.66 with an MCID of 2.65. The validity testing was also found to be excellent.[28] This instrument again is designed to measure nasal obstruction and has been used in nasal airway studies.

Allergy Outcomes Survey

The Outcomes Measures of Immunotherapy in Allergic Rhinitis Project was designed to study the benefits of immunotherapy in patients suffering from allergic rhinitis. The Allergy Outcomes Survey was created for this project. It is a disease-specific QOL instrument with seven items in four domains, surveying symptoms, overall allergy medication use, allergy pill use (over the counter and prescription), and prescription nasal spray use. Psychometric testing demonstrated good to excellent test–retest when each item was evaluated individually. Cronbach's alpha was 0.73 for all seven items but increased to 0.88 when only including the symptoms domain. This instrument has been used in at least one additional study evaluating the effect of immunotherapy.[29]

Sinonasal Assessment Questionnaire

The Sinonasal Assessment Questionnaire (SNAQ-11) is an 11-item survey created as a modification of the SNOT-20, removing redundant items and adding in questions on nasal obstruction and sense of smell. The SNAQ-11 scores range from 0, completely asymptomatic, to 80, worst possible impact of the symptoms.[30] The instrument has been studied and compared to the SNOT 20. Good correlation to the SNOT 20 but with a better SRM; however, the data and methods are poorly explained by the authors.[9]

SN-5

Kay and Rosenfeld introduced the SN-5 in 2003. It originated as the SN-6, but after statistical analysis, it had an item regarding medication use removed to improve psychometric testing. It is designed for the pediatric population

to measure sinonasal symptoms. The survey is to be completed by the child's parent, addressing domains of sinus infection, nasal obstruction, allergy symptoms, emotional distress, and activity limitations. Symptoms were graded on a 7-point scale and were to represent the 4 weeks leading up to the date of survey completion. The instrument also included a 10-cm visual analog scale using a global faces scale for overall HRQOL. The test–retest reliability was found to be good. Cronbach's alpha was 0.62, below the 0.7 threshold considered to have good reliability. The remainder of the psychometric testing was good, but the design for pediatric patients has prevented the widespread use of the SN-5.[9,31]

Rhinosinusitis Quality-of-Life Survey

Rhinosinusitis QOL Survey (RhinoQoL) is a 17-item survey assessing frequency and severity of sinusitis symptoms. The survey is broken down into three subareas, including frequency, bothersomeness, and impact scales with a score range from 0 to 100 with higher scores suggesting better health. The Cronbach's alpha was 0.89 for the nine-item impact subscale but lower for the bothersomeness and frequency subscales. The test–retest scores were high and the construct validity and reliability were both found to be comparable with the CSS.[32]

Sinusitis Outcomes Questionnaire

The Sinusitis Outcomes Questionnaire was first described in 2004 as a variation of the ROQ, a previously validated instrument from the same group. It consists of 26 items scored on a Likert scale with scores ranging from 0 to 5. There are five sections assessing global symptoms, symptoms of the nose and sinuses, eyes, chest, and economic burden of their disease. Scores range from 0 to 130 with a higher score signifying more health burden from the disease process.

Validity methods are referenced, but no data on the psychometric testing are presented other than the mentioning of the Cronbach's alpha of 0.84 for the sinus questions.[33]

Major Symptom Score Utility Index

One of the instruments available for acute rhinosinusitis is the Major Symptoms Score Utility Index (MSSUI). It is a five-item instrument that was shown to have good convergent validity and responsiveness. The original article describing the MSSUI has not been cited in any published studies using the instrument.[34]

Additional Instruments

There have been many other HRQOL instruments proposed for the study of rhinologic diseases. One example is the Sinusitis Survey. The Sinusitis Survey consists of visual analog scales regarding various patient's symptoms associated with CRS. The Sinusitis Survey has not undergone formal psychometric testing.[35] The General Nasal Patient Inventory was introduced in 2001 but has no studies using the instrument.[36] The Chronic Sinusitis Technology of Patient Experience (Type) Specific Questionnaire is a symptom duration-based survey that reportedly has a very poor ease of use. It was described by Hoffman et al. in 1993, but did not undergo psychometric testing, and although it has been referenced several times, no follow-up studies have used the instrument.[9,37] Fairley's Symptom Questionnaire was published only as an abstract. It is not easily accessible or widely available. No additional studies have been performed using the tool. Similarly, the Cologne Questionnaire has been reported, but there are no published validation studies.[9,38]

USE OF RHINOLOGIC HRQOL INSTRUMENTS

Several studies have evaluated the existing HRQOL instruments, evaluating the supporting data and widespread use of the specific instruments. Morley and Sharp reviewed the data on 15 disease-specific and 5 generic QOL instruments. They concluded that the SNOT-22 Questionnaire provides the most suitable outcome tool for QOL in CRS management by ESS.[9] van Oene et al. performed a systematic review evaluating the data through 2007. They identified 13 questionnaires, six for rhinitis, five for rhinosinusitis, and the remaining two were nasal and asthma. Of those, they found only four that had adequate levels of discriminant validity and responsiveness. Those four included the RQLQ and RQLQ(S) for rhinitis and the RSOM-31 and RhinoQOL for rhinosinusitis.[7] Recently, a group out of Spain published a review article evaluating the specifics of the generic and disease-specific QOL instruments for rhinitis and rhinosinusitis. They too agreed with van Oene in that only two instruments, the RSOM-31 and RhinoQOL, currently offer adequate levels of discriminant validity.[8]

Quintanilla-Dieck et al. did a systematic review and found that the most commonly used disease-specific QOL instruments for rhinosinusitis were the CSS, used in 37 of the 121 studies identified in their review, the SNOT-20 (32/121), the RSDI (29/121), and the SNOT-22 (8/121).

Of note, almost half of the studies included used more than one instrument. They found that the RSDI and the SNOT-22 were highly correlated, whereas the RSDI had relatively poor correlation to the CSS. Given the correlation, it was felt that using both the RSDI and the SNOT-22 would be redundant. They also suggested that the RSDI, with its measurement of more general QOL domains related to social and emotional functioning, reduced the need for a more general health instrument such as the SF-36.[6]

LIMITATIONS OF HRQOL INSTRUMENTS

The most common criticism and biggest limitation of HRQOL instruments and outcomes studies is the lack of a control group within the studies. Control groups minimize the chances of placebo or natural progression of the disease process from impacting the results of the study. Unfortunately, surgically based studies do not ethically allow for a control group, limiting their usefulness. As such, surgeons have continued to work on outcomes using HRQOL instruments.[10] In addition, weaknesses inherent to the QOL instruments themselves exist. These include the use of unfamiliar scales, failure to describe the MCIDs, failure to explain the clinical importance of the instruments, failure to differentiate between inferences for individuals versus groups, identifying sample size requirements, and statistical power.[39] Despite these weaknesses and the limitations of the instruments, they remain the best option available to study outcomes of various interventions.

CONCLUSION

Many different disease-specific QOL instruments exist for rhinology. It is important to utilize the instrument that is specific for the disease to be studied, namely rhinitis, rhinoconjunctivitis, or CRS. In addition, investigators may consider using more than one instrument as outlined above to capture both disease-specific and general health outcomes. Using the appropriate instrument allows for collection of valuable data, measuring the response to various medical and surgical interventions in our patients.

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CHAPTER

11 Practice Management, Coding, and Career Pathways in Rhinology

Seth M Brown, Michael Setzen

This chapter focuses on the often ignored but critical aspects of medicine: how to choose a career, set up and run an office, and the nuisances of coding. The following sections are geared toward the rhinologist but applicable to the general otolaryngologist as well. The practice section focuses on choosing the right location, office, staff, and equipment to develop a successful practice. In the coding section, we review some of the most important and controversial aspects in rhinology. Finally, we discuss the various career pathways that one may choose in rhinology.

PRACTICE MANAGEMENT

Practice Setup

Equipment

It is essential for the rhinologist to have proper equipment when setting up an office. A recommended examination room would include rigid endoscopes, preferably 0° and angled endoscopes, as well as a flexible endoscope. The rigid endoscopes are important as it allows the surgeon to perform office-based procedures, such as cultures, biopsies and debridement. Rigid endoscopes are more practical if smaller; 3 mm scopes are recommended to provide optimal viewing as well as patient's comfort. Flexible endoscopes are useful in pediatric patients and to evaluate the larynx. Having an adequate number of endoscopes cannot be stressed enough. There is time required for sterilizing this equipment, and it is imperative that one is not waiting for endoscope processing resulting in inefficiency. Office recording equipment is useful for both documentation as well as patient education. When designing an office it is useful to consider secondary monitors for patient viewing on the opposing wall. Having adequate outlets and circuit breakers is important when an office is designed.

It is important to decide if you will be doing office-based procedures such as balloon sinus dilation. In this situation, two light sources are needed: for the endoscope and the balloon system. Perhaps an often overlooked aspect of an office is the strength of suction and the power of the light source. Both of these are critical for optimal visualization and instrumentation during office-based procedures. Additional items may include a microdebrider, electrocautery, and equipment for turbinate reduction.

Real Estate and Office Space

An ideal office would have enough space to expand but not so much space that one is overpaying. Renting tends to be preferable as buying space can limit practice expansion. It is ideal to have space in a medical office building, as these create a known location for patients, access to other specialists and primary care providers, and have parking that is not competitive with retail space. Every doctor practices differently but at least two rooms per doctor is recommended, with at least one of those rooms set up with video and equipment for procedures. Additional space requirements may include a dictation area, a consultation room, a nursing station, back office, an audiology booth, and room for an office computed tomography (CT) scanner. When building or expanding space, it is important to know local code, as there are requirements, which must be met for fire safety as well as adhering to the Americans

with Disability Act, for handicap access. Location is essential for access to patients such as availability to public transportation, highway access and adequate parking.[1]

Staffing

Staffing requirements are practice dependent. The key to office staff is to work at the highest level of one's license. Staff should be rooming patients, setting up rooms between patients, and performing other basic tasks. In an office, it is helpful to have a designated person in charge of staffing (such as an office manager), a medical assistant to prepare rooms, manage the rooming of patients and deal with basic patient questions and staff who can answer phones and check in/check out patients. Additional staffing could include audiology staff, allergy staff, such as an allergy nurse, and, depending on the patient load, physician extenders, such as a physician assistant or nurse practitioner. It also needs to be decided if billing will be done on site or outsourced to a central business office. As medical practices became more complex, staffing needs have changed with many tasks being done in a central office. The core to a successful, well-run office still depends on the staff as they interact directly with patients, answer phones, greet patients and schedule tests.[1]

Contracting

Today, most doctors have become removed from the contracting process. This is usually done as part of a larger group or a Physician Hospital Organization. A discussion of how to negotiate contracts is outside the scope of this chapter. It is important that the practitioner understands basic contracts and is able to negotiate for those procedures, which are done regularly.

Development of Practice

Networking

Networking with referring physicians is essential for both the general otolaryngologist and the rhinologist. A general otolaryngologist may market directly to patients and focus on primary care providers, whereas a rhinologist might focus on being a tertiary referral center and market to other otolaryngologists, allergist, and pulmonologists. Marketing can include brochures and literature as well as Web site development, visits to offices, and lectures to doctors and patients.[1] Many hospitals have networking and marketing personnel that help with practice development on behalf of the doctors on staff.

Web Site and Social Media

In this day and age, patients look toward the Internet for information regarding physicians. This not only includes phone numbers and hospital affiliations, but also rating of physicians and information, which can be provided by a Web site. If not versed in these areas, it makes sense to hire someone with significant Internet experience to develop a Web site and Internet tools. It is recommended that each practice has a Web site with at least basic practice information. This is an essential aspect of marketing. Additional information on the Web site can include: patient forms, policies and services offered. Ideally, patients can contact the practice through the Web site. It is critical to monitor the various physician rating sites in order to make sure the information is accurate and that inappropriate comments are noted. In addition, a practice can offer a Facebook site as well as a Twitter account. Marketing is part of the growth potential of a practice and should not be seen as additional cost but an essential investment.

Ancillary Services

Audiology

Audiology can be useful in any otolaryngology practice. Although not directly related to rhinology, the ability to offer this service to patients can be beneficial both to the patient and the provider. Diagnostic audiology is important as many patients with sinus problems have coexisting Eustachian tube pathology and possible middle ear fluid. It is not infrequent that aspiration myringotomy or ventilation tubes need to be inserted. To support the cost of diagnostic audiology, one can dispense hearing aids. This can be a lucrative opportunity. The development of audiology services requires a market analysis. This includes an evaluation of the surrounding competitors; the potential number of patients that could benefit from audiology; and the costs including staffing, equipment and space requirements. It may make sense for a doctor to subcontract or partner with an audiologist if the expected clinical volume is limited. However, audiology can be a significant income stream for the provider and should not be overlooked prior to an analysis. Like most ancillary services, rules and regulations are state dependent and one must understand this prior to embarking on a new venture.

Speech Pathology/Videostroboscopy/ Transnasal Esophagoscopy

Although not common in a rhinology practice, a speech pathologist that can perform swallowing testing in the office can be an important addition. In addition to swallowing dysfunction, there are numerous patients in need of vocal rehabilitation, and this is a possible adjunct to the office practice. This would expand the services offered to videostroboscopy. Many physicians have contracts with speech pathologists that come in on a limited base to both evaluate and treat patients with swallowing and vocal disorders. This might be the best option for a physician more interested in rhinology then voice and swallowing issues.

A growing body of evidence exists that reflux may play a role in sinonasal pathology. The ability to test patients with transnasal esophagoscopy and pH probes can be a useful adjunct to the practice both financially, but more importantly, to help evaluate and treat this condition.

Sleep Medicine

Many rhinologists treat sleep-related disorders such as sleep apnea and snoring. Sleep medicine testing has become easier with the advent of home sleep tests and can easily be added to an office practice. There now exists subspecialty certification in this area. In addition to testing, surgery can be offered if continuous positive airway pressure compliance is an issue. Oral appliances can be fashioned in the office as a service to patients instead of referral to dental specialists. Turbinate and limited palatal surgery in the office can be an option.

Cosmetics

Many patients coming in for nasal evaluation are looking for cosmetic procedures as well. It is not uncommon for rhinologists to specialize in cosmetic rhinoplasty as well. This should be taken into account when looking for office space, and designing an office as a cosmetic practice should have a different flavor than a standard rhinology practice. Furthermore, a procedure room with more space would be useful to provide some office based-cosmetic procedures such as botulinum toxin injections and facial fillers. As procedures shift toward outpatient office-based care, having the ability to perform more office-based procedures is a useful strategy. Proper steps should be taken if this is to be done, such as accreditation of the facility and relationship with an anesthesia group to provide safe, effective sedation.

Physician Assistants and Nurse Practitioners

Physician assistants and nurse practitioners can be a useful addition to a practice. They can help with preoperative counseling, answering questions and concerns from patients, and helping with histories and physicals. A physician extender can also work alongside a physician to increase access and revenue. If adequately trained, physician assistants can see postoperative patients, can perform minor procedures and scope patients, and provide useful services such as ear wax removal.

CODING

Coding Basics

Coding is a critical aspect that is often not taught during residency. The main aspect of coding is to inform insurance companies of what was done in order for the physician to be reimbursed appropriately. In essence, this is a language in and of itself. It is prudent for the doctor to be the coder, as they are the one who knows exactly what was done and will be responsible if the code does not reflect the service provided. There are three main aspects of coding:

1. Good documentation
2. Medical necessity
3. Proper CPT coding aligned with appropriate ICD diagnostic codes.

An additional aspect is the proper use of modifiers, which informs the payers of unique circumstances that require additional attention.

Office-Based Coding

Office Notes

The most important part of documentation is the office note. This is something that must reflect what service was provided. This must be legible and in this era is most often based on an electronic medical record. It is important when using an electronic record that the note reflects the examination accurately and is not just an automated note that is hard to read or describes elements, which were not completed by the physician. The documentation should support the level of service, which is selected by the provider. It must also include documentation of a procedure, such as diagnostic nasal endoscopy, 31231. This should be a separate document and reflect: the indications, the technique and the findings of the examination. If a separate visit is to be billed, the note must reflect the

Patient Name: _____

Flexible laryngoscopy: Involves passing a thin flexible fiber-optic scope through the nasal cavity and into the throat. The fiber optic scope enables the physician to visualize areas of the throat not readily seen using laryngeal mirrors.

Nasal endoscopy: Uses a flexible or rigid scope attached to a light source to view areas of the nasal cavities that cannot be viewed using a nasal speculum.

Nasal endoscopy with debridement or biopsy: Same procedure as above with removal of crusting or tissue.

We will bill as a distinct procedure from the office visit. This procedure may be separate and not included in the standard office visit. As such, **your health plan may consider it surgery and may apply its charge to a higher deductible** amount of your health plan.

By signing this form, you are acknowledging that you are aware of this billing policy

Patient Signature **Date**

Fig. 11.1: Sample patient notification for payer payment policies for in-office procedures.

additional work required to bill for this visit. The modifier 25, separate identifiable procedure, will inform the payers of this. This modifier should be placed on the office visit to allow the procedure to be billed separately.

Office Procedures

It is commonplace in a rhinology practice to perform many in-office procedures. Perhaps, the most common is nasal endoscopy. The proper code for this procedure is 31231. This is a bilateral code, thus it can only be billed once per visit, regardless if one or both sides of the nose were evaluated. This is frequently done as a procedure in the setting of an office visit.[2] When this is the case, modifier 25 should be used, informing the payer that this is a separate, identifiable procedure. In the era of high deductible plans, patients not infrequently are responsible for the bill for procedures. This can be an area of contention in an office. In the authors' experience, this is best handled by pre-emptively informing the patient in writing that an endoscopy procedure is a common and necessary aspect of medical care for otolaryngologic disorders and that this is a separate fee from the office visit. The form can be reviewed and signed by the patient at the time of registration. A sample form can be found as Figure 11.1.

Office Visit and Procedure on Same Day

Concepts

- New patient visit, consultation or established patient.
- *Modifier 25*: Significant, separately identifiable evaluation and management service by the same physician on the same day of the procedure or other service.
  - Must have work that goes beyond the work required for a nasal endoscopy to use modifier 25.
  - Preferable if there are two diagnoses so that nasal endoscopy can be linked to the nasal problem and the E&M code for the second diagnosis.

Endoscopic sinus surgery has a zero global period
1–3 Postop debridements are reasonable
4–6 Postop debridements in complex cases
This is a unilateral code, thus can be billed twice if needed; append modifier 50
Append a 79 modifier if done during the setting of another procedure with a global period
Debridement is not just suctioning mucus, packing removal or cleaning the nose, it is a minor surgical procedure[3]

Fig. 11.2: Postop debridement–31237—coding tips.

Postoperative Debridement

An important aspect of clinical care for many rhinologists, is the performance of postoperative debridements to remove crusting and debris from the surgical cavity after an endoscopic sinus surgery. This promotes healing, limits adhesion formation, and decreases infection rates.[3] The proper code for endoscopic nasal debridement is 31237. This is a unilateral code, and both sides can be billed, using modifier 50 appended to 31237, which notifies the carrier, this was a bilateral procedure (Fig. 11.2).

Endoscopic sinus debridement—31237

- Endoscopic sinus surgery has zero global days, thus endoscopic debridements may be reported in the early postoperative period, including 1 week after surgery.
- Debridements may be reported for endoscopic sinus surgery if done in conjunction with other procedures including septoplasty and inferior turbinate surgery but must be appended by modifier 79.
- Append modifier 79 on the debridement during the global period of other surgeries (i.e. septoplasty) this modifier notifies carrier that a debridement is being done for a procedure with a zero global period but within a 90-day global period of another procedure (namely a septoplasty).
- Determine if the patient's insurance payer requires precertification.
- Obtain prior authorization if precertification is necessary.
- Postoperative debridements are done at the discretion of the operating surgeon. One to three debridements

may be necessary with limited endoscopic sinus surgery, whereas more may be necessary in diffuse nasal polyposis or more complex disease.

One must document as follows:

- Tissue removed and from where
- Which sinuses were entered
- What landmarks were preserved
- Local anesthetic used
- Document any bleeding, pain or complications during the procedure.

Office-Based Imaging

Recently, many providers have obtained CTs for point of service imaging. This provides the ability for a doctor to see a patient, order imaging, obtain the testing, and review with the patient at the same setting. This can be an enormous advantage for patients. To provide imaging services for patients, guidelines must be followed to make this worthwhile and clinically important.[4]

- In-office CT-guidelines, billing, coding
- Abide by guidelines for CT sinus scans
- Obtain preapproval
- Review films with patient
- Official report by radiologist preferably or by otolaryngologist
- CT #70486—CT sinus without contrast
- CT #76380—follow-up CT sinus limited
- Global, technical, or physician component
- Always link with appropriate ICD diagnosis
- Document medical necessity in the chart
- Facility accreditation is necessary for reimbursement

31230—Diagnostic nasal endoscopy
31237—Endoscopic biopsy or debridement
31238—Endoscopic control of hemostasis
31254—Anterior ethmoidectomy
31255—Total ethmoidectomy
31256—Endoscopic maxillary antrostomy
31267—Endoscopic maxillary antrostomy with removal of tissue
31276—Endoscopic frontal sinusotomy
31287—Endoscopic sphenoidotomy
31288—Endoscopic sphenoidotomy with removal of tissue
31295—Nasal/sinus endoscopy, surgical, with dilation of maxillary sinus ostium, transnasal, or via canine fossa
31296—Nasal/sinus endoscopy, surgical, with dilation of frontal sinus ostium
31297—Nasal/sinus endoscopy, surgical, with dilation of sphenoid sinus ostium
61781—Intraoperative, intradural navigation
61782—Intraoperative, extradural navigation

Fig. 11.3: Commonly used rhinology CPT codes.[14]

Operative Coding

Operative note

This is a note that must be detailed and align with the CPT code used (Fig. 11. 3). The operative note should ideally allow another provider the opportunity to understand what was done and why it was done. It should also cover the physician from a potential audit or malpractice case. As such, it should include the risks, benefits, and alternatives of the procedure performed, as well the specific aspects of the procedure, which were performed. One can include the CPT code placed alongside the operative procedure. For a sinus procedure, the operative report should include which sinuses were opened and if tissue was removed from this sinus; this must be documented as it determines which CPT code must be used. One should dictate that CT images were in the room and reviewed throughout the case. If image guidance was used, it should include the system used, how it was registered, the accuracy, and where it was used in the surgery.

Image Guidance

Extradural image guidance is coded as CPT code 61782. For instances, requiring intradural navigation, CPT code 61781 should be used. One is not allowed to bill both codes during the same surgery. Image-guidance codes are add-on codes and are paid at a full fee and should be placed on the bottom of the list of CPT codes. This should be used based on the American Academy of Otolaryngology—Head and Neck Surgery guidelines (Fig. 11.4). In recent years, many payers have started to deny providers reimbursement for image guidance. The main reason for rejection has been inadequate documentation. This is often because indications are not clearly stated in the dictation. The need for use must be clearly delineated as well as which areas were used for navigation and localization. The image-guided code includes preoperative surgical planning and intraoperative use. This should be

Revision sinus surgery
Extensive nasal polyposis
Frontal, posterior ethmoid, and sphenoid sinus pathology
Disease abutting the skull base, orbit, optic nerve, or carotid artery
CSF rhinorrhea or conditions where there is a skull base defect
Benign and malignant sinonasal neoplasms
Distorted anatomy-congenital, acquired, traumatic[5]

Fig. 11.4: American Academy of Otolaryngology—Head and Neck Surgery guidelines for IGS.[5]

dictated into the operative report including: downloading of images, viewing images, patient registration, instrument calibration, anatomic localization, and confirmation during surgery.[5]

Endoscopic Sinus Surgery

Endoscopic sinus surgery is a unique situation as each sinus operated on is billed separately. Payers reduce payment when multiple sinuses are operated upon at the same setting. It is important to bill each CPT code as a full fee and let the payers reduce this. This should also be submitted as the CPT code with the highest value to be listed at the top of the list of procedures. All endoscopic sinus CPT codes are unilateral procedures, thus can be billed bilaterally when both sides are operated upon. Furthermore, the majority of endoscopic sinus codes have a zero day global period, thus postoperative care can be billed separately. When done in the setting of a septoplasty or another procedure with a global period, a 24 modifier should be used on the additional visit if the visit is for purposes of another diagnosis (the authors do not routinely bill for an office visit when the purpose of the visit is debridement). Furthermore, a 79 modifier should be added to the endoscopy code in this setting, provided that the procedure is done for the sinus portion and not the septoplasty. It is also important to understand that when multiple procedures are done on the same sinus (i.e. an open and endoscopic approach is used to open a frontal sinus) that only one procedure CPT code can be billed. The proper method to code this is to choose the primary procedure CPT code and add a 22 modifier to this code, to let the payer know that this procedure is more complex than the standard procedure. When submitting this bill, include a letter explaining why the 22 modifier is being used.

When documenting for endoscopic sinus surgery there are some pearls that the authors suggest in dictating which allows both the billers as well as the insurance carriers assistance in reviewing the codes submitted.

Endoscopic sinus surgery coding tips

- Document open versus endoscopic.
- Document unilateral versus bilateral (sinus codes are reported for each sinus operated upon).
- Document total versus partial (there are different codes for an anterior ethmoidectomy versus a total ethmoidectomy).
- Document tissue removal vs. no removal (there are separate maxillary and sphenoid codes based on whether tissue was removed).
- Diagnostic endoscopy is included in all surgical endoscopies and should not be billed separately.
- Gaining access to the surgical site is included in the surgical endoscopy code and should not be billed separately.
- Nasal polypectomy is included in all endoscopic sinus surgery CPT codes, so it is not a separate charge unless done as the only procedure.
- Report CPT codes in descending order of RVU value and submit the full fee to the payer.
- Make sure the proper diagnosis code is linked to each procedure code.

Balloon Sinus Dilation

In the last few years, we have seen a new era in sinus surgery with the advent of balloon sinus dilation. The question often comes up of how to bill for new technology. When a code does not exist, an unlisted code should be used. For balloon sinus dilation, new codes were created in 2012. These codes are for dilation of the sinus without tissue removal. These are unilateral codes and can be billed with a bilateral modifier (-50) if both sides are addressed. If the balloon is used as a tool and subsequent bone and tissue are removed, the standard sinus codes should be used. One may only use one code per sinus opened and thus you cannot use both an endoscopic code and a balloon code.[6]

Balloon sinus coding

- 31295 nasal/sinus endoscopy, surgical, with dilation of maxillary sinus ostium (e.g. balloon dilation),transnasal, or via canine fossa.
- 31296 nasal/sinus endoscopy, surgical, with dilation of frontal sinus ostium (e.g. balloon dilation).
- 31297 nasal/sinus endoscopy, surgical, with dilation of sphenoid sinus ostium (e.g. balloon dilation).[6]

Inferior Turbinate Surgery

Often, the inferior turbinate is addressed during sinus surgery or a septoplasty. This is a separately billed procedure. Some individual payers require the use of modifier 59 on a turbinate code to alert the payer that this is a separate procedure not related to the septoplasty. Depending on the method to reduce or reposition the turbinate, this is a unilateral or bilateral code (Fig. 11.5). A basic rule is that when bone is removed, as in 30130 and 30140, this is a unilateral code, and bilateral surgery should be appended with the bilateral modifier. For the other codes, including

-22	More extensive surgery
-24	Office visit during global period
-25	Separate, identifiable procedure
-50	Bilateral
-51	Multiple procedures
-59	Distinct procedural service
-62	Cosurgery
-79	Procedure during global period of another procedure

Fig. 11.5: Commonly used modifiers in a rhinology practice.[14]

intramural or surface inferior turbinate coblation (30802 and 30801), these are bilateral codes and modifier 50 should not be used. All inferior turbinate surgery has a 90-day global period, thus postoperative care is included in the code and cannot be billed separately.[7]

Inferior turbinate coding

- 30930—turbinate outfracture.
- 30801—submucosal cautery of inferior turbinate.
- 30802—intramural cautery of inferior turbinate.
- 30130—resection (partial or total).
- 30140—submucosal tissue resection (including bone).[7]

Middle Turbinate Surgery

Another area of controversy in rhinology coding is the use of 31240. This is the code that should be used for resection of a concha bullosa. This is a procedure that can be separately billed if a concha exists and disease exists because of the concha. One must append a modifier to the concha bullosa code, such as a 51 or 59, to alert the payer that this is a separate procedure from the ethmoidectomy. The following are guidelines which are helpful in deciding if a concha bullosa should be billed.[8]

Guidelines for concha bullosa billing

- Middle turbinate surgery is included in endoscopic sinus procedures as part of "gaining access" to the sinus and should not be billed separately in this setting.
- An endoscopic resection of a separately identifiable concha bullosa (31240) may be coded; unilateral code; however, getting paid is difficult.
- The concha surgery must be performed because the concha is causing disease and not simply for access to the ethmoid cavity.
- Literature to support 31240 as additional work beyond middle turbinate surgery is available.[8]

Epistaxis

In the past, epistaxis management consisted of nasal packing, simple cautery and artery ligation. In the endoscopic era, there are additional procedures in the armamentarium of the otolaryngologist. This includes endoscopic control of epistaxis as well as endoscopic ligation of the sphenopalatine, anterior, and posterior ethmoidal arteries. Some of these procedures are done in the office, whereas others are done preferentially in the operating setting. It is important when doing more advanced procedures, such as artery ligation, that one does not use the codes designed for a nonendoscopic approach and thus uses an unlisted procedure code, comparing this to the nonendoscopic code. All epistaxis codes are unilateral and thus can be billed twice if this is done bilaterally.

Epistaxis coding

- 30901—control of nasal hemorrhage, anterior, simple (limited cautery or packing).
- 30902—anterior, complex (more extensive cautery or packing).
- 30905—control of nasal hemorrhage, posterior.
- 30906—posterior, subsequent procedure.
- 31238—nasal endoscopy with control of nasal hemorrhage (the endoscopy must be used for visualization during cautery because anterior rhinoscopy is inadequate).
- 31299—unlisted sinus procedure (use for sphenopalatine or endoscopic artery ligation).

Cosmetic Procedures

Many rhinologists offer cosmetic and functional rhinoplasty as part of their practice. This can include repairing a nasal valve, which can be done alone or as part of a septoplasty. Repairing the nasal valve, 30465 can be billed along with a septoplasty, 30520. This does not include the harvest of the graft if this is done from an additional site. There are also guidelines, which must be followed, if a cosmetic procedure is done along with a functional procedure. These are as follows:

Functional and cosmetic rhinoplasty—How to code?

- Discuss functional versus cosmetic with patient.
- Dictate one operative report.
- CPT codes for functional component.
- Cosmetic part needs prepayment as this is usually an uncovered procedure.
- Get this in writing.
- Be honest with insurance company.

Skull Base

Skull base coding has become a topic of hot debate since a number of these procedures have moved to endoscopic

procedures. Open skull base procedures are easier to code as codes exist for these and the appropriate approach, resection, and reconstruction codes should be used for this. Endoscopic skull base codes exist only for a select number of procedures at the time of this publication including pituitary surgery, cerebrospinal leak repair, and optic nerve decompression. When done in conjunction with neurosurgery, the surgeon should append the 62 modifier, informing the insurance company that this is a team surgery. When a surgeon does an endoscopic procedure that does not have an endoscopic code, the most appropriate approach is to use an unlisted code and submit a letter to the insurance carrier, explaining the need for an unlisted code since a code does not exist that explains the work that was done.

The proper method would include choosing the appropriate unlisted code—either 31299 (unlisted sinus code) or 64999 (unlisted neurosurgery code) describing the surgery done. The surgeon should then describe the procedure done; the time, equipment, and expertise required and why it was done in this manner. The surgeon should choose like codes for comparison purposes only and request similar reimbursement, more or less than these codes based on the work done. If this is rejected by the payer, the physician should appeal this decision, and in some instances this may require a discussion with the insurance carrier's medical director.[9]

Use of unlisted codes

- Choose the proper unlisted code (i.e. 31299—unlisted sinus code).
- Write a letter explaining what was done and that there is no code for this procedure.
- Choose a comparison code(s).
- Request a proper amount of reimbursement.
- Appeal if rejected.

Future Challenges

We continue to see changes yearly for coding and billing. Rhinology is no exception to this. Most policies are driven by Medicare, although some payers make policies either nationally, regionally, or locally. Some of the recent changes Medicare has made are mentioned below.

CMS/Medicare Reimbursement Issues

Related to consultations after 2010

- Consultation CPT codes for new patient in the office, hospital, and emergency room were deleted.[10]
- All CPT E&M codes will be new or established for office, hospital, or emergency room with physician referral being of no significance.[10]
- Careful scrutiny of all office-based radiology codes.

CAREER PATHWAYS IN RHINOLOGY

Training

Career development within rhinology has undergone major evolutionary steps in the past decade, namely its identification as a distinct subspecialty and the widespread proliferation of postresidency fellowship training. Fellowship training has been formalized as a match process and the number of programs offering positions and the number of resident applicants continue to thrive. The fellowship experience primarily allows for a higher level of training for advanced surgical procedures and complex clinical care of sinonasal patients. Other aspects of career development are also fostered by rhinology fellowship, including research, academic activities, and mentorship by senior faculty. Although common rhinologic disorders are still an integral component of general otolaryngology, the increasing breadth and complexity of the field has resulted in the need for dedicated training and career focus on rhinology. For residents considering a career devoted to rhinology, fellowship training is crucial.

Academic

Although once a clear distinction could be made between an academic career and a private practice career, these lines have since been blurred in many areas of the country. It is not uncommon for academic doctors to have a portion, if not all of their income, based on production and for private practitioners to have academic appointments and responsibilities. For the most part, it can be anticipated that an academic career would have less income potential than a private practice. This is because an academic career often includes many other duties in addition to clinical responsibilities, including research, teaching and administrative roles. Each academic model has varying emphasis on these different activities with greater or lesser time spent performing nonclinical activities. Within rhinology, the clinical scope of academic practice may place a greater emphasis on advanced pathologies and surgical procedures, including skull base surgery. In addition, participation in clinical and basic science research is inherently tied to academic medicine.[11]

Private

There are many different private practice models. For all practical purposes, in the absence of a cash-based practice such as is common in plastic surgery, the complexity of medicine and consolidation of services has made the solo practitioner a rarity unless one has a significant reputation and name in the community. Most doctors today will have several options for private practice. This includes a hospital based practice, single-specialty group practice, multispecialty group practice, or a faculty practice plan.

Hospital-based practitioners have several advantages and disadvantages. First, the doctor usually has defined work hours, responsibilities and call. The doctor often has little business responsibilities and usually has a salary or an incentive-based contract. The idea is that the doctor can just show up and work. However, income and practice growth potential are often limited and not infrequently, tied to the health of the overall organization. It may be harder to control work hours, staffing and equipment needs. This needs to be considered when applying and accepting these jobs.

A single-specialty group likely will give the practitioner the most flexibility. These are usually structured as a partnership where the doctor will have the most control over staffing, office space, work hours and income potential. In return, it is useful for a doctor to have some basic understanding of business and often requires doctors to market themselves within the community. Many single-specialty doctors end up working more hours to accommodate patients and referring doctors and often require multiple office locations and hospital affiliations. To join a single-specialty group, most practices will have some form of buy-in to become a partner.

Multispecialty groups often have the advantage of built in referrals within the network. They are usually larger groups where a central office takes care of administrative details such as contracting and billing. It is not uncommon, however, that within a multispecialty group the specialists make a little less money to supplement other traditionally lower grossing specialties.

A faculty practice is usually an off-shoot of an academic hospital. Instead of being financially tied to the hospital the faculty practice usually has a separate governance and administration. In many respects, it functions as a hospital-based practice model.[12]

ACO Development and Opportunities

With the advent of the Patient Protection and Affordable Care Act (Obamacare), there has been a push toward the development of Accountable Care Organizations (ACOs). These are still in the development form, and the final product is still yet to be determined. The premise is that by empowering physicians to manage care and reap some of the financial benefits of potential savings, that a physician group will offer a cost-effective, high-quality product to patients, also limiting the cost of care. What this means for the otolaryngologist is that they will be scrutinized to provide patients with high-quality care at a lower cost. For the rhinologist, this will require utilizing evidence-based guidelines. Imaging should be based on clinical guidelines and not driven by patient demand. Physicians will likely be rated by insurance companies and physician groups and high utilizers/high-cost providers will likely be cut out of the ACOs. For a start, following guidelines such as Choose Wisely is advisable. Information about this can be found on the Academy's Web site.[13]

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SECTION 4

Allergy

CHAPTER

12 Epidemiology and Pathophysiology of Allergic Rhinitis

James W Mims

INTRODUCTION

Allergic rhinitis represents a hyperactivity of the immune system to otherwise innocuous particles creating an inflammatory response where none is required. The inflammation caused by the environmental exposure produces symptoms including sneezing, itching, rhinorrhea and nasal congestion. Although allergic rhinitis has no significant risk of mortality, the symptoms have a substantial impact on sleep, productivity and quality of life. The ubiquity and impact of allergic rhinitis combine to make it an important condition affecting the health of hundreds of millions of people worldwide.

DEFINITION

A precise definition of allergic rhinitis that is linked to a single-specific pathophysiologic abnormality does not currently exist. Allergic rhinitis more likely arises from a combination of ill-defined genetic predispositions interacting with a varied slate of environmental stimuli. The prevalence of allergic rhinitis varies with age, race, geographic location, socioeconomic class, infectious exposures, family history, and criteria used for diagnosis. Thus, the broadness of the definition and prevalence are associated with some controversy, and disparate information is common in the medical literature.

The 2008 ARIA (Allergic Rhinitis and its Impact on Asthma) review defined allergic rhinitis as "a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE) inflammation".[1] Although this is a reasonable definition, there may be notable exceptions. A non-IgE-mediated nasal reaction to a mold causing nasal inflammation would not be considered "allergic rhinitis" under this rubric. An individual with sneezing and rhinorrhea during tree pollen season, who exhibits inducible symptoms on nasal challenge with tree pollen, and who is skin prick test (SPT) negative, would not be included as having "allergic rhinitis" either. Rhinitis is categorized as allergic or nonallergic, but making this distinction is not always clear. The clinical diagnosis of allergy is complicated by nonspecific nasal symptoms and nonspecific allergy testing. Recently, reports of allergen-specific IgE detected in nasal secretions when not detected on skin tests or serum testing has generated interest in "local allergy" or "entopy".[2] This may explain some of the discrepancies between testing and symptoms; however, the role of "local allergy" in rhinitis is not currently well understood.

GENETICS OF ALLERGIC RHINITIS

Genetic studies of allergic rhinitis suggest the predisposition toward allergic rhinitis is regulated by multiple genes and gene–environment interactions.[3] Genetic research into allergic rhinitis can be divided into hypothesis-dependent and hypothesis-independent investigations.

In hypothesis-dependent studies, a genetic substitution in a particular segment of the genetic code is compared in those with and without allergic rhinitis. Most studies have focused on genes that produce the components of IgE-mediated inflammation, such as interleukin 4 (IL-4) or the high-affinity IgE receptor. Multiple single aberrations in the genetic code of those with allergic rhinitis have been

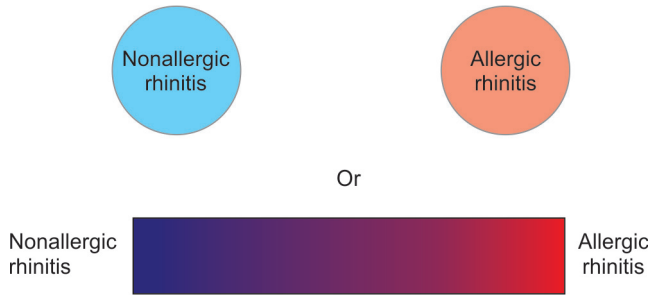

Fig. 12.1: Allergic and nonallergic rhinitis. The definition of allergic rhinitis implies two distinct groups. Rhinitis with testing showing IgE-mediated inflammation and rhinitis with negative testing. The genetics of allergic rhinitis suggests different pictures where multiple genes shift the spectrum of chronic rhinitis along a spectrum between allergic and nonallergic.

published, but reproducibility has been elusive. Some substitutions have been repeated in multiple studies and include STAT6, IL4, IL4 receptor, IgE receptor, HLA receptors, CD14, and ADAM33.[4]

In hypothesis-independent studies, thousands of genetic variations throughout the genome are compared between affected and nonaffected populations. These studies have tended to identify different genes in allergic conditions than the hypothesis-dependent studies such as ORMDL and RAD50. The function of some genes that seem to be associated with allergies and asthma is unclear. In addition, all of the individual genetic variances identified to date only occur in a modest percentage of those with allergies.[3-5]

However, genetic studies suggest that it is not just variations in the inflammatory cascade that contribute to the allergic phenotype, but also epithelial integrity, environmental sensing, eosinophilia mediators, and tissue response. Alterations in the broader immune system play a role in allergic expression.[3] This may underpin the clinical observation that allergic and nonallergic rhinitis presents more as a continuum than two distinct disease states (Fig. 12.1).

Gene–environment interactions and epigenetics also influence allergic disease. One example would be how a single-nucleotide substitution in IL-17 did not affect the expression of asthma unless associated with maternal tobacco use during pregnancy.[6] Other nonallergenic exposures have been shown to influence the expression of allergic inflammation, such as lipopolysaccharide levels in dust samples appear to affect allergic sensitization.[7]

Like many other chronic inflammatory diseases, which are increasing in the population, the genetic predisposition to allergic rhinitis is most likely controlled by multiple genes and gene–environment interactions. This complexity correlates with the broad clinical variances observed.

EPIDEMIOLOGY

Several factors confound determining the prevalence of allergic rhinitis in a large population. Standardizing the diagnosis of allergic rhinitis has been problematic as objective testing alone without clinical impression lacks specificity. Combining clinical impression with objective skin or blood testing is the preferred way to make the diagnosis but introduces subjectivity. Allergen exposure has multiple variables including pet ownership, home and work environment, and geographic location. In addition, the prevalence of allergic rhinitis within a community varies with socioeconomic class and ethnicity.[1,8]

The prevalence of allergic rhinitis, diagnosed based on history, physical examination, and allergy testing, which is severe enough to significantly impair quality of life, is incompletely defined for the US population. The National Health and Nutrition Examination Survey of 2005–2006 was conducted by the Center for Disease Control and asked about allergies in a sample of nearly 10,000 individuals selected to represent the US population. Overall, 2676/9882 (27%) reported a problem with sneezing in the last 12 months, 1704/9882 (17%) answered "yes" to allergy symptoms in the last 12 months, and 2614/9882 (26%) answered "yes" that a doctor or healthcare professional had ever told them that they have allergies.[9]

In a similarly large study, allergy skin prick testing for inhalant allergens was performed on a representative sample of the US population independent of clinical allergy symptoms, and 54% tested positive for one or more inhalant allergens.[10]

A cross-sectional Swiss study nicely illustrates issues in assessing the prevalence of allergic rhinitis.[11-13] A total of 9651 adults were evaluated with the following questions in the SALPADIA (Swiss Study on Air Pollution and Lung Diseases in Adults): "In the last 6 months, did you suffer from allergic rhinitis, including hay fever?" and "Did you experience a runny or stuffy nose, the urge to sneeze, or itchy or watery eyes related to common allergen exposure?" Participants were also tested objectively using SPT and specific IgE tests. Either skin prick testing or specific IgE testing was positive in 32.3% of the population (females 29%, males 36%). They diagnosed allergic rhinitis in those who answered positive to one of the screening questions and either a positive SPT or specific IgE test. Allergic rhinitis was diagnosed in 13.5% (females 13%, males 14%).

The positive predictive value for an SPT was 48.7% and 43.5% for specific IgE testing. This study illustrates how epidemiologic estimates on the prevalence of allergic rhinitis vary substantially with whether both clinical assessment and testing were used to make the diagnosis.

In addition, there are large regional variations. The International Study of Asthma and Allergies in Childhood (ISAAC) is a large, world-wide study conducted in three phases.[14-17] Phase I assessed symptoms of asthma, rhinoconjunctivitis, and eczema in >700,000 children in two age groups, 6–7 years and 13–14 years of age. Variations in reported rhinoconjunctivitis symptoms varied 25-fold between countries. Phase III repeated these assessments 5 to 10 years later. The results are varied and probably best described as an increasing prevalence where initially low, especially in developing countries and a plateau or decrease at the centers where the prevalence was initially high. In the United States, the reported prevalence in the 13–14-year-old age group changed from 13.4 to 19.1 over 8 years.[18]

Phase II of ISAAC[15] involved testing of dust samples, allergy skin tests, pulmonary functions, and blood sampling to provide more detail in 9–11 years old. The portion of rhinitis symptoms attributed to atopy (defined in this study as positive skin testing or increased specific IgE) varied from 0% to 71%. In affluent countries, this percentage was higher (36% seasonal, 25% perennial) than in nonaffluent countries (1.3% seasonal, 12.6% perennial). The authors observed that the importance of allergy in rhinitis was less than previously thought.

In the United States, the prevalence of allergic rhinitis in childhood is frequently cited as 40%. In 1994, the prevalence of physician diagnosed "allergic rhinitis" was published as 42% as part of the Tucson Children's Respiratory Study in 747 children up to age 6.[19] However, their definition did not require positive skin testing. Of the 311 children diagnosed with physician diagnosed "allergic rhinitis", 129 (40%) were skin test positive, 129 (40%) were skin test negative, and 53 (20%) were not tested. Of the 747 children in the study, 129 (17.2%) were both skin test positive and had physician diagnosed allergic rhinitis. Of the 216 children with "no rhinitis" who had skin testing, 69 (31%) were skin test positive. Rhinitis of some type was reported in 474 of 747 (63%) of the children.

Adult studies in the United States also show significant discordance between specific IgE testing and reported rhinitis. Abraham et al. investigated specific IgE testing and self-reported allergies in a series of 702 pregnant women under the assumption that allergic rhinitis and pregnancy were independent.[20] Of the 24.5% who reported "hay fever", 66.7% had positive specific IgE tests, and of those who denied "hay fever", 49.8% had positive specific IgE tests. Although this represents a statistically significant difference, the authors affirmed that clinically allergy testing in the absence of history is not that meaningful. This again highlights both a lack of specificity with self-reporting and a lack of specificity with objective testing. This study also supports that about 16% of the studied population had both the self-reported symptoms and objective testing to diagnose allergic rhinitis, whereas 54% of the tested pregnant women had at least one positive specific IgE test for an inhalant allergen independent of symptoms.

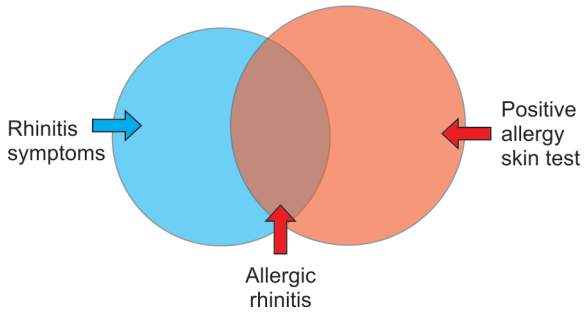

Fig. 12.2: Allergic rhinitis, rhinitis, and specific IgE sensitization. Rhinitis symptoms may occur in 40% of the US population, and 54% of the population has a positive reaction to at least one common inhalant allergen on skin prick tests. Allergic rhinitis is diagnosed in those who have both, given that symptoms and testing are plausibly related.

In conclusion, rhinitis symptoms are common, especially in children, but may be allergic, nonallergic, or mixed. Positive allergy tests are also common in the general population but not very specific at predicting symptoms. Allergic rhinitis is diagnosed in those with clinical rhinitis and positive allergy tests that correspond to their symptoms (Fig. 12.2). Allergic rhinitis defined by symptoms and corresponding allergy testing affects 15–20% of the US population and varies considerably worldwide.

Classification of Allergic Rhinitis

Allergic rhinitis is frequently subdivided by age (children vs adults), severity (mild, moderate or severe), and duration of symptoms (intermittent or persistent) (Table 12.1).

Although frequently cited that allergic rhinitis is more common in children than in adults, results of the Phase II ISAAC studies do not strongly support that view.[21] The prevalence in children is highly variable between countries.

Table 12.1: Allergic Rhinitis and its Impact on Asthma 2008 classification of allergic rhinitis

Duration	Intermittent	Symptoms are present < 4 days a week or < 4 consecutive weeks
	Persistent	Symptoms are present > 4 days per week and > 4 consecutive weeks
Severity	Mild	Moderate/severe impairments absent
	Moderate/Severe (One or more of the listed effects)	Sleep disturbance Impairment of daily activities, leisure, or sport Impairment of school or work Troublesome symptoms

Severity of allergic rhinitis is divided by the impact on quality-of-life measures and allergic rhinitis is classified as either "mild" or "moderate severe". "Moderate severe" allergic rhinitis has one of the following: sleep disturbance, impairment of daily activities, impairment of school or work, or troublesome symptoms. "Mild" allergic rhinitis requires the absence of the same criteria.[1]

The duration of symptoms has been generally categorized as intermittent/seasonal or perennial/persistent. ARIA guidelines argue that intermittent exposure to some allergens, such as mold spores, may not follow seasonal variations. Studies have shown that intermittent and seasonal are not interchangeable. Persistent allergic rhinitis is defined as >4 days per week for >4 consecutive weeks.[1] In four studies conducted in Spain, the proportions of intermittent/seasonal allergies ranged from 59.5% to 64% compared with 35.1 to 40.5% for perennial/persistent.[22-25] Results were similar between adults and children. Contrarily, a large survey in the United States found seasonal rhinitis to be more common in children.[26]

Risk Factors

Why some individuals develop allergic rhinitis and others do not remain poorly understood. Both genetic and environmental influences have been implicated, but most theories have attracted supporting and conflicting data, suggesting that allergic rhinitis may be a diverse disease.

A family history of allergic rhinitis likely confers some risk.[27] Most other risk factors fall under the rubric of the "hygiene hypothesis".[28] The hygiene hypothesis suggests that children in developed countries have been exposed less to infectious agents and other immune system stimulants early in childhood (increased hygiene), which results in a lack of immune tolerance and an increasing prevalence of immune hyperactivity disorders. Studies supporting this show higher rates of allergic diseases in higher socioeconomic class, children without siblings, first-born children, and children in developed countries. Meanwhile, having a cat in infancy, daycare, siblings, close contact with livestock, and rural living have been found to be protective against developing allergies in some studies.[29] However, growing evidence has shown a more complicated relationship where early childhood infections can be either conducive or protective toward developing allergies depending on the organism, timing, and individual genetics.[30]

An example of the complexity of assessing risk in allergic disease is represented in the studies that have investigated pet ownership in infancy. In 1999, two studies in Sweden found that cat ownership in infancy was protective against allergic asthma.[31,32] A 2002 study contrarily showed in "high-risk" infants whose mothers had asthma, that cat ownership increased the risk of later developing asthma.[33] This suggested that cat exposure may be protective for some infants while increasing allergic risk in others. In 2012, a meta-analysis of 11 prospective studies involving over 22,000 children showed no association between any pet ownership and allergic rhinitis or asthma.[34] Whether this should be interpreted that the protective and conducive effects cancel each other out or that smaller studies were prone to sampling error is controversial. It is also possible that parents with dander allergies are less likely to own cats, which would skew the results (Fig. 12.3).

Other theories have linked allergy to the larger idea of immune dysregulation. Whether vitamin D, environmental chemicals, dietary fiber or changes in the microbiome have any effect of the development of allergy has yet to be sufficiently proven, but multiple theories have emerged.[35]

Economic Burden

Estimates of the economic costs of allergic rhinitis have varied but are consistently in the billions of US dollars. In 1995, the National Health Interview Survey and earning estimations from the Bureau of Labor Statistics were used to calculate $601 million in lost productivity from allergic rhinitis. When the use of sedating antihistamines was included, lost productivity was estimated at $2 to $4 billion for the United States.[36] In 2004, Reed et al. reported that United States studies varied significantly on indirect costs, finding studies that estimated only indirect costs of allergic rhinitis reported higher estimates ($5.5 to $9.7 billion)

Fig. 12.3: Household cat in infancy and allergy development. The relationship between cat exposure during infancy and allergic asthma nicely represents the complexity in assessing risk factors in allergic disease. A large Swedish study found cat ownership to be protective.[31] A later study found if there was maternal asthma that cat ownership increased risk of allergic asthma.[33] A meta-analysis concluded there was no effect.[34]

than studies estimating direct and indirect costs ($1.7 to $4.3 billion). They also found calculations of direct costs varied threefold ($1.6 to $4.9 billion).[37]

Impact on Quality of Life

Allergic rhinitis is not considered a life-threatening condition but has a significant impact on quality-of-life measures. Nasal congestion is frequently listed as the most bothersome symptom[26] and may contribute to sleep disturbance and fatigue. One survey found that decreased job performance was reported by 36% of those with allergic rhinitis compared with 19% with asthma.[38]

Sleep impairment has been reported in patients with moderate/severe allergic rhinitis as compared with those without rhinitis or those with mild rhinitis. The impairment is not restricted to a specific stage of sleep; however, the role of allergic rhinitis in sleep apnea remains unclear.[1] Published studies have reported sleep disturbance in 57% of adults and 88% of children with allergic rhinitis.[26] A recent review of allergic rhinitis and sleep-disordered breathing in children found the majority of studies showed a significant association, but the evidence levels were low, 3b and 4.[39]

The impact of allergic rhinitis may be underestimated by missed work or school days. Allergic rhinitis may result in decreased productivity at work or school, denoted as "presenteeism", as compared with missed work or school, "absenteeism". In a detailed survey of children with allergic rhinitis and their families, absenteeism from school was similar in those with and without allergic rhinitis. However, parental concern over diminished performance while at school was reported by 40% of parents of children with allergic rhinitis, which was statistically higher than the controls.[26] This was also evidenced in a study in England where students with grass allergy were more likely to perform poorly on a summer examination (as compared with their performance in the winter) than nonallergic students.[40]

Presenteeism has also been estimated as a major concern among adults with allergic rhinitis. It was estimated in 1994 that workers in the United States had 4.23 million "reduced activity" days per year attributed to allergic rhinitis.[41]

Comorbidities

Allergic rhinitis is linked both to other allergic conditions and other conditions arising from chronic respiratory inflammation. Other allergic conditions include allergic asthma, allergic conjunctivitis, atopic dermatitis, and food allergies. Inflammatory comorbidities include eustachian tube dysfunction, headaches, sinus problems, and asthma.[26]

Asthma is consistently diagnosed three- to fourfold more frequently in those with rhinitis symptoms.[1,26] This has prompted advocacy for the "Unified Airway" with recommendations that individuals with rhinitis or asthma be evaluated for both.[42] The upper and lower respiratory systems have a common epithelium and common inflammatory mediators. Asthma and rhinitis symptoms are more severe in those who have both than in those with only asthma or rhinitis. Also, rhinitis frequently precedes the diagnosis of asthma[42] (Fig. 12.4).

The relationship between allergen sensitization (positive specific IgE or skin prick test) and multiple allergic manifestations (food allergy, dermatitis, rhinitis, and asthma) is frequently referred to as atopy. Using this definition, not everyone with allergic rhinitis is atopic. Atopy is thought to be an undefined genetic predisposition that is often associated with a progression of symptoms commonly known as the "allergic march". Classically, the allergic march begins with atopic dermatitis and food allergy in infancy, allergic rhinitis in middle childhood, and asthma in later childhood and young adults. Cohort studies demonstrate that significant variance from this narrative is common,[43] and a trustworthy estimate of those that follow the classic progression is not known. However, atopic markers are used in diagnosing allergic asthma in young children who are too young to participate in spirometry.[44]

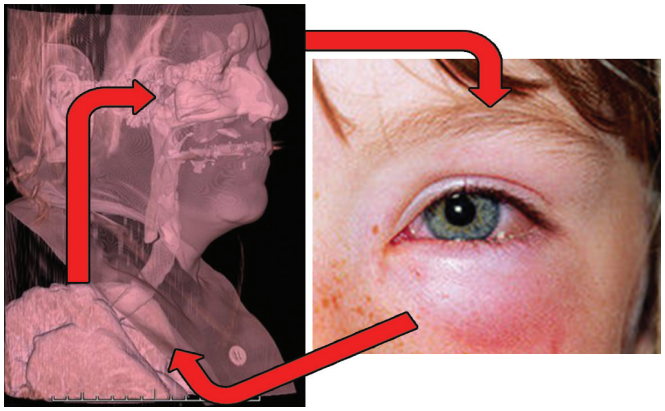

Fig. 12.4: Major comorbidities of allergic rhinitis. Allergic rhinitis, allergic conjunctivitis, and allergic asthma frequently coexist in the same patients. While there are other comorbidities, the relationship between rhinitis and asthma is well documented.[1] Allergic rhinitis and allergic conjunctivitis may have up to 80% overlap.

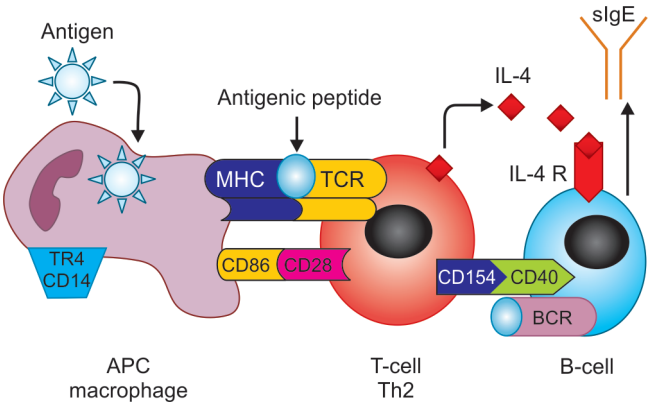

Fig. 12.5: Classic pathophysiology of IgE production. Allergen is recognized by antigen presenting cell (APC) and the allergenic peptide presented to a T-cell receptor (TCR) via binding with major histocompatibility receptors (MHC). Costimulation of the APC through Toll-like receptor 4 (TR4) with cluster of differentiation 14 (CD14) may influence the presentation to the T helper 2 lymphocyte (Th2 cell). The Th2 cell will generate proallergic mediators such as interleukin 4 (IL-4). Undifferentiated B cells through a combination of allergenic binding with B-cell receptors, Th2 cytokines, and T cell binding can transform into an IgE producing plasma cell.

The relationship between ear disease and allergic rhinitis remains controversial. Some studies have not supported a significant relationship between recurrent acute otitis media in infancy and allergic rhinitis.[45,46] This may be explained by the prevalence of viral rhinitis in infancy and that allergic sensitivity to inhalant allergens is usually not observed until later in childhood. Some studies have found an association between otitis media with effusion and allergic rhinitis in older children, although there have been concerns about bias in patient selection.[46] In adults, there may be an increased rate of allergies seen in those with vertigo, but studies are few and small. Nasal inflammation certainly neighbors the Eustachian tube and the middle ear seems susceptible to symptoms when inflamed.

The relationship between allergic rhinitis and chronic sinusitis is surprisingly not well documented in the literature. Several studies suggest nasal polyps are seen at similar frequency in allergic and nonallergic individuals.[47] Many patients with severe allergic rhinitis do not have nasal polyps. The etiology of chronic sinusitis without polyps is not well understood. When allergic rhinitis is present with chronic sinusitis, controlling allergy is likely helpful. Some studies have shown that allergic rhinitis is over-represented in patients who continue to have symptoms after sinus surgery.[48]

PATHOPHYSIOLOGY

Using the ARIA definition, allergic rhinitis is an IgE-mediated disease.[1] While there is a large amount of interconnectedness and duplication in immune system, there is a basic understanding of IgE sensitization that provides a framework for clinical use (Fig. 12.5).

Inhalant allergens are presented to mucosal membranes of the eye and respiratory mucosa (nose and lungs) on particles small enough to be suspended in "disturbed" air. These particles range in size of 0.1 to 100 micrometers and tend to include pollens, mold spores, dried dust mite feces, desiccated insect parts, and mammalian dander. Larger particles tend to deposit in the nose while smaller particles travel to the lung by properties of physics. Proteins on the particles that can stimulate the immune system to produce IgE are considered allergenic. The particular sequences that bind IgE on the proteins are known as allergic epitopes.

Particles on the mucus membranes encounter antigen presenting cells (APCs), which bind allergen proteins with major histocompatibility complex (MHC) receptors. Each individual has unique set of MHC receptors, which are integral in the immune system's ability to identify self- from nonself- and harmful from nonharmful substances. Examples of APCs included dendritic cells, Langerhans' cells, and macrophages. Recently, there has been considerable attention to role of APCs in regulating inflammation, but classically their role has been considered to transfer the allergen to a regulating T-helper lymphocyte (also known as a Th lymphocyte or CD4 lymphocyte).[49,50]

The Th lymphocyte must also recognize the allergen and specific signals from the APC. To aid in the immune system's ability to adapt to different types of infections, Th cells are biased to produce different groups of mediators, and this bias in function has two major groups, Th1 and Th2. Th1 lymphocytes help the immune system primarily with bacterial infections. Th2 lymphocytes release mediators that help defeat parasites. Interestingly, the Th2 lymphocytes regulate the type of inflammation seen in allergic conditions.[49,50]

Allergen stimulated Th2 lymphocytes release a host of mediators that promote allergic inflammation including IL, which activates other inflammatory cells, and chemokines, which primarily recruit inflammatory cells. IL-4, IL-5 (eosinophil activation), and IL-13 are especially important Th2 cytokines. T-cell receptors are thought to play an important role in regulating inflammation.[49,50]

In the presence of IL-4, Th2 cells may again present the allergen to a B lymphocyte. Complex signaling allows the B cell to change to an IgE-producing plasma cell that produces IgE specific for the allergen initially encountered by the APC. The monoclonal IgE is released and if free to bind with IgE receptors on other cells. Many of the cells with roles in the immune system have IgE receptors that may play a role in regulation, but the high-affinity IgE receptors on effector cells that degranulate (mast cells and basophils) are the most responsible for allergic symptoms.[49,50]

Mast cells tend to congregate in epithelial tissues of the skin, conjunctiva, nose, and lung where allergic responses are observed. Once a predisposed individual is re-exposed to the allergen, the allergen can bind directly to the IgE molecules on the mast cell and trigger degranulation of preformed mediators (Fig. 12.6). The degranulation of mast cells releases mediators that cause and promote inflammation. In allergic reactions, histamine and leukotrienes have important contributions.[49,50]

Exposure of the nose to histamine results in immediate rhinorrhea, vasodilation and congestion, itching, and sneezing by binding to histamine (H1) receptors on nerves, vascular endothelium, and smooth muscle.[51]

Leukotrienes, once known as the slow reacting substance of anaphylaxis, mediate a delayed reaction partially through recruitment of inflammatory cells, which also contributes to symptoms of nasal congestion and mucus production in the nose. Leukotrienes are synthesized through the arachidonic acid pathway rather than released as a preformed mediator that contributes to the delay.

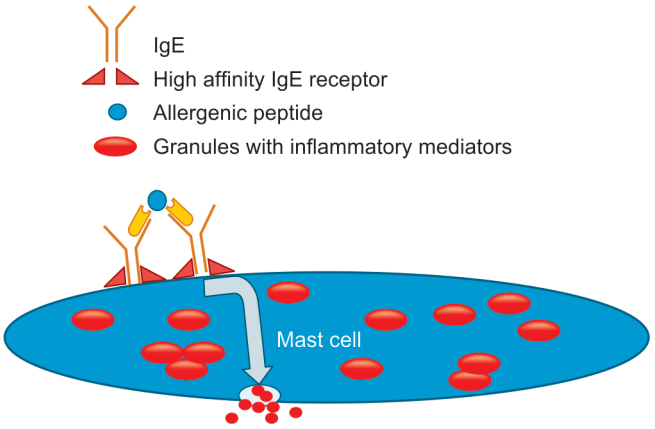

Fig. 12.6: Allergen triggered mast cell degranulation, IgE specific for the allergen is bound to the surface of the mast cells. When two IgE molecules cross link to the allergen on re-exposure, mast cell degranulation is triggered. The granules contain preformed mediators of allergic inflammation such as histamine that quickly produce symptoms.

In both allergy skin tests and allergen challenges to the nose, immediate and delayed reactions (around 6 hours later) are often observed.[52]

The above outlined pathway of IgE-mediated inflammation is balanced by mechanisms to reduce inflammation that include T regulatory lymphocytes and IL-10 along with the Th1 system. Whether the hyper-reactivity to harmless particles that occurs in allergic rhinitis is a function too much "upregulation" or too little "downregulation" (or both) is not known. However, current theories on the how allergen desensitization may work note increases in IL-10 and T regulator lymphocyte function among other changes.[49,50]

CONCLUSION

The immune system has the complex task of reacting to harmful nonself proteins that could represent infectious organisms. Allergic hypersensitivity reactions occur when the immune system over reacts to otherwise harmless proteins via IgE-mediated inflammation. The most common manifestation of inhalant allergic disease is allergic rhinitis.

Allergic rhinitis arises from a heterogeneous assortment of gene–environment interactions that are not well characterized. Allergic rhinitis affects approximately 16% of the US population, but estimates vary substantially. Specific IgE sensitization independent of rhinitis and rhinitis independent of specific IgE sensitization are both common. Allergic rhinitis is increasing by most reports

and more common in developed nations. The prevalence of IgE-mediated allergic rhinitis varies widely in global studies.

Although not life threatening, allergic rhinitis has a profound effect on quality of life, sleep, school performance, and work productivity with direct and indirect costs estimated in billions of US dollars annually. Allergic rhinitis is also associated with other inflammatory and allergic conditions, particularly allergic asthma and allergic conjunctivitis.

The IgE-mediated inflammation arises in a two-step process where allergen exposure must trigger specific IgE production. Subsequent allergen exposure results in immediate IgE-mediated degranulation of mast cells and basophils with preformed mediators, such as histamine, leading to symptoms.

Understanding the basic epidemiology and pathophysiology of allergic rhinitis provides a foundation for better interpreting allergic testing and planning treatment strategies.

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CHAPTER

13

Evaluation and Diagnostic Testing of Allergic Rhinitis

David L Rosenstreich, Elina Jerschow, Purvi Parikh, Gabriele de Vos

INTRODUCTION

Allergic rhinitis is a relatively common disorder affecting 10–25% of individuals in Western societies.[1] In part, because of its commonality, most practitioners are familiar with this condition and in most cases it is relatively easy to diagnose.[2] Nevertheless, patient outcome is greatly improved by a more thorough diagnostic evaluation that goes beyond what is sometimes performed for this condition. In this regard, the initial evaluation is the most critical part of a patient's management, and sets the stage for all subsequent therapeutic decisions.

Allergic rhinitis is due to the deposition onto the nasal mucosa of allergens to which the patient has already produced specific immunoglobulin E (IgE).[3] The interaction of the allergen with IgE receptors on tissue mast cells causes a biphasic reaction with an early and a late phase. The early phase occurs within minutes after the cross-linking of mast cell-bound IgE and involves the release of allergic mediators (primarily histamine) that induce the acute symptoms characteristic of the disease (sneezing, rhinorrhea and nasal congestion). The late phase occurs after 4–6 hours and is due to the production of slower and longer-acting mediators (leukotrienes) and the influx of inflammatory cells (primarily eosinophils, basophils and lymphocytes), and is characterized clinically by more prominent nasal congestion.

Allergic rhinitis may be classified based on its temporal pattern.[4]

Acute intermittent disease: This is seen in patients who are allergic to substances; they encounter only occasionally. An example of this pattern involves patients who are allergic to cat dander and develop symptoms whenever they are near a cat. Another example involves patients who are allergic to dust and only develop symptoms when exposed to a dusty environment (e.g. when performing extensive house cleaning). This form of allergic rhinitis is relatively easy to diagnose with a proper medical history.

Seasonal disease: Seasonal allergic rhinitis occurs in patients who are allergic to allergens that are only present in the ambient air at specific times of the year. Most commonly, this is seen with allergies to airborne pollen, is usually limited to warmer times of the year in temperate climates, and will often occur at the same time every year. In addition to airborne pollens, warm weather symptoms can also be induced by allergies to airborne mold spores that usually peak when the weather is warm and humid. Other patients will report that they develop symptoms in colder weather, often in cooler climates when "the heat in the house comes on" and this may be due to exposure to indoor allergens such as dust, pet dander, or indoor mold spores.

Chronic (perennial) disease: Many individuals with allergic rhinitis experience symptoms throughout the year. These individuals are usually allergic to allergens that are present in the environment all year round, such as dust, pet dander, feathers, and indoor mold spores. This form of allergic rhinitis can be the most problematic to diagnose and treat because the symptoms overlap with those of many other nonallergic causes of chronic nasal congestion that have to be excluded.

Chronic disease with seasonal exacerbations: Individuals who are allergic to perennial allergens as well as seasonal allergens will often experience increased symptoms when airborne allergen levels are increased.

AEROBIOLOGY

Accurate diagnosis and management of allergic rhinitis are dependent on knowledge of when and where specific allergens exist.[5] Generally speaking, aeroallergens are otherwise innocuous proteins that DO NOT affect most individuals. However, atopic (i.e. allergy-prone) individuals make IgE against these proteins and will develop allergic reactions when exposed to them. Pollination patterns vary in different geographic areas throughout the world and diagnosing pollen-induced allergic rhinitis requires a basic understanding of when allergenic plants pollinate in a given location. Because specific plants pollinate at almost the same time every year in any given region, it is often possible to establish the primary cause of acute allergic rhinitis, based on when an individual patient experiences symptoms. For instance, in the northeast United States, oak trees pollinate around the beginning of May, so that patients who experience symptoms that time of year are usually allergic to oak pollen. Later in the spring when roses begin to bloom, patients develop a form of allergic rhinitis that is termed "rose fever." However, these symptoms are not due to a reaction to rose pollen, but rather to the increased levels of grass pollen that occur at that time. Similarly, ragweed pollinates in the Northeast United States at the end of the summer, and allergic rhinitis due to ragweed pollen is usually the cause of the acute allergic rhinitis ("hay fever") that occurs at that time of the year. Within pollen seasons, patient symptoms can vary with the amount of pollen in the air. For instance, on rainy days, when pollen counts tend to be low, patients will often report symptom relief. This type of history can be an important diagnostic clue.

It is also essential to understand the aerobiology of perennial allergens. Exposure to most of these occurs in indoor environments (home, school or workplace). History of exposure to many of these allergens that are obviously present can usually be elicited with simple questioning ("do you have any exposure to pets, mice, rats, cockroaches or feather bedding?"). However, exposure to other perennial allergens such as dust mites or mold spores is not always obvious to the patient and requires some probing on the part of the physician. It can be assumed that most patients who sleep in a westernized environment (pillow and mattress) and who have not implemented specific antidust mite measures are usually being exposed to dust mite allergen when they sleep. Mold spores are often the most problematic indoor allergen to identify. It is reasonable to assume that anyone who has any type of water intrusion inside their home (roof leak, damp basement or leaky pipes) is probably being exposed to increased and clinically relevant levels of mold spores. As with most perennial allergen exposure, mold spore exposure is most relevant clinically when it occurs in the bedroom. Evidence for mold spore exposure during the medical history can often be elicited by asking if there is a "musty smell" in the home or in a closet, or if there is dark staining, or mold growth on any of the walls or ceilings. Finally, since allergen can be deposited anywhere in the body, allergic rhinitis is often associated with symptoms in other organs. Other systems typically involved include the eyes, pharynx, ears, bronchial airways (asthma), and skin.

CLINICAL EVALUATION

There are two overriding goals for the initial evaluation of patients with allergic rhinitis: to establish that the diagnosis is truly allergic rhinitis and rule out any other potential diagnoses/causes of the nasal symptoms and to determine the environmental factors responsible for the allergic rhinitis. Establishing these causative factors greatly facilitates the institution of correct treatment, with either targeted environmental control measures (eliminating/avoiding causative factors) and/or appropriate allergic immunotherapy.

Differential diagnosis: As indicated above, one of the critical functions of the evaluation is to be certain that the symptoms are not being caused by a condition other than allergic rhinitis. This is most often a problem when the symptoms are chronic or persistent rather than acute. Possible causes of allergic rhinitis-like symptoms that may be confused with allergic rhinitis are covered in greater detail in several other chapters of the book and are summarized in Table 13.1.[4-17]

Patient history: Proper evaluation of allergic rhinitis should begin with a detailed medical history. William Osler, the father of modern medicine, famously taught, "Listen to your patient, he is telling you the diagnosis" (www.oslersymposia.org). This is especially true for allergic rhinitis, despite the role of allergy skin testing. The general approach that may be useful in the management of chronic nasal symptoms is to approach the history

Table 13.1: Conditions that mimic allergic rhinitis

Conditions
Cerebrospinal fluid leak
Rhinitis medicamentosa
Medication-induced (ACE inhibitors, birth control pills, alpha-adrenergic blocker antihypertensives, NSAID's some psychiatric medications)
Hormone induced (pregnancy hypothyroidism)
Systemic medical conditions (Sjögren's syndrome, rheumatoid arthritis, Wegener's granulomatosis, relapsing polychondritis)
Anatomic (adenoid hyperplasia, choanal atresia, foreign body, ciliary dysfunction, cystic fibrosis, deviated nasal septum)
Chronic nonallergic rhinosinusitis (gustatory or vasomotor rhinitis)
NARES (nonallergic rhinitis with eosinophilia syndrome)
Atrophic rhinitis
Chronic nonallergic rhinosinusitis
Chronic polypoid rhinosinusitis
Foreign body
Acute viral rhinitis
Acute bacterial sinusitis

chronologically. Begin with where the patient was born and then track where they lived up to the present time. At each life stage, determine where they were and whether they had symptoms. Focus on childhood since that is the time when many allergy symptoms often begin, because of the "allergic march" (the staged progression of eczema, asthma, and then allergic rhinitis/sinusitis). Often adults with new onset allergic rhinitis will claim that they have no allergies, but when questioned carefully will reveal that as children they suffered from allergy-associated conditions such as asthma or eczema. The presence in the past of these types of allergic problems makes it more likely that the patient has allergic rhinitis rather than some other condition. Having established the chronological pattern of symptoms, it is then useful to focus on the most recent symptoms and determine what makes them worse and what makes them better.

Elicit a complete inventory of all relevant symptoms. The presence of extranasal symptoms is often very helpful in establishing that the diagnosis is truly allergic rhinitis, since most of the nonallergic chronic nasal conditions are not usually associated with symptoms outside the nose. The only exception would be chronic rhinitis due to systemic medical diseases such as Wegener's granulomatosis or Sjögren's syndrome.[10,18] Typical nasal symptoms of acute allergic rhinitis include nasal congestion, clear watery rhinorrhea, nasal itching, and sneezing. Sneezing may be paroxysmal. In chronic or perennial allergic rhinitis, nasal congestion tends to predominate, while itching and sneezing and rhinorrhea tend to be less severe. Nasal congestion is frequently unilateral and often alternates sides.[19] Patients with long-standing chronic allergic rhinitis often begin to manifest symptoms secondary to long-standing nasal inflammation such as increased congestion and/or sneezing after exposure to odors or fumes. They will also begin to complain of anosmia and/or ageusia, although when very severe, these latter symptoms are suggestive of the presence of nasal polyposis.

Eye symptoms occur most frequently in acute allergic rhinitis and are characterized by bilateral tearing, itching and sometimes burning. Acute ocular symptoms tend to be most severe during periods of very high pollen counts. This is sometimes especially bothersome in young boys during the spring tree pollen season ("vernal conjunctivitis").[20] With chronic allergic rhinitis and associated conjunctivitis, patients will sometimes complain of eye itching, irritation or foreign body sensation ("something is in my eyes").[20]

Itching of the ears is common in acute allergic rhinitis but is seen less often with chronic allergic rhinitis. With both acute and chronic allergic rhinitis, there can be accompanying Eustachian tube dysfunction or even serous otitis media, which will cause symptoms of clogged ears and decreased hearing. In addition, patients may complain

of a hard-to-characterize sense of unsteadiness that they will describe using terms such as dizziness, lightheadedness or just having a "cloudy feeling in their head."[21]

Palatal itching is common in acute allergic rhinitis. Children and even some adults will use their tongues to scratch the palate, which sometimes produces a characteristic clicking noise ("palatal click"). Palatal itching tends to be less common with chronic allergic rhinitis.[22] Patients often complain of sore throat, which is again somewhat more common in acute compared to chronic allergic rhinitis. The presence of sore throat sometimes misleads both patients and physicians into thinking that symptoms are due to a viral infection rather than an allergic problem.

Allergic bronchitis (asthma) is common in patients with allergic rhinitis. It is often mild in severity and patients will often only complain of cough.[23] The cough is frequently dry but can sometimes be productive of copious amounts of mucus. Patients may also complain of shortness of breath, chest congestion and wheezing. During acute pollen seasons, some patients will develop anterior chest pain especially when performing outdoor exercise such as running. This symptom is usually a manifestation of acute allergic bronchitis, but can be very anxiety-producing for patients, since they worry that it may be due to cardiac disease.

Sleep disturbance is common with both acute and chronic allergic rhinitis, but patients frequently only complain of fatigue or trouble concentrating and may not be aware that the actual problem is poor sleep quality or actual sleep apnea exacerbated by nasal congestion.[24] This may be a particular problem in children with chronic nasal congestion who suffer from impaired sleep quality that results in poor school performance.

Headache, due to nasal congestion or sinus inflammation, is frequent in both acute and chronic allergic rhinitis. Pain can be over one or both maxillary sinuses and is sometimes more of a dull facial discomfort rather than a severe or painful headache. As with other causes of acute sinusitis, patients with maxillary allergic sinusitis will sometimes complain of tooth pain.[25] Pain can also be over one or both frontal sinuses. Very persistent, nonlocalized headaches are sometimes sign of acute sphenoid allergic sinusitis.[25] When headaches are very severe, patients will often refer to them as "migraines," but occasionally allergic rhinitis will trigger actual, unilateral vasomotor migraine headaches.[25] Persistent headache may be an indicator of a secondary bacterial infection that might necessitate antibiotic therapy.

Allergen exposure is not just limited to the respiratory system and can induce symptoms in any contacted organ system. In some patients, skin symptoms can be induced either by direct contact with the allergen on the skin or indirectly after allergen is swallowed or inhaled. Skin-associated symptoms associated with allergen exposure commonly include generalized pruritus and/or an acute urticarial rash. In highly allergic individuals, especially children, persistent allergen exposure may result in more chronic forms of allergic dermatitis such as eczema. Eczema may occur in the typical areas (antecubital and/or popliteal fossae) or may occur as isolated lesions anywhere on the body ("nummular eczema").

During times of very high allergen exposure such as the height of a pollen season or after extensive dust or mold exposure, patients frequently experience enough allergen exposure to induce systemic symptoms such as fatigue or malaise. Fever has been reported to occur in highly allergic individuals when pollen counts are very high.[26] The presence of fever often causes practitioners to misdiagnose allergic rhinitis as an infection.

Risk factors: The presence or a prior history of other allergic diseases such as eczema, asthma, or food allergies makes the diagnosis of allergic rhinitis much more likely.[26] However, the absence of any other concomitant allergic problem in the patient with chronic nasal symptoms should raise suspicions that the condition is nonallergic and may be due to some other cause.[27] There are several other factors that are thought to be associated with an increased risk of allergic rhinitis based on birth cohort or cross-sectional studies, including birth during a pollen season, being a firstborn male child, and early childhood antibiotic exposure.[28] However, inquiring about these factors during a standard medical examination is not usually helpful, either because the patient does not know the answer or the strength of these associations is not very strong, and possibly influenced by unrecognized confounders. In general, these factors tend to be more relevant for population studies and are less helpful diagnosing individual patients.

Allergic disorders including allergic rhinitis are somewhat unique among medical problems because they are among the few conditions that are so closely tied to the patient's environment. For instance, a patient can be highly allergic to ragweed pollen, but be completely asymptomatic during the time of year when hay fever is prevalent if they live in an area such as Southern California or Western Europe where there is little or no ragweed.[28]

Such a patient could be symptom free their whole life, but develop late summer/early fall allergic rhinitis for the first time at an older age, after moving to an area where ragweed is prevalent. For this reason, it is very useful to determine where individuals have lived and what type of symptoms they experienced at each locality. In addition to determining their previous geographical locations, it is important to find out what they were doing in previous locations such as employment or school situations, and whether specific exposures caused allergic symptoms during those times. On close questioning, patients will sometimes recall having increased nasal symptoms while working in a particularly dusty library or after being exposed to their college roommate's pet cat.

As outlined above, the temporal nature of patients' symptoms will furnish important clues about the diagnosis and the cause of symptoms. The presence of symptoms that are episodic or seasonal makes it much more likely that the diagnosis is allergic rhinitis. However, symptoms that are present all year-round make it imperative to ascertain that there is no other cause of the problem, except allergic rhinitis.

Environmental analysis: As part of a comprehensive evaluation it is important to know where patients spend their time over a 24-hour period, including home, work and school, and how symptoms vary depending on location. The average home environment is filled with different allergens. It is essential to obtain an accurate inventory of all potential allergens to which the patient is being exposed in the home. Done properly, this may tell the physician what is causing the problem and what measures can be taken to eliminate the causes of disease. The potential home allergen exposures should be reviewed with the patient.

All mammalian or feathered pets in a home can be significant pathogenic factors. The closer the pet is to the patient's sleep environment, the more likely it is causing disease, but any pet anywhere in the home can be a problem. The physician should determine if the pet goes in the patient's bedroom and if the pet actually goes in the patient's bed. All mammalian pets and birds are potentially allergenic. There is no good evidence that there is a truly nonallergenic dog, although patients will frequently select dogs because they are advertised as being nonallergenic. It is also possible to buy cats that have been genetically modified to not produce Fel D1, the major cat allergen.[29] However, there have not yet been any studies comparing the allergy symptom-inducing potential of Fel D1-deficient compared to normal cats. Pet size matters, and the larger the animal is, the more allergen it will shed and the more likely that it will cause allergic symptoms.

Feathers or down pillows or comforters can be a significant source of allergen for some patients. It is important to remember that patients can become allergic to any substance at any time, so the fact that someone has been sleeping on the same feather pillow for their whole life does not preclude the fact that the pillow may now be causing disease. Down refers to the very small, soft feathers that come from birds. Many patients think that feathers and down are distinct and will state that they do not have feather pillows if they have down pillows, so patients need to be queried about both.

Cockroaches and mice are highly allergenic, and in some homes may be a significant cause of allergic rhinitis.[30] Generally, patients have a good idea how much exposure they have to these creatures. In multifamily dwellings, dead cockroaches disintegrate and their allergens become part of the dust, especially dust behind walls. As a result, cockroach-allergic patients will frequently report increased allergic symptoms when walls are opened during home renovations or when leaks are being repaired. Mice can be an important source of allergen in a home especially since their urine, which can be widely disseminated, naturally contains an allergenic protein (Mup 1).[31] Rats tend to be less common in homes, but if present can also be a significant source of allergen.

Dust is considered a major potential allergen. Some patients will report that their home is dusty. More often, patients are unaware of the allergenic potential of items in their bedroom. Particular problems include large numbers of stuffed animals, old books, and newspapers that patients would not usually report unless queried directly about them because they do not think their presence is out of the ordinary. Additional bedroom dust reservoirs include carpets of any type and heavy drapes that are not frequently cleaned.

Any water intrusion in a home can result in mold spore growth and can be a significant cause of allergic rhinitis. Sometimes patients are unaware of mold growth in the bedroom especially when the dampness occurs behind a piece of furniture such as a chest of drawers or a headboard. One clue to the presence of molds of which the patient is unaware is if visitors to the home complain of a "musty odor" or develop allergic symptoms (sneezing or coughing) when entering the home, so patients should be queried about this. In general, excess humidification,

Table 13.2: Pollen cross-reactive foods that induce oropharyngeal symptoms in pollen allergic patients (pollen-food allergy syndrome)

Inhalant allergen	*Cross-reactive food*
Tree (birch) pollen	Apple, pear, plum, cherry, hazelnut
Grass pollen	Melon, tomato, orange
Weed pollen	Carrot, celery, spices (coriander), sunflower
Ragweed pollen	Melons, cucumber, zucchini, chamomile

especially in the bedroom, can promote the growth of dust mites and mold spores. More importantly, the water reservoirs of cold mist humidifiers, if not kept clean, can actually be a significant source of mold growth and allergenic mold spore exposure.[32] Patients often become allergic if there are large numbers of chemicals in the home. This is often seen with artists who are working with oil paints, acrylics and various solvents.

It is important to question the patient about possible food allergies. Although food allergies occasionally cause allergic rhinitis symptoms, food allergies are not a common cause of allergic rhinitis.[33] More important, however, is the fact that food allergies are very common in patients with allergic rhinitis and their presence is an important clue that allergic rhinitis is the correct diagnosis. The most important food allergy problem related to allergic rhinitis is the pollen-food allergy syndrome (also termed "oral allergy syndrome").[33] Symptoms are caused by deposition of allergen in the oropharynx and are usually manifested as oral itching, tongue and/or lip swelling, or dysphagia. Patients who are highly allergic to specific plant pollens become allergic to foods that contain proteins that are also present or are cross-reactive with proteins in those plants. For instance, patients who are allergic to tree pollen become allergic to fruits such as apples, pears, and cherries that come from trees. Patients who are allergic to grass pollen frequently report allergies to grass cross-reactive vegetables such as melons and tomatoes, and patients who are allergic to weed pollen become allergic to weed cross-reactive vegetables such as carrots and celery, or spices such as coriander and parsley (Table 13.2).[34] The presence of this type of food allergy is an important confirmatory clue that the patient it is truly suffering from allergic rhinitis.

Allergenic exposures outside the home can be an important cause of allergic rhinitis symptoms. Work exposures can include all of the factors that cause symptoms in the home plus some that tend to be more work specific such as fumes, chemicals or powders (e.g. flour in bakery workers), or laboratory animals. Less obvious factors in schools can include carpeting or classroom pets. Occasionally, symptoms in a student or a teacher can come from vermin or mold spore exposure in a school.

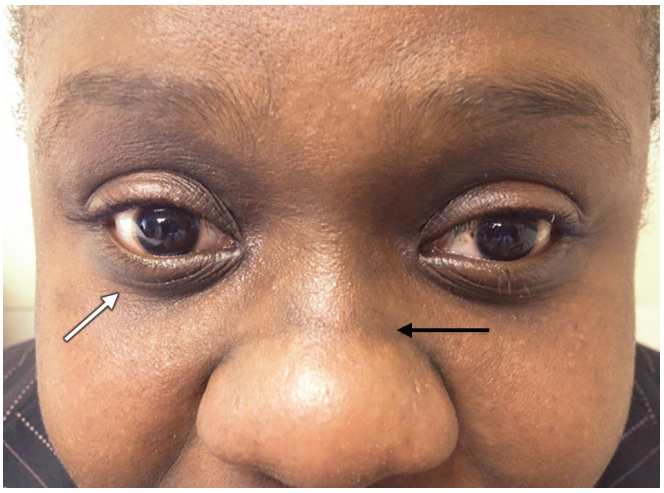


Fig. 13.1: External appearance of patient with chronic allergic rhinitis. Darkened areas under the eyes from chronic nasal congestion ("allergic shiners") (white arrow). Hyperpigmented line across the nose after repeated pushing up of the nasal tip ("allergic crease") (black arrow).

Family history: A family history of atopic disease is a strong risk factor for patients developing allergic rhinitis.[35] It is helpful to assess the presence of allergic disorders in parents, siblings and children. The more relatives with allergic diseases that a patient has, the more likely it is that the correct diagnosis is allergic rhinitis.

Social history: As part of a comprehensive evaluation, it is important to know with whom the patient lives and whether these individuals are experiencing allergic symptoms. This information will often furnish an important clue about potential allergens in a home.

PHYSICAL EXAMINATION

General appearance: In children, long-standing allergic rhinitis typically results in an facial appearance characterized by mouth breathing, dark rings under the eyes ("allergic shiners"), and performance of an "allergic salute" (pushing up the tip of the nose with the heel of the hand in order to relieve nasal congestion or nasal itching) (Fig. 13.1). Chronic performance of the allergic salute eventually results in a dark transverse line across the tip

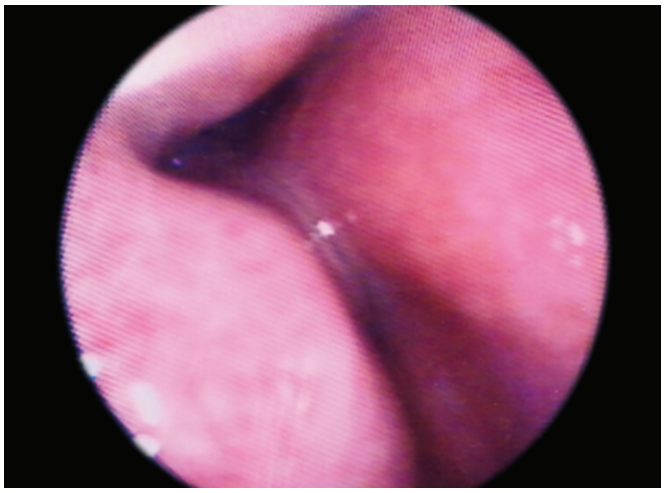


Fig. 13.2: Appearance of nasal turbinates in acute allergic rhinitis. The inferior and middle turbinates are swollen and pale. The mucosal surface is glistening and the mucus is clear.

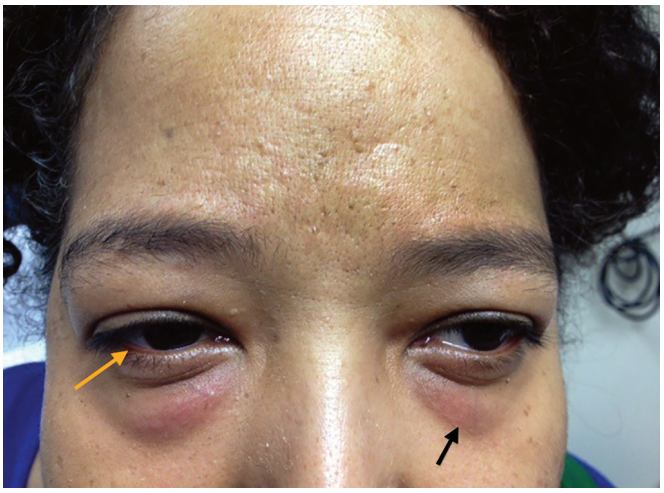


Fig. 13.3: External appearance of allergic conjunctivitis. As a result of chronic allergen exposure around the eyes, this patient has developed both acute allergic conjunctivitis (orange arrow) and suborbital edema (black arrow).

of the nose, the "allergic crease" (Fig. 13.1). An allergic crease can persist long into adulthood and can be an important clue to the presence of childhood or even current allergic rhinitis. Long-standing, early onset allergic rhinitis in children can also be associated with anatomic changes such as a high arched palate, widening of the bridge of the nose, and dental malocclusion. The characteristic appearance of children with chronic allergic rhinitis (with or without the palate and dental changes) is sometimes termed the "allergic facies."

Nose: Specific internal nasal findings often depend on whether the rhinitis is acute or chronic. In regard to external nasal findings, as noted above, the presence of an "allergic crease" is an indicator of the presence of long-standing allergic rhinitis. Internally, acute allergic rhinitis is typically manifested by enlarged inferior nasal turbinates that are pale and sometimes described as being "blue." Mucus is usually thin and clear (Fig. 13.2). The inferior nasal turbinates in chronic allergic rhinitis can also be swollen, but tend to be erythematous rather than pale, and less moist. More long-standing chronic rhinitis is often associated with crusted mucus and patchy epistaxis.

Eyes: Most cases of allergic rhinitis-associated conjunctivitis tend to be mild and nonpurulent. However, in some patients, typically young boys, allergic conjunctivitis can be fairly severe with a purulent discharge, and is often associated with a cobblestone appearance of the conjunctiva (Fig. 13.3).

Throat: Allergic pharyngitis is usually nonspecific and maybe associated with some generalized pharyngeal erythema. However, long-standing chronic rhinitis, especially with associated postnasal drip, causes hypertrophy of the posterior pharyngeal lymphoid tissues producing a "cobblestone" appearance.

Chest: In patients with associated allergic bronchitis, there will sometimes be wheezing or rhonchi.

Skin: Occasionally, patients with allergic rhinitis will develop skin symptoms after exposure to offending allergens or during pollen seasons. In general, these symptoms tend to be minimal and are usually limited to generalized pruritus. However, acute allergen exposure can sometimes cause either small numbers of typical urticaria or erythematous, maculopapular lesions. As with other extranasal manifestations, the appearance of these more typical allergic reactions helps confirm the diagnosis of rhinitis.

DIAGNOSTIC TESTING

Although a careful history will strongly suggest the diagnosis and causes of allergic rhinitis, tests for confirming this diagnosis are simple, rapid, specific, and can be very helpful. Most clinical testing is done either in vivo (skin testing) or in vitro (allergy blood testing). In general, for most allergens that cause allergic rhinitis, skin testing is somewhat more sensitive than currently available allergy blood tests. Estimates vary, but on average the sensitivity of blood testing is only 70–75% of skin testing.[36]

However, blood testing is more convenient for physicians who do not perform skin testing regularly and is useful for testing patients who cannot or will not undergo skin testing for a variety of reasons. There is some evidence that a more complete assessment of patients' allergic status is obtained by performing both skin testing and allergy blood testing.[37] Both forms of testing only establish that patients have allergen-specific IgE (i.e. are sensitized to the allergen) and do not unequivocally prove that the allergens are responsible for disease. In every case, results of allergy testing must be used in conjunction with the results of the clinical examination in order to make the correct diagnosis.

Skin testing: Immediate-type allergy skin testing is a means of measuring the presence of allergen-specific IgE in patients' skin. It involves exposing dermal mast cells to small amounts of allergen. If there is allergen-specific IgE bound to the mast cell surface, the mast cells degranulate within minutes and release histamine. Histamine binds to local vascular and neuronal histamine receptors and rapidly triggers local vasodilation, swelling, erythema, and itching. This local reaction looks like a typical mosquito bite and is termed a "wheal and flare" reaction.

Patients with any type of rhinitis commonly take H1 antihistamines for symptom relief. These drugs all block skin test reactions and need to be stopped prior to testing. The length of time that they need to be discontinued depends on whether they are short-acting or long-acting antihistamines. In general, in order to be certain but there is no antihistamine blocking effect, it is usually recommended that H1 antihistamines be stopped for 7 days prior to testing.[38] It is also recommended that H2 antihistamines, which have a lesser suppressive effect, be stopped for 2 days prior to testing. Some antidepressant drugs or phenothiazines will also suppress skin test reactivity, but these are often more difficult to withhold.[36] Oral corticosteroids, decongestants, and leukotriene antagonists do not significantly inhibit skin test reactivity and do not need to be discontinued.[36] Some authorities recommend discontinuing beta-blockers because of the potential problem of not being able to treat skin testing-induced anaphylaxis if it occurs. However, because significant systemic allergic reactions are so rare after skin testing, it is not clear that this is necessary.[36]

Most patients can be skin tested without a problem. The only exceptions are individuals who previously experienced severe anaphylactic reactions to the allergens being tested. However, this is very rarely an issue with the environmental allergens responsible for allergic rhinitis. Patients with uncontrolled asthma should not be tested until the asthma is brought under control. For patients with skin rashes (eczema or urticaria), testing should be performed on an area of uninvolved skin. Some patients have dermatographism, which will cause small positive reactions to all the allergens tested, including the negative control buffer, making interpretation of the results difficult. For such individuals, intradermal skin testing (which does not cause dermatographic responses) or allergy blood testing may be required. Age is usually not a relevant factor for deciding whom to skin test. Infants as young as 1 month can be tested and positive skin tests occur in patients over 65 years of age.[36]

Percutaneous skin testing is performed either on the forearm or on the back. The forearm is more convenient for the patient, while the back tends to be easier to access in infants. There is some evidence that the skin of the back is more sensitive than the arm, but this is usually not a clinically relevant issue.[36] Intradermal skin testing is more conveniently performed on the upper arm, both because of access and because the injections at this site tend to be less painful. The area should be wiped with 70% alcohol and allowed to dry before applying the allergens. For the diagnosis of allergic rhinitis, we have found that a relatively small panel[16-20] of common aeroallergens (relevant pollens, dust constituents, pet danders, mold spores, negative buffer control, and positive histamine control) is usually sufficient. However, there is wide variety in the number and the types of allergens tested depending on practitioner preference as well as geographic differences. The Joint Task Force of Practice Parameters of the American Academy of Asthma Allergy and Immunology (AAAAI) and the American College of Asthma, Allergy and Immunology (ACAAI) concluded that up to 70 puncture skin tests and 40 intradermal (intracutaneous) skin tests for inhalant allergens are justified for an initial diagnostic evaluation.[36] Allergens are available from several suppliers in the US or worldwide and their customer service departments are usually very informative about what types and forms of allergens need to be ordered for any geographic locality. One typical panel is shown in Table 13.3.

Percutaneous skin testing is preferred for initial screening because it has the best combination of sensitivity, specificity, ease of application and safety.[36] Allergens should be at a high concentration (1:10–1:40 w/v). Different devices are used to inject a small amount of allergen into the epidermis without going deeper into

Table 13.3: Typical allergy skin testing sheet

Allergen	*Percutaneous*	*Intradermal (1/100 dilution)*	*Intradermal (1/10 dilution)*
Date			
Tree mix			
Grass mix			
Weed mix			
English plantain			
Ragweed mix			
Dust mite			
Feathers			
Cat dander			
Dog dander			
Cockroach			
Mold spore mix #1			
Mold spore mix #2			
Mold spore mix #3			
Mouse dander			
Buffer negative control			
Histamine positive control			

Percutaneous tests recorded on a scale, 0–4+.
Intradermal tests recorded as maximum wheal diameter/maximum flare diameter (e.g. 10 mm/25 mm)

the dermis, and a number of different devices exist for this purpose. When using single puncture devices (i.e. Morrow Brown needle, Greer-pick, Quintest or even a 27 gauge hypodermic needle), a drop of allergen is first placed on the skin. There are also a number of multihead devices (Multitest, Quintip, or Comfort Ten) that will apply 8–10 tests at a time. For these, the allergen is applied directly to the device rather than to the skin, and the allergens need to be suspended in a 50% glycerol solution to maintain the allergen bead at the top of the prongs. Some typical devices are shown in Figure 13.3. Although there are differences in the size of the buffer and histamine wheals induced by each of these different applicators, there does not appear to be a significant clinical advantage of any type of device.[36] Positive allergens induce a wheal and flare reaction that can be read at 15–20 minutes (Figs. 13.4 and 13.5). Reactions start to fade and become more diffuse after 30 minutes and are usually completely gone by about 3 hours.

Scratch testing refers to the technique where a linear scratch is made in the skin and a drop of allergen is then placed on top of the scratch line. This technique was used in the past but has been largely abandoned in favor of epicutaneous testing because of better reproducibility and less patient discomfort.[36]

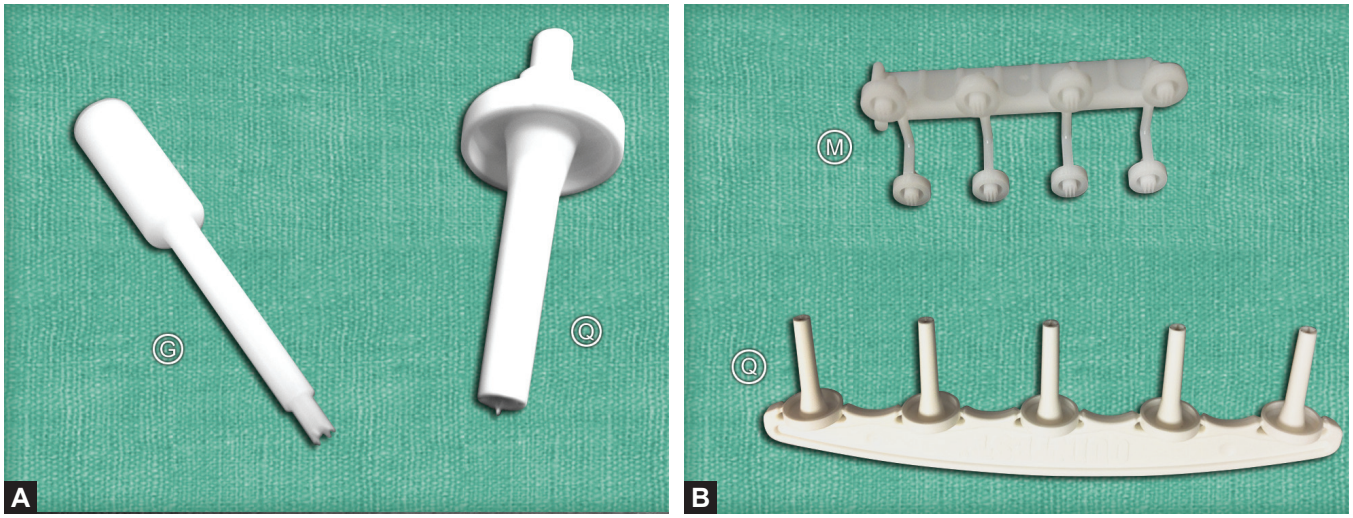
There are many different ways of scoring and recording the size of the reactions. In general, most involve measuring the maximum diameter of the wheal and the maximum diameter of the flare. In order to be considered an accurate test, the positive histamine control should have a wheal diameter 3 mm greater than the negative buffer control. Many scoring systems use a range from 0 to 4+, based on the maximum wheal diameter. In some systems, the histamine reaction is considered to be a 2+ and can be a useful guideline for scoring reactions. In many large epidemiologic studies, a reaction is considered positive if the maximum wheal diameter is 3 mm greater than the maximum wheal diameter of the negative control. Some typical scoring systems are shown in Table 13.4.[39] Other practitioners prefer recording the actual wheal and flare diameters.

Permanent records of the reaction sizes can be made by tracing the outer limits of the wheal and flare with a fine tip felt marker, overlaying transparent tape over

Table 13.4: Systems for grading percutaneous skin reactions

Grade	*Wheal diameter*	*Wheal diameter*	*Wheal/erythema diameters*	*Wheal/erythema diameters*
0	= negative control	= negative control	= negative control	< 5 mm/< 5 mm
+/–	na	na	na	5–10 mm/5–10 mm
1+	> negative control but < histamine	<1/2 histamine	Erythema < 21 mm	5–10 mm/11–20 mm
2+	= histamine	½- <1x histamine	Wheal< 3 mm/erythema > 21 mm	5–10 mm/21–30 mm
3+	> histamine but no pseudopods	= histamine	Wheal > 3 mm + erythema	10–15 mm/21–40 mm
4+	> histamine + pseudopods	> 1x–2x histamine	Wheal with pseudopods + erythema	> 15 mm + pseudopods/ 41–50 mm
5+	na	> 2x histamine	na	na

Source: Modified from Hamilton.[38]
na: Not available.



Figs. 13.4A and B: Typical percutaneous skin testing devices. (A) Single applicators. G—Greer Pick (Greer Laboratories, Lenoir, NC); Q—Quintip (Hollister-Stier Laboratories, Spokane, WA). (B) Multiple head applicators. M—Multi-Test (Alk Abello, Round Rock, TX); Q—Quintest (Hollister-Stier Laboratories, Spokane, WA).

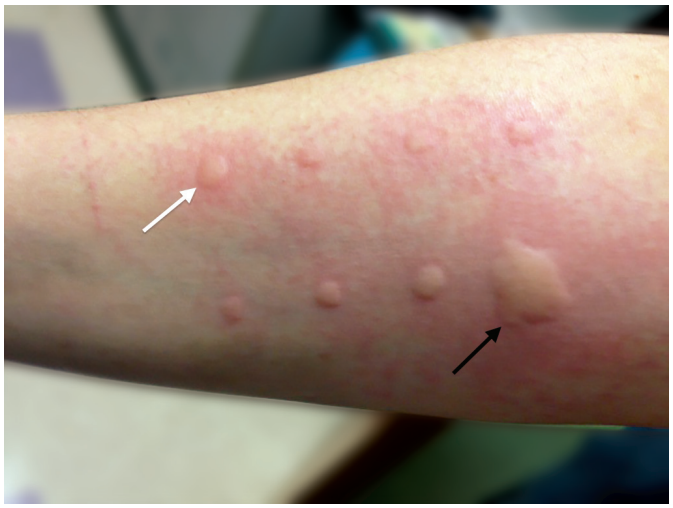


Fig. 13.5: Typical results of percutaneous skin testing with a Multi-Test applicator. White arrow points to a 2+ reaction (tree pollen). Black arrow points to a 4+ reaction (ragweed pollen). The finger-like extensions of the wheal in the latter reaction ("pseudopods") make this a 4+ reaction.

the reaction sites, and then transferring the tape with the outline of the reaction onto paper. There is currently no standardized method of scoring skin test reactions, but in regard to diagnosing/treating allergic rhinitis, the exact type of scoring system used is rarely important and the most important determination is whether there is an unequivocal positive reaction.

Some reactions will only become positive at times after patients leave the office (2–6 hours), and some reactions will continue to enlarge for several hours. Patients should be told that this may happen and to record and report such reactions since they are often indicative of significant allergic reactivity that may be clinically relevant. Some reactions may produce residual hyperpigmented spots that trouble patients and may persist for several weeks or more.

Intradermal (intracutaneous) skin testing: Intradermal skin testing is more sensitive than percutaneous skin testing and can be used to detect lesser degrees of allergic reactivity.[36] In general, because of its greater safety, patients should always be first tested percutaneously.[36] In contrast to percutaneous testing, intradermal testing is associated with a higher risk of systemic reactions. Therefore, it is recommended that intradermal testing should only be performed with allergens to which the patient exhibited negative reactions on previous percutaneous skin testing. Allergens should be diluted 1/100 from the percutaneous test strength. A standard intradermal injection, similar to a PPD test, is performed, except that a much smaller volume is injected (approximately .02 mL). It is usually too difficult to accurately measure the exact volume for an intradermal allergy skin test using a regular 1 mL syringe, so standard practice is to inject enough allergen to raise a 3 mm intradermal bleb, using a 26 or 27 gauge needle. Similar to the percutaneous tests, reactions are read at 15–20 minutes and reactions can be scored on a 0–4+ basis, or the actual wheal and erythema diameters can be recorded (i.e. 5 mm/15 mm). Any allergens that are negative on intradermal skin testing with the 1/100 dilution can be tested again at a higher strength (1/10 dilution). In general, intradermal skin tests are felt to be more sensitive than percutaneous skin tests, but are less specific. However, for some weaker antigens, such as mold spores, intradermal skin testing is often the only way to demonstrate allergic reactivity in a patient.

Allergy blood testing: As mentioned previously, immediate hypersensitivity skin testing is a method that measures the presence of allergen-specific IgE in the skin. Alternatively, levels of allergen-specific IgE can also be measured in serum. While the Allergy Practice Parameters suggest that skin testing is preferred for the evaluation of allergic rhinitis, measuring serum levels of specific aeroallergen IgE can be helpful in several different clinical situations: when patients are taking medications such as antihistamines that interact with skin testing, in dermatographic (sensitive skin) patients, in patients with extensive skin lesions, or if there is a possibility of anaphylaxis from the skin testing.[36] Allergy blood tests are also useful in needle-phobic or frightened patients, and are convenient for nonspecialist practitioners who usually do not have skin testing materials available. In general, potential problems with allergy blood testing compared to skin testing is that blood testing tends to be more expensive, is less sensitive (70–75% as sensitive on average), and it takes longer to get the results (days vs. minutes).[36]

There are a variety of blood allergy tests that can measure serum levels of allergen-specific IgE in allergic rhinitis.[39,40] The first commercially available test was a radioimmunoassay termed RAST (from Radio Allergo Sorbent Test). Currently available tests no longer use radioactive tracers but the tests are still referred to generically, although inaccurately as "RAST tests." There are currently three commercially available blood allergy tests in general use, (Immunocap, Immulite, and HYTEC-288), all of which use some form of allergen bound to a solid phase and an enzymatic or fluorescent detection system.[39] Each of the test systems can measure serum levels of IgE to a wide variety of allergens. Tests can be ordered for individual allergens or for groups of allergens in specific panels, based on locality or clinical indications (i.e. Northeast pollen panel or Insect panel).

IgE levels are usually reported as kU/L and range from 0.1 kU/L to 100 kU/L. Results vary between laboratories, but generally levels of either 0.1 ku/L or 0.35 kU/L are used as the thresholds for clinically significant specific IgE levels. Often, laboratories will also report results on a scale of 0–6, where a class 0 indicates no detectable IgE, and a class 6 indicates the highest level. Other types of specific IgE assays are being developed including microarray chip methods that can measure IgE against over 100 allergens at a time (e.g. ISAC) or a 2-hour, point-of-care method that allows the detection of IgE against 5 common allergens (ImmunoCAP Rapid).[39]

Similar to allergy skin testing, with all specific serum IgE tests, patients can have elevated allergen-specific IgE levels even though exposure to that allergen does not induce any obvious clinical allergy symptoms. False-negative results also occur (a negative serum IgE despite the

fact that exposure to that allergen produces unequivocal allergic symptoms) since these tests only measure blood levels of specific IgE and not levels in the relevant target organ (i.e. the nasal mucosa). Specific serum IgE test results must therefore always be interpreted in the light of the clinical history and other clinical findings.

It is also possible to measure total (nonallergen specific) serum IgE levels, which are sometimes helpful in diagnosing allergic rhinitis. In general, the presence of very low levels of total serum IgE makes atopic disease less likely, while conversely, the presence of very high total serum IgE levels make atopic disease more likely. However, the utility of this test is limited by the large overlap in levels between allergic and nonallergic individuals.[39,40] However, knowing the level of total serum IgE can be very useful in interpreting specific IgE results. A modestly increased level of IgE to a specific allergen (i.e. class 1 or 2) in the presence of a low total serum IgE level may be clinically significant, while similar levels of specific IgE in a patient with very high total serum IgE levels may be less likely to represent clinically relevant sensitization. For this reason, it is often helpful to measure total serum IgE levels in conjunction with measuring allergen-specific IgE.

Nasal cytology: In trying to differentiate allergic rhinitis from other causes of nasal symptoms, it is sometimes helpful to analyze the cellular content of the nasal mucus. Acute allergic rhinitis is often characterized by a high percentage of eosinophils in the nasal mucus, while in many other forms of rhinitis the predominant cells are neutrophils.[1] Nasal cytology is easily performed by having the patient blow their nose onto a nonabsorbent material such as a vinyl glove or piece of Saran wrap. The mucus is then smeared on a glass slide, stained, and a cell count performed. Nontraumatic scraping of the nasal mucosa to collect cells can also be performed using a commercially available, disposable plastic curette (Rhinoprobe).

Inhalation challenge: The most direct way of establishing that a specific allergen is the cause of allergic rhinitis is by documenting the induction of symptoms by the direct application of that allergen onto the nasal mucosa. Small amounts of an allergen solution are instilled in the nose and a response is measured. In the past, some practitioners would use small amounts of dry pollen or dust. Responses can be assessed on either subjective (visual-analog scale of nasal and ocular symptoms) or objective parameters (change in the nasal cavity volume evaluated by acoustic rhinomanometry).[41] A positive clinical response can also be determined by measuring the change in levels of various allergic mediators in the nasal lavage fluid after allergen challenge (histamine, TAME esterase, tryptase, or eosinophil cationic protein levels).[41,42] In the past, nasal inhalation challenges were rarely done in a clinical setting and were mostly performed for research purposes. However, with the more recent recognition of local allergic rhinitis as a significant clinical entity, this procedure may begin to be used more widely in clinical practice (*see* following section).

LOCAL ALLERGIC RHINITIS

Most allergen-specific IgE production is local, and most IgE remains at the tissue site where it was produced.[43] In order for a patient with allergic rhinitis to have enough allergen-specific IgE to be measurable in the blood by RAST, or in the skin to be measurable by a skin test, the patient has to have produced enough excess IgE in the nose to first saturate all the nasal mucosal mast cells. It is only under conditions where there is excess IgE that IgE then enters the circulation and finally binds to skin mast cells.[42] It is important to understand that all allergy diagnostic tests, except for the direct application of allergen to target tissue, are only indirect, surrogate measures of the presence of allergen-specific IgE in the target tissue. As a result, some patients can develop allergic rhinitis despite having all negative diagnostic allergy tests. This phenomenon is referred to as "local allergic rhinitis." One typical scenario is the patient who develops acute symptoms every spring during the tree pollen season but whose allergy skin tests and blood tests are repeatedly normal, or the patient with chronic nasal congestion who develops acute nasal symptoms whenever they inhale dust, but whose dust-specific tests are always negative. Recent evidence suggests that local allergic rhinitis could be diagnosed in as many as a quarter of rhinitis patients presenting to the allergy clinic.[44] This entity appears to be more common among females and the main trigger is house dust mite, although grass and tree pollens have been implicated as well. In the clinic, local allergic rhinitis can be diagnosed by conducting a nasal provocation test with single or multiple allergens as described above.[42] The treatment of local allergic rhinitis is similar to that of the more typical forms of allergic rhinitis.[43]

CONCLUSION

Allergic rhinitis is a common problem that is usually easy to diagnose and treat. Evaluation should be directed

toward two major aims: identifying the allergens causing the problem and considering other disorders in the differential diagnosis. Skin and serologic testing are complementary methods of diagnostic evaluation. Immediate hypersensitivity skin testing is a rapid and safe method for determining the identity of clinically relevant allergens. Allergy blood testing can be useful for identifying relevant allergens in certain situations. Other less commonly used methods of testing include intradermal testing, nasal cytology analysis, and inhalation challenge. Local allergic rhinitis is a relatively common problem and may require a nasal inhalation challenge to confirm the diagnosis. When performed properly, the correct evaluation and diagnosis of allergic rhinitis will facilitate the institution of appropriate and effective therapeutic measures, including medication, environmental control measures and allergic immunotherapy.

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CHAPTER

14

Treatment of Allergic Rhinitis

Stella Lee, Michael Platt, Sandra Y Lin

INTRODUCTION

Allergic rhinitis (AR) is a common clinical problem, with recent estimates of 20% to 40% of the population in the United States being affected.[1] Inhalant allergens are typically classified as seasonal, such as plant pollens, or perennial, such as pet dander, cockroach, or dust mite. Nine percent of the general US population has asthma, with approximately 60% of these individuals having evidence of atopy (i.e. one or more positive specific IgE).[2,3] The medical management of patients with AR includes allergen avoidance, pharmacotherapy, and immunotherapy.[4]

ENVIRONMENTAL CONTROLS

Comprehensive management of the allergy patient involves counseling and management of the patient's environmental exposures. Traditionally, environmental controls, also known as avoidance measures, are considered to be one of the cornerstones of AR management in addition to pharmacotherapy and immunotherapy. In comparison to existing literature for pharmacotherapy and immunotherapy, the evidence for clinical efficacy of environmental controls is still unclear. The reasons are likely due to variability in controlling the patient's environment, but also the complex interplay that exists between the patient and environmental factors that can result in tolerance on one spectrum or hypersensitivity on the other. The development of hypersensitivity may be related to timing of exposures, the dose, and concomitant exposures. A comprehensive, tailored approach to the allergic patient is crucial to managing symptoms, and the individual allergens that have been the subject of most study will be discussed in more detail.

Dust Mite

House dust mites (HDMs) are in the same family as spiders and ticks and are considered the most common indoor allergen. The major allergens, Der f 1 and Der p 1, are derived from the two species, *Dermatophagoides pteronyssinus* and *D. farinae*, which are commonly found in North America. Several studies have investigated reduction of HDM allergen due to increased risk of asthma as well as AR in patients sensitized to HDM.[5] The HDMs thrive in humid, warm conditions. High humidity, at least above 50% and temperatures between 65 and 84°F are optimal. HDM require an external water source, namely, skin cells shed on mattresses and pillows. HDMs are found in homes, work environment, and schools. Allergic individuals react to the dust mite and its waste product particles. Previous observational studies showed that patients with dust mite allergy relocated to high-altitude regions such as the Alps[6] or in a controlled setting such as a hospital room had improved symptoms and airway hyper-responsiveness.[7] Several methods of HDM control have been studied. These include barrier methods, physical removal, and chemical treatments. A recent Cochrane review evaluated nine randomized controlled trials of 501 participants.[8] The studies investigated the use of HDM impermeable covers, acaricides, and high-efficiency air filters. Seven of the nine studies found efficacy of the intervention, but meta-analysis could not be performed secondary to lack of robust data, and the authors concluded that HDM impermeable bedding by itself was unlikely to be beneficial. A systematic review of 54 trials investigating physical and chemical methods also did not show improvements in symptom scores or

medication usage.[9] Most trials only used 1 method but on average, no clinical benefit was seen. Studies have shown that HDM-proof covers can potentially reduce the level of exposure to the allergen, but significant clinical benefit has not been demonstrated.[10,11] The combination of interventions may be most effective in helping improve outcomes. A study evaluating the use of bedding encasement, vacuuming twice weekly, washing/refrigerating toys once weekly, and avoidance of pets demonstrated improvement in asthma outcomes by 8 weeks, including median number of hospitalizations and forced expiratory volume in the first second (FEV1). Based on these results, the authors recommended a combination of physical control measures for families with asthmatic children.[12] Since children with AR and asthma become sensitized to HDM allergen at a frequency proportional to levels of current exposure, at-risk children may be spared sensitization by reducing HDM burden in their homes if it is high or by maintaining already low levels.[13] Decreasing dust mite burden in homes may be helpful for those who are atopic to other inhalant allergens, because they are at added risk of becoming sensitized to mites. The exposure is complex; however, dust mite exposure can occur outside the home, which may explain the limited efficacy of single interventions.[14]

In general, minimizing dust mite exposure can be divided into first line and second line measures.

- First line:
  - Encase pillows, mattress, and box springs with zippered allergy impermeable covers
  - Wash bedding weekly in hot water (>130°F) and dried in high heat. Hot water kills HDMs, but even cold water and using detergent/bleach can be effective in decreasing dust mite particles
  - Place pillows and down comforters in the dryer on high heat every 2 weeks for half an hour
  - Avoid dust collectors such as picture frames, books, magazines, and newspapers bedroom
  - Remove stuffed animals from the bedroom. For children, limit the amount of stuffed animals and wash them weekly

The above measures are fairly simple and inexpensive. If they do not bring significant relief, the patient is recommended second line measures, including the following:

Second line:

- Reduce indoor humidity to or below 60%, ideally between 30% and 50%
- Remove carpeting from the house, especially the bedroom
- Avoid sleeping or lying on upholstered furniture
- Keep large collections of books in some form of enclosed bookcase
- Limit wall hangings and drapes that can collect dust.

Cockroach

Cockroach sensitization is typically found associated with other allergens characteristic of urban living, including mouse, dust mite, and molds. Due to risk of early childhood asthma development and exacerbation, efforts to remove cockroach antigen have been advocated.[15,16] Cockroach avoidance methods as part of a multifaceted approach to allergen avoidance in innercity children with asthma has shown clinical efficacy as well as cost-effectiveness.[17] Elimination of food debris, caulking of potential cockroach entryways, the use of an exterminator or appropriate insecticides can be helpful. Cockroach allergen is usually spread widely throughout the home, even in bedding, because the cockroach is highly mobile. Studies of allergen distribution showed that the strongest relationship between exposure and sensitization was seen in the bedroom.[18]

Animal Dander

The allergic component of animals is usually found in the saliva and dander. The major cat antigen is Fel d 1 and 90% of cat-allergic patients are sensitized to it. Fel d 1 is mainly found in cat skin and hair follicles. The major dog allergen is Can f 1. These allergens are carried on smaller particles and are readily airborne. It is possible for dander to remain in the house years after the animal is no longer present, especially for cats.[19] In addition, cat allergen is ubiquitous, found in up to 40% homes that did not have a cat[20] as well as in schools, hotels, buses, and trains.[21] For patients who are sensitized, removal of the pet from the home has shown benefit[22] and has been advocated in patients who are allergic.[23] In homes in which removal of the pet is not feasible or desirable, a combination of interventions such as keeping the animal out of the bedroom, washing the animal, air cleaning with a high-efficiency particulate air filtration (HEPA) device, improving ventilation, and mattress/pillow covers has been advocated,[23] but studies have shown only temporary decrease in allergen levels and clinical efficacy could not me demonstrated.[24-26] There is controversy whether early-life exposure to cats and dogs can induce tolerance. Some studies have suggested a protective effect

of exposure in early infancy, but the evidence is largely observational. Effects may be dependent on the degree of exposure, the timing of exposure, and the genetic predisposition of the patient.[27] At the present time, the current practice parameter states that the risk reduction is not sufficient to justify a decision to obtain a cat or dog to avoid development of allergy.[23]

Mold

Mold can present problems for the sensitized patient both indoors and outdoors and is implicated in the development of asthma.[28-30] Mold spores are present year-round, but more prevalent in the spring and fall. A mold allergy is especially problematic since mold can grow invisibly anywhere in the house where it is damp as well as in soil and moldy food. Common species of problematic molds include *Alternaria*, *Aspergillus*, *Cladosporium*, *Epicoccum*, *Helminthosporium*, and *Penicillium*. Sensitized patients are advised to avoid potential sources of mold by avoiding mowing or raking leaves, avoiding areas where mold thrives including barns and wooded areas with decaying vegetation. Elimination of potential sources of mold growth in the home includes remediation of mold secondary to water damage, keeping houseplants to a minimum, ensuring adequate ventilation of the home, use of air conditioners, and avoidance of humidifiers. Patients are also advised to avoid cleaning cat litter and birdcages and to discard all old newspapers, books, old furniture, bedding, and clothing. In some patients, an allergic reaction may be brought on by different foods containing or contaminated by mold, such as cheese, dried fruit, mushrooms, soy sauce, wine, or beer. Patients are also advised to avoid foods that potentially may be associated with a mold allergy.

Pollens

Pollen grains are produced and released by plants for fertilization of that particular species. In general, tree pollens are highest in the spring, grass pollens in the early summer, and weed pollens in the late summer and fall. Determination of patient's seasonal symptomatology can be helpful in identifying the offending pollens. Exposure to grass[31] and ragweed[32] have been associated with seasonal asthma, and recent data suggest that persistent pollen exposure in infancy could also increase the risk of asthma in children with a family history of atopy.[33]Pollen counts are usually highest on hot, dry, and windy days. Patients are advised to limit early morning activities outdoors since pollen is usually emitted between 5 and 10 am. Patients are advised to avoid hanging clothes outside to dry and to keep windows closed at night especially during the season in which they are most symptomatic. Keeping windows closed while driving and using air conditioning may be helpful. Taking care to avoid bringing pollen into the house by showering and washing clothing worn outside once entering the house after spending time outdoors is recommended.

Other Environmental Exposures

As approximately 90% of our time in the developed world is spent indoors, a multifactorial approach to assessing and improving the quality of indoor air seems to hold the most promise. In US homes, over 50% had at least six detectable allergens and over 45% had at least three allergens exceeding elevated levels.[20] In addition to the usual allergens that are implicated in perennial AR, other indoor pollutants such as toxins found in tobacco smoke, pesticides, plastics, gases, cleaning products, and heavy metals can cause significant irritation and inflammation of the upper and lower airways. Risk factors for the development of allergic sensitization and resulting asthma include exposure to tobacco smoke, pollution, and mold.[34] Air pollutants that can accumulate indoors include volatile organic compounds, radon, particulate matter, and allergens. Moisture and water accumulation can lead to dust mite and mold growth.[35] Appropriate maintenance of homes and buildings including the control of moisture problems, rodents, cockroaches, testing for radon, lead, asbestos, carbon monoxide, and other toxins are all important in improving our living and working environment. Choosing ventilation and building materials that limit toxins can help improve indoor air quality and potentially the health of the allergic patient.

Environmental Controls in Primary Prevention of Sensitization

In general, results from randomized, controlled trials of primary prevention have largely been mixed. These trials enrolled high-risk children with the goal to reduce environmental exposures and determine if dietary modifications could also help decrease allergic sensitization. Studies from Canada[36] and the Isle of Wight, United Kingdom[37] have shown decreased prevalence of asthma, although there was no difference in development of AR. Another study from Manchester also showed some improvement

in measurements of lung function, but paradoxically, increased risk of HDM sensitization.[38] Other large studies have failed to show significant improvement in allergy and asthma outcome. A large randomized double-blind study, the Prevention and Incidence of Asthma and Mite Allergy study, included 1282 children in the Netherlands and found reduction in Der f 1 but not Der p 1 allergen levels among participants using impermeable covers at age 8 and only a temporary reduction in symptoms at age 2 without long-term improvement in asthma symptoms.[39] Single environmental controls measures using dust-mite impermeable covers in a large randomized, controlled birth-cohort study of 696 newborns failed to show a protective effect of avoidance on sensitization or allergy.[40] A recent meta-analysis demonstrated that a combination of interventions including dietary avoidance reduced the risk of asthma by up to 50%.[41] Based on these trials, it appears that there may be some benefits of avoidance measures, prevention of allergic sensitization was not achieved.[42]

Conclusions

A multifaceted approach including consideration of the patient's living environment and a combination of control measures can provide clinical benefit to the patient with AR and asthma. Clinical trials have shown that single measures are generally ineffective.

MEDICAL THERAPY

Of the various treatment modalities for AR, pharmacotherapy is the most recent addition to clinical practice with the first use of antihistamines in the 1940s.[43] The advent of numerous medication options for AR over the past 70 years has led to a wide variation in treatment regimens that differ by patient-specific symptom quality, location, and severity (Table 14.1). The primary symptoms of AR, nasal congestion, sneezing, pruritus, and rhinorrhea, can vary widely between patients. This variation is partly due to the specific allergen sensitizations, the pattern and severity of symptoms, and any associated comorbid conditions, such as asthma or conjunctivitis. Targets for medical therapies are directed at blocking symptoms from either the histamine-mediated early-phase response within the target tissue or the late-phase response that occurs several hours after when infiltrating immune cells are recruited to the site of early-phase response and release proinflammatory molecules. Individual nasal allergy symptoms can be specifically targeted (i.e. congestion vs rhinorrhea) with medication or with broader agents that target all major allergy symptoms. Selection of treatment regimens are further determined by the duration of symptoms, compliance with daily treatment schedules, prior response to treatments, tolerance or side effects to particular medications, patient age, and costs. The availability of over-the-counter allergy medications has allowed for easy access to multiple classes of medications making it common for patients to have tried numerous medications prior to seeking care from an allergy specialist. Pharmacotherapy for AR in the modern era began when histamine was identified as a mediator of the acute allergic response.[43] During the acute phase of the allergic reaction, histamine is released from mast cells and basophils in response to specific IgE-mediated binding to antigens (allergens) within the nasal cavity. The immediate release of histamine into the local tissue results in neural stimulation that causes pruritus and sneezing. Histamine-mediated increase in vascular permeability and glandular secretions results in clear rhinorrhea and congestion from engorged capillaries in the nasal mucosa. A late-phase response occurs hours later when infiltrating immune cells are recruited to the site of reaction and release additional inflammatory substances that propagate the tissue edema that patients experience as congestion and obstruction.

Antihistamines

Antihistamines block the binding of histamine to the H1 histamine receptor that is involved in the early phase of the allergic reaction. Histamine released by mast cells within nasal mucosa binds to glandular, neurogenic, and vascular target cells that cause pruritus, sneezing, rhinorrhea, and congestion. Antihistamines are safe and effective for episodic control since they have a short onset of action, or as a preventive measure taken on a daily basis for persistent symptoms.[44] The early antihistamines (first generation) provided a rapid and effective blockage of the H1 receptor, resulting in relief of pruritus, sneezing, and rhinorrhea. There are six classes of first-generation antihistamines, including ethanolamines (e.g. diphenhydramine), alkylamines (e.g. chlorpheniramine), piperazines (e.g. hydroxyzine), and phenothiazine (e.g. promethazine). These early antihistamines are lipophilic and readily cross the blood–brain barrier, resulting in central nervous system (CNS) side effects, including sedation and decreased cognitive and motor performance.[45] These medications are also limited by adverse effects due to anticholinergic stimulation, resulting in blurry vision, dry

Table 14.1: Overview of pharmacotherapy options for allergic rhinitis.

Class	*Subclass or route*	*Representative*	*Nasal symptom relief*	*Benefits*	*Limitations/ adverse effects/ precautions*
Antihistamines*	First generation (oral)	Chlorpheniramine Diphenhydramine Hydroxyzine	Sneezing, pruritus, rhinorrhea, +/– congestion	Quick onset, effective	CNS: sedation, cognitive impairment anticholinergic side effects
	Second generation (oral)	Cetirizine Desloratadine Fexofenadine Levocetirizine Loratadine	Sneezing, pruritus, rhinorrhea, +/– congestion	Effective, long acting, well-tolerated, quick onset	Possible sedation
	Intranasal	Azelastine Olopatadine	Sneezing, pruritus, rhinorrhea, congestion	Quick onset, effective, also helps congestion	Taste, Cost Cost
Corticosteroids*	Intranasal	Budesonide Beclomethasone dipropionate Ciclesonide Flunisolide Fluticasone propionate Fluticasone furoate Mometasone furoate Triamcinolone	Sneezing, pruritus, rhinorrhea, congestion	Effective	Slow onset, local irritation, epistaxis, avoid in patients with glaucoma and cataract
	Oral	Methylprednisolone Prednisone		Quick onset, effective	Systemic adverse effects/risks with long-term use, rare serious risks in short term
Leukotriene modifier	Receptor agonist (oral)	Montelukast	Sneezing, pruritus, rhinorrhea, congestion	Indicated for asthma	Efficacy < first line medications
Decongestants	Intranasal	Oxymetazoline Phenylephrine	Congestion, rhinorrhea	Quick onset, effective	Rhinitis medicamentosa, nasal dryness, elevated blood pressure
	Oral	Pseudoephedrine			Elevated blood pressure, nasal dryness
Mast cell stabilizer	Intranasal	Cromolyn	Sneezing, pruritus, rhinorrhea, congestion	Prevent onset	QID dosing, efficacy < first line medications
Anticholinergic	Intranasal	Ipratropium	Rhinorrhea	Quick onset, effective	Only effects rhinorrhea
Expectorant	Oral	Guaifenesin	Thick secretions	Quick onset, effective	Only works as an expectorant

*First-line treatment
(CNS: Central nervous system; QID: Four times a day).

mouth, and increased mucous viscosity. The sedation side effects from early antihistamines can be tolerated in some patients if taken at night before sleep, but it is important to note that paradoxical stimulation of the CNS can

also occur in children. Second-generation antihistamines include cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine. The major improvement of these medications include less permeability to the blood–brain barrier and thus decreased CNS side effects, with perhaps the exception of cetirizine, which can still cross the blood–brain barrier and cause sedation in a dose-dependent manner.[45] The anticholinergic side effects seen in earlier antihistamines are not present with second-generation medications.[45] The second-generation oral antihistamines appear to have similar efficacy.[46] Of the primary symptoms associated with AR, nasal congestion is generally less well controlled with oral antihistamines.[46] Nasal congestion can be due to both the histamine release, causing increased permeability in the early-phase response, as well as the other cellular and soluble inflammatory mediators involved in the late-phase response. If the late-phase response has already been initiated, oral antihistamines may not be of as much value in blocking the immune response and alleviating nasal congestion. Oral decongestants or intranasal steroid sprays are often taken in combination therapy with antihistamines to specifically address the symptom of nasal congestion.More recently, introduction of topical intranasal antihistamine sprays (e.g. azelastine, olopatadine) allows for delivery of a higher concentration of the medication to the site of reaction, although there is systemic absorption with potential sedation as a side effect.[44] Topical antihistamines offer improved efficacy for nasal symptoms including nasal congestion compared with systemic anthistamines.[44,47,48] Intranasal antihistamines have a fast onset of action allowing for symptomatic use. Additional anti-inflammatory properties of intranasal antihistamines may be responsible for additional benefit over oral antihistamines in addressing nasal congestion.

Corticosteroids

Corticosteroids are anti-inflammatory medications that are thought to downregulate immune responses in AR and decrease mediators in the late phase of the allergic reaction. Steroids are lipid soluble and bind to cytoplasmic receptors, which are then transported to the nucleus to effect transcription of immune molecules that downregulate the inflammatory response. Both the anti-inflammatory properties and the adverse effects of corticosteroids are dose dependent, requiring clinical monitoring of patients who have systemic or long-term exposure with higher dosing. Oral corticosteroids have greater potency than topical steroids and may provide relief of nasal allergy symptoms but should be limited in long-term use for AR due to side effects and potential complications associated with their use.[44] A short burst (5–7 days) of oral corticosteroid is helpful for acute, severe symptoms, but should be limited to sporadic use. Clinicians and patients need to weigh the risks and benefits of oral corticosteroid use in deciding systemic dosing frequency and amount. Intranasal corticosteroids have the greatest efficacy at relieving all primary nasal symptoms of AR and are considered a first-line treatment for AR.[44,49] Nasal steroids avoid the side effects and risks of oral corticosteroid use while decreasing the local influx of inflammatory cells and mediators that propagate the allergic response in the nasal mucosa. Although intranasal corticosteroids are effective for AR and serve as a first-line treatment, their slow onset of action requires daily use to achieve maximal effectiveness.[50] In addition, technique of medication delivery is important for deposition of medication onto the nasal mucosa and turbinates rather than along the nasal floor or septum. There are many intranasal corticosteroids available for prescription use including beclomethasone dipropionate, budesonide, ciclesonide, flunisolide fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone. Intranasal corticosteroid sprays offer improved efficacy over other classes of medications for AR, and there is no direct evidence of superiority of any particular preparation over another.[49,51] Patients may have individual preferences of an aqueous or aerosol preparation (ciclesonide, beclomethasone dipropionate). All intranasal steroids have Food and Drug Administration (FDA) approval for treatment over age 6 and FDA pregnancy category C with the exception of budesonide that has FDA pregnancy category B safety rating. Local adverse effects of long-term topical intranasal steroid use can result from mucosal irritation that causes discomfort, mild bleeding, dryness, or rarely septal perforation. More serious risks of worsened glaucoma or cataracts limit their use in patients with these conditions. Initial concerns of risks associate with systemic corticosteroid use, including hypothalamic pituitary suppression, growth suppression in children, bone loss do not seem to be significant concerns.[50]

Decongestants

Nasal decongestants are useful for treatment of nasal congestion until the underlying acute process resolves or

another acceptable long-term treatment option is instituted or becomes effective. Decongestant medications stimulate adrenergic receptors, resulting in vasoconstriction in the nasal mucosa that leads to a rapid decrease in edema and patency of the nasal cavities. Topical decongestants, such as oxymetazoline and phenylephrine directly stimulate sympathetic alpha receptors in the nasal mucosa, resulting in rapid relief of nasal congestion and rhinorrhea. The potential for abuse is seen with topical decongestants, which is why they are only indicated for short periods of time (< 3 days of consecutive use) due to risks of dependence, rebound, and rhinitis medicamentosa. Oral decongestants (e.g. pseudoephedrine) stimulate both alpha- and beta-adrenergic receptors, resulting in additional risks and side effects with systemic absorption. Adverse effects of palpitations, irritability, nasal dryness, hypertension, urinary retention, dizziness, and tachycardia may be seen with short-term use of systemic decongestants. Their use is contraindicated in patients with hypertension, closed-angle glaucoma, hyperthyroidism, cardiovascular diseases, urinary retention, and cerebrovascular disease. The drying of the nasal cavity is usually more significant in the winter months when there is less humidity in heat-conditioned environments. Long-term decongestant use is often be limited by adverse effects.[44]

Expectorants

Normal functioning of the nasal airway epithelium requires mucous secretion for mucociliary clearance of particulates, allergens, and bacteria from the sinonasal passages. Increased viscosity of the mucous can lead to stasis of immunogenic particulates that contribute to the inflammatory response in AR. Expectorants such as guaifenesin are thought to decrease mucous viscosity and allow for improved mucociliary clearance. Although not FDA approved for rhinitis, patients with difficulty clearing thick secretions may have benefit from use of expectorants.[52]

Nasal saline irrigations have been shown to provide significant symptom relief without significant side effects.[53] Nasal saline works by direct thinning and clearance of mucous and allergy particles from the nasal mucosa. The onset of the allergic response is dependent upon contact of allergens with immune cells in the nasal mucosa. A simple cleaning of the nasal cavity can decrease immune exposure to airborne allergen triggers that are filtered and trapped but the nasal mucosa. Irrigation regimens where patients make their own saline solution and use simple delivery methods offer a low-cost and safe option. Infectious contamination of irrigating solution can be avoided with use of clean water source and delivery devices.

Leukotriene Modifiers

Leukotrienes are inflammatory mediators released from white blood cells that partake in the allergic pathway early- and late-phase response and have significant contribution to the pathogenesis of asthma by causing bronchoconstriction and mucous secretion in the lungs. Leukotriene D4 receptor antagonists such montelukast and zafirlukast block leukotriene D4, which reduces the inflammatory response in nasal tissue. Montelukast has indications for both the treatment of AR and asthma, whereas zafirlukast is only indicated for the treatment of asthma. Comparison of leukotriene receptor antagonists to oral antihistamines and intranasal corticosteroids has shown inferior efficacy for leukotriene receptor antagonists making them a second-line treatment. However, they may enhance the effects of other treatments for AR.[44,54] For patients with concurrent asthma and AR, montelukast can improve both conditions. The leukotriene inhibitor, zileuton, blocks 5-lipoxygenase in the leukotriene pathway, but it is only indicated for the treatment of asthma.

Anticholinergics

Anticholinergic medications decrease parasympathetic tone, which results in less secretion of mucous from glandular mucosa and less watery rhinorrhea in patients with rhinitis.[44] Ipratropium, the only available topical intranasal anticholinergic spray, is often used for nonallergic vasomotor rhinitis to decrease mucous secretion. For patients with AR who have a primary symptom of clear rhinorrhea, ipratropium nasal spray can be used to decrease nasal secretions. The onset of action is rapid, but dosing needs to occur three times daily to achieve maximal effect. Although ipratropium has an excellent safety profile, anticholinergic side effects limit their use in patients with prostate hypertrophy and narrow-angle glaucoma. Anticholinergic medication does not address nasal congestion, sneezing, or pruritus.

Cromolyns

Cromolyns are mast-cell stabilizers that block the acute-phase reaction by preventing mast cell degranulation and release of histamine. Intranasal cromolyns are available

over the counter and have an excellent safety profile. Cromolyns require continuous use since they are primarily effective at preventing the allergic response rather than blocking the cascade once mast cell degranulation has occurred. The inferior efficacy of cromolyns compared with other first-line medications for AR,[55] and short half-life requiring four times daily dosing their effectiveness in treating AR.

Selecting a Medication Regimen

Many patients with AR suffer from symptoms of both the acute-phase and the late-phase response. Treatment of both phases is often needed to address different pathways that lead to nasal symptoms. In addition, medications are not intended to be curative, and patients often do not have complete relief of symptoms with a single therapy. The use of combination therapy for AR is commonplace and safe when medications from different classes are used. The side effects seen with antihistamines are dose dependent, which limit the maximal safe doses for these treatments. There are no severe cross-reactions between classes of allergy medications, allowing for the concurrent use of multiple classes of medication for AR. First-line treatment regimens include concurrent use of an intranasal corticosteroid spray and an antihistamine medication.[44] Using both a topical nasal corticosteroid and a topical antihistamine resulted in improved symptoms compared with each medication alone[56] and faster and more complete symptom improvement compared with each medication individually or placebo.[57] Many patients with AR experience incomplete response to medication or ongoing symptoms despite multiple medications. It is common for patients to have tried several medications before seeking specialty care. With numerous medication options available, patients often are confused about the appropriate or optimal medication regimen. For patients with intermittent symptoms, antihistamines used on an as-needed basis are appropriate (Fig. 14.1). For persistent symptoms, daily use of intranasal corticosteroid spray or daily antihistamine is first-line therapies for treatment.[44] Patient's preference, individual efficacy, and tolerability of medications often dictate whether an antihistamine or intranasal corticosteroid spray is used for daily therapy. Antihistamines have the advantage of a quick onset of action and blocking of the acute-phase reaction, whereas intranasal steroid sprays require daily use for maximal effectiveness but are able to block the late-phase

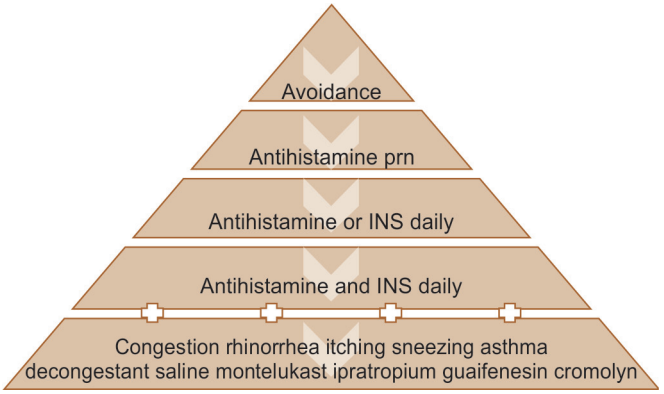

Fig. 14.1: Step-up pharmacotherapy strategy for allergic rhinitis based on persistence and severity of symptoms. Antihistamines and intranasal corticosteroid sprays are first-line therapies. Persistent symptoms can be targeted with an individualized therapeutic plan that focuses on patient-specific factors based on specific symptoms, comorbid conditions, such as asthma, tolerance to medications, costs, age, medical contraindications, and prior efficacy. prn = as needed; INS = intranasal corticosteroids.

reaction that causes ongoing nasal congestion. For persistent symptoms, a combination of an oral or topical nasal antihistamine and an intranasal corticosteroid spray are appropriate. The choice of antihistamine, oral or intranasal, is often determined by individual preferences regarding route, cost, availability (OTC), prior effectiveness, and tolerability.[58] The addition of nasal saline to treatment regimens should routinely be considered given its favorable risk, cost, benefit profile.[53] Addition of a leukotriene modifier to the above medications is safe and can be helpful especially if there is concurrent asthma. If symptoms are persistent despite use of a daily antihistamine and intranasal corticosteroid pray, the use of decongestants, cromolyns, anticholinergics, and expectorants can be added to target specific symptoms in certain clinical scenarios; however, each of these treatments have limitations in the treatment of AR. Many patients suffer from polysensitization that includes both intermittent and persistent allergens. The use of prophylactic pharmacotherapy for intermittent (seasonal) AR can be performed with either intranasal corticosteroids or antihistamines, although administration of antihistamines at the onset of symptoms may provide comparable symptom relief to preventative therapy.[59] For patients who have improved symptoms between allergy seasons, step-down therapy can be performed by first removing all medications other than the intranasal corticosteroid and antihistamine. When deciding to stop either an antihistamine or intranasal steroid spray, removing the intranasal steroid may

result in a longer time to reach maximal effectiveness if symptoms return and step down is halted, whereas an antihistamine can quickly be stopped and restarted without delay in symptom management.

Emerging Therapies

Improved understanding of the pathways involved in AR has led to development of specific therapies that target immune dysfunction. Omalizumab, a monoclonal anti-IgE antibody, has been FDA approved for the treatment of severe asthma. Based on immunologic principles of AR, blocking of IgE antibodies would be expected to provide a significant relief of allergy symptoms. Clinical trials have shown efficacy in intermittent[60] and persistent AR.[61] The lack of direct comparison with other treatments, high costs of this medication, and need for intravenous therapy are current limitations of anti-IgE therapy. Interleukin (IL)-5 has a well-established role in mediating the Th-2 response and activating eosinophils in the allergy response. An anti-IL5 antibody has been developed for use in eosinophilic diseases,[62] such as asthma; however, its efficacy for AR has not yet been demonstrated. As seen with other classes of directed medications, blocking a specific molecule within a complex pathway may not be sufficient to alter the course of the disease. Conversely, side-effect profiles are greatly improved by the improved specificity of targeted therapies. The role of the innate immune system in AR has received attention recently.[63] Toll-like receptors use pattern-based recognition to initiate an immune response. A new bioactive molecule that stimulates toll-like receptor 8 has been proposed for the treatment of AR.[64] A theoretical improvement would be expected with shift in the Th1/Th2 balance that is seen with response to allergen-specific immunotherapy (SIT).

A novel formulation of botulinum toxin (Botox) has been studied in animal models with promising results for reducing the signs of AR by blocking the acetylcholine pathways.[65] Current formulations of botulinum toxin are not approved for intranasal use, and introduction of a new gel formulation would allow for easier application. A longer acting anticholinergic would be beneficial compared with the current anticholinesterase treatment, ipratropium, which requires three times daily dosing.

Conclusions

Pharmacotherapy is one of the three pillars of treatment for AR. Intranasal corticosteroids and antihistamines are first-line treatments with established efficacy and favorable safety profiles. Combination therapy is often used to target both early-phase and late-phase responses for optimal relief, in addition to refractory or severe symptoms that require multimodality therapy. Emerging therapies that are directed as specific pathways in the allergic response offer promise to addressing gaps in treatment and continued symptoms despite maximal pharmacologic therapy.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

For patients, whose allergic rhinoconjunctivitis and allergic asthma symptoms cannot be controlled by environmental avoidance, are not well controlled by medications, or cannot tolerate medications, allergen SIT is another treatment option. SIT involves controlled, repeated allergen administration over a period of time to desensitize the allergic patient with the goal of decreasing symptoms. A pre-requisite to SIT is to identify the specific positive inhalant allergens by history and physical examination, with confirmation by objective testing (skin testing or in vitro testing). The clinical use of immunotherapy in the United States has been in widespread practice for inhalant allergens, which will be the focus of this chapter. Currently, the use of SIT is not recommended for clinical treatment of IgE-mediated food allergies, and if performed should be in a highly controlled setting.[66] There are two forms of SIT that are currently being used in the United States. Subcutaneous immunotherapy (SCIT) for the treatment of seasonal and perennial AR and allergic asthma has been practiced for decades in the United States, and the US FDA has approved the use of allergen extracts for this route of administration. A patient receives frequent subcutaneous injections of an allergen extract, in increasing doses, in an attempt to improve allergic symptoms by gradual modification of the allergic response. SCIT has been used in the United States for close to a century. However, in recent years, there has been interest in using sublingual immunotherapy (SLIT) as a potential alternative to SCIT. SLIT involves placement of the allergen under the tongue for local absorption to desensitize the allergic individual as opposed to injection. Similar to SCIT, SLIT desensitization also takes place over a period of months to years and diminishes allergic symptoms. The World Allergy Organization cited the emerging clinical data on SLIT, recognized it as

Table 14.2: Immunotherapy terms

Term	*Definition*
Anaphylaxis	Immediate systemic reactions caused by rapid release of vasoactive mediators from mast cells and basophils. Treatment should be with rapid administration of epinephrine
Build-up or escalation phase of immunotherapy	During initiation of immunotherapy, patient received increasing doses in strength of allergen
Cluster immunotherapy	Accelerated build-up schedule, several escalating doses given in a single day, on nonconsecutive days
Effect therapeutic dose	Dose that provides symptom relief without significant adverse reactions
Local reaction	Adverse reaction caused by immunotherapy at the site of administration
Major allergen	Antigen which binds to IgE sera from over 50% of clinically allergic patients
Rush immunotherapy	Accelerated buildup with increasing doses in 15–60-minute intervals until target dose reached
Systemic reaction	Adverse reaction caused by immunotherapy that is distant to the site of administration, can involve any organ system
Target maintenance dose or maintenance goal	Projected dose to provide effective treatment

an alternative to subcutaneous therapy and encouraged continued clinical investigation to characterize optimal techniques in 1996.[67] However, at the time of preparation of this chapter, there are no FDA approved sublingual forms of immunotherapy in the United States. Despite the lack of FDA approved sublingual forms of immunotherapy, some physicians in the United States are exploring off-label use of subcutaneous aqueous allergens for sublingual desensitization. Elsewhere in the world, and particularly in Europe, SLIT is readily available in approved aqueous and tablet forms.

Mechanisms of Allergen-SIT and Immunologic Responses

The goal of SIT is to produce long-term immune tolerance to provide relief of clinical symptoms.[66] It appears that T-cell tolerance is particularly important in producing this type of allergen tolerance. After basophils and mast cells are desensitized, various cytokines and other factors are released, and T-cell responses are modulated toward a regulatory T-cell response, leading to a healthy immune response to allergens. With immunotherapy, there also appears to be a shift from specific T-cell response from a T helper 2 to T helper 1 profile. Both SCIT and SLIT induce changes in skin testing, increase in allergen-specific IgG_4, and decrease in allergen-specific IgE over time. The increases in allergen-specific IgG_4 also appear to mirror increases in clinical symptom improvement.

Safety of Specific Immunotherapy

SIT has the potential for untoward side effects. The reactions of SIT fall into two general categories, local reactions or systemic reactions (Table 14.2). Local reactions occur at the site of allergen immunotherapy administration and can be either immediate or delayed in onset; for SCIT, this is a reaction that develops at the injection site, and in the case of SLIT this is the oral cavity. Typical local injection reactions include redness and swelling at the injection site, and common SLIT local reactions include itching and irritation of the oral mucosal. Local reactions can usually be managed by conservative measures such as application of ice or treatment with antihistamines. Systemic reactions are any reactions that occur distant from the site of allergen administration and can vary from mild to life threatening. Symptoms attributed to different organ systems can be involved in a systemic reaction to SIT: urticaria, headache, rhinitis, asthma, and gastrointestinal upset. Anaphylaxis is the most severe systemic reaction, can be life threatening, and should be treated with the timely administration of epinephrine.

The rate of adverse events for SIT varies. A recent review found the rate of systemic reactions was 0.6% for SCIT versus 0.056% for SLIT; deaths 1 per 2.5 million for SCIT versus no reported deaths for SLIT.[68] In a separate 3-year survey, the rate of systemic reactions to SCIT was found to be 0.1% without fatalities, with most systemic reactions occurring within 30 minutes of administration.[69]

Therefore, recommendations have supported the administration of SCIT in a physician's office familiar equipped to handle anaphylaxis, and patient observation for 30 minutes in the office after injection.[66] The following are potential risk factors for severe systemic reactions to SCIT: poorly controlled asthma, large local reactions, and administration during the height of pollen season. In addition, patients taking beta-blocker mediations are at risk for serious anaphylaxis resistant to treatment with epinephrine.

Although there have been no reported fatalities from SLIT, a recent paper reviews 11 nonfatal cases of SLIT-related anaphylaxis reported in the medical literature.[70] The authors of this review felt these reports of anaphylaxis with SLIT represented nonstandard practices of SLIT and found several of these patients had previous serious adverse reactions to SCIT. Reports of anaphylaxis from the first dose of sublingual tablets have led to the recommendation that in Europe the first dose of a sublingual tablet be administered in a physician's office capable of recognizing and treating adverse reactions.[71] However, risk factors for severe systemic reactions to SLIT have not been clearly delineated. In Europe, where there has been the largest experience with SLIT, the perceived safety improved profile of SLIT over SCIT has led to the home administration of SLIT. Efficacy of Specific Immunotherapy.

Efficacy of Immunotherapy

SCIT Efficacy

The effectiveness of SCIT for AR and allergic asthma was the topic of a recent large systematic review. Erekosima's review included 61 randomized controlled trials and found high-grade evidence that SCIT reduces asthma symptoms, asthma medication usage, rhinitis/rhinoconjunctivitis symptoms, conjunctivitis symptoms and improves rhinitis/rhinoconjunctivitis disease-specific quality of life in comparison with placebo or usual care.[72] The study found moderate evidence that SCIT decreases rhinitis/rhinoconjunctivitis medication usage. These finding are consistent with prior systematic reviews.[73-75] A Cochrane review by Calderon et al. concluded that SCIT for seasonal AR results in a significant reduction in symptom scores and medication use with a low risk of adverse events.[74] Matricardi et al. compared four recent meta-analyses, concluding that SCIT is at least as potent as pharmacotherapy, with potential onset of beneficial effects as early as the first season of treatment.[75]

The effectiveness of SCIT in children has also been demonstrated. A 2013 systematic review by Kim et al. focused on the effectiveness of SIT specifically in children.[76] The authors reviewed 13 randomized controlled pediatric trials of SCIT, concluding that the strength of evidences is moderate that SCIT improves asthma and rhinitis symptoms in children. Another systematic review, by Roder et al. reviewed immunotherapy for allergic rhinoconjunctivitis in children and identified six SCIT studies, which showed conflicting results for clinical efficacy.[77]

SLIT Efficacy

Several recent large-scale systematic reviews and meta-analyses have examined the efficacy of SLIT for the treatment of environmental allergies. Wilson et al. published the first landmark large-scale review, a Cochrane meta-analysis of SLIT in 2003, which examined 979 adult and pediatric subjects from 22 randomized double-blind placebo controlled studies.[78] While this meta-analysis found significant reduction in symptom and medication use with SLIT and concluded that SLIT was effective for AR, there was noted heterogeneity in studies as far as dosages/treatment schedules and safety data reporting. This review was updated in 2011, with 60 randomized controlled trials of SLIT with similar conclusions regarding efficacy.[79] This updated review found the efficacy greatest for studies with HDM. This meta-analysis also found aqueous and tablet forms of SLIT to have similar effectiveness. The most recent systematic review of the effectiveness of SLIT for AR and allergic asthma published in 2013 found strong evidence to support the use of SLIT for allergic asthma in comparison with usual care; moderate strength evidence was found support the use of SLIT to improve the following outcomes: rhinitis/rhinoconjunctivitis symptoms, conjunctivitis symptoms, decreased medication usage, and improvement in allergy-specific quality of life.[80]

SLIT has been considered to be a favorable alternative for children, based on the ease of administration. The efficacy of SLIT in the pediatric population has been confirmed in multiple systematic review and meta-analyses. Calderon et al. examined nine pediatric studies and showed significant reduction in allergic conjunctivitis symptoms in children treated with SLIT.[81] Although Sopo et al. in their systematic review of the clinical efficacy of SLIT in children with respiratory allergies found no significant clinical results with the use of SLIT in children for seasonal allergens or dust mites allergen, they did

demonstrate low to moderate clinical effects in mild to moderate persistent asthma due to HDMs.[82] Penagos et al. performed a meta-analysis of nine studies on the efficacy of SLIT in children with allergic asthma; there was a significant reduction in asthma symptoms and medication usage.[83] A meta-analysis by Olaguibel et al. found statistically significant reductions in asthma and medication scores with SLIT in children, but not for rhinitis or conjunctivitis symptoms, although decreasing trends were observed for all symptoms.[84] Kim et al. in their 2013 systematic review of SIT in children concluded that the strength of evidence is high that SLIT improves asthma symptoms, moderate to support the use of SLIT for rhinoconjunctivitis symptoms, and moderate to support the use of SLIT to decrease medication use.[76]

Long-Term Efficacy and Disease Modification with SIT

Treatment with SIT may have long-ranging effects. Studies have shown that after several years of either SCIT or SLIT, continued positive effects on allergic symptoms persist for 7–12 years after discontinuation of immunotherapy.[84-89] Both SCIT and SLIT have been shown to have preventative effects toward the development of asthma and new allergen sensitivities.[90] Studies examining the cost-effectiveness of SIT versus pharmacotherapy have shown costs savings up to 80% 3 years after completion of a course of immunotherapy.[91]

Specific Immunotherapy Dosing

SCIT Dosing

For those standardized SCIT allergens whose effective doses are established, a typical starting immunotherapy dose may be 1000 to 10,000 less than the target maintenance doses.[92] For nonstandardized extracts, a suggested maintenance dose of 3000–5000 protein nitrogen units or 0.5 mL of a 1:100 or 1:200 weight per volume dilution of manufacturer's extract is recommended. The typical target maintenance dose for inhalant allergens by major allergen content is 5–20 μg. During the build-up or escalation phase, the dose is gradually increased at weekly intervals over several months until the target maintenance dose is reached. However, some patient may have difficulty reaching or tolerating the target maintenance dose if they develop large local reactions or systemic reactions. After maintenance dosing levels are reached, maintenance doses can be then administered one to two times a month. A full course of SCIT is 3–5 years in duration. Rush and cluster dosing schedules decrease the time to reaching maintenance dosing with accelerated administration but may also carry increased risks of provoking adverse reactions in some patients. Rush immunotherapy decreases the time spent in the build-up phase by escalating allergen dosing in 15–60-minute intervals over 1–3 days to reach the target maintenance dose. Cluster immunotherapy involves giving 2–3 build-up doses in 1 day as opposed to only one, to reach maintenance more quickly.

SLIT Dosing

The dosing of SLIT has been determined primarily from the European literature, where approved formulations of SLIT are available. The frequency of dosing described in the literature varies widely, but daily dosing appears to be most frequently utilized, with short or no escalation periods, and duration of clinical therapy lasting several years. In different trials, SLIT has been delivered perennially, preseasonal and coseasonal, with all three demonstrating symptom relief.[93] It appears that the effective cumulative dose of SLIT is 30 times greater than SCIT maintenance doses.[94] European antigen manufacturers' recommendations for monthly maintenance SLIT dose typically range between 5 and 45 times the dose recommended for SCIT maintenance.[95] However, due to differences in US versus European allergen standardization and potency, there may need to be some caution when attempting to translate European dosing to the United States. In the United States, the FDA establishes for each standardized allergen a national in vitro potency test, which all manufacturers must use to compare their extracts; in Europe, each allergen manufacturer has its own in-house reference standards.[96] A recent study comparing European and US allergens found that US extracts were found to have relative potency up to 10 times greater than European extracts.[97] As further studies are performed with allergens manufactured in the United States, or if an FDA approved product becomes available, this will allow for clearer determination of effective US SLIT dosing.

However, there are some US studies that do provide some information regarding effective US SLIT dosing. A recent study evaluated the efficacy of SLIT for short ragweed utilizing liquid short ragweed antigen product currently labeled for subcutaneous injection use.[98] The study demonstrated a reduction in rhinoconjunctivitis symptom and antiallergy medication use scores for both the 4.8 and 48 Amb a 1 Unit doses versus placebo. The reduction only reached statistical significance only at the higher dose. A study in the United States was conducted

Table 14.3: Comparison of SCIT and SLIT

	SCIT	*SLIT*
Efficacy	Supported by scientific literature	Supported by scientific literature
Safety	Fatalities very rare	No reported fatalities, but anaphylaxis reported
Administration	Injections in physician's office	Home administration
Dosing	Weekly to monthly after period of time, rush/cluster accelerated build-up schedules exist	Schedules vary, but daily dosing common
FDA	Approved formulations for SCIT	No approved formulations specifically for SLIT; "off-label" use of SCIT allergens
Recommended duration of therapy	Several years	Most studies seem to support several years

(FDA: Food and Drug Administration; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy).

in the pediatric population using SLIT grass tablets.[99] This study showed a significant reduction in total combined symptom and medication scores, with the maintenance dose utilized in this study was approximately 15 μg of Phl p 5 timothy antigen. A similar adult study[100] performed in the United States of grass mix tablets demonstrated that the 300 IR tablets significantly improved combined symptom medication scores compared with placebo.

Subcutaneous Versus Sublingual Immunotherapy

When comparing SCIT with SLIT, each form of immunotherapy has its potential advantages (Table 14.3). SCIT is well established in the United States, has a long duration of clinical use, and there are FDA approved allergens for SCIT. SLIT has been used for over two decades in Europe, but use in the United States is "off-label" as there are no approved FDA allergens, but has the advantage of ease of administration, and dosing at home as opposed to physician's office for SCIT. When considering the comparable efficacy of the two forms of immunotherapy, a recent systematic review of randomized controlled trials in which these forms of immunotherapy were compared head to head was published.[101] Although the authors found evidence to support improved outcomes with SCIT over SLIT in asthma and rhinitis, there was no difference in medication outcomes; they concluded additional studies were required to strengthen this evidence base for clinical decision making and may change these conclusions.

Unanswered Questions Regarding SIT

There are still many unanswered questions regarding SIT. There is a specific need for studies investigating the efficacy and safety of multiple allergen regimens, as these are commonly used in the United States in clinical practice, as the current literature comprises primarily of single antigen studies. In the pediatric population, there is a need to determine if immunotherapy can prevent or modify the atopic march in high-risk children. Additional pediatric considerations include identifying the optimal age for immunotherapy initiation. Although studies have found SLIT effective for improving symptoms of allergic rhinoconjunctivitis and asthma, there are several lingering questions regarding SLIT use in the United States. The target maintenance dose, dosing strategies, and the necessary duration of treatment for SLIT with various allergens have not yet been fully determined. In addition, further head to head studies will be helpful to clarity the relative effectiveness of SCIT versus SLIT.

Conclusions

SIT, both SCIT and SLIT, has been shown to be effective in the treatment of AR and allergic asthma. Immunotherapy does carry with it inherent risks of adverse reactions, practitioners need to be aware of the potential for local and systemic reactions and be prepared for timely treatment. Although dosing is large established for SCIT, optimal SLIT dosing in the United States is still being clarified.

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CHAPTER

Allergy, Reactive Airway Disease, and Rhinosinusitis: The Unified Airway

15

Rachel Georgopoulos, Elina M Toskala, John H Krouse

INTRODUCTION

The association of the upper and lower airways as an integrated system has been referred to as the "unified airway" model.[1,2,26] In this paradigm, the nose and paranasal sinuses, through the trachea and larynx, to the distal bronchioles are viewed as one functional unit. It is well known that local and systemic influences that affect one part of this functional unit have distal effects. Epidemiologic analysis has shown that rhinitis and rhinosinusitis are comorbid conditions with asthma at a rate much higher than would be predicted by baseline prevalence of these diseases alone. It has also been shown that the biological mechanisms underlying these disease states are similar and that treatment of inflammatory diseases of the upper airway can improve asthma control. While otolaryngologists frequently manage rhinitis, chronic rhinosinusitis (CRS) and laryngitis, the diagnosis and management of asthma is infrequently considered in these patients. A more thorough understanding of how these disease processes are interrelated will help to optimize patient outcomes.

RHINITIS AND ASTHMA

The relationship between rhinitis and asthma is well founded. Rhinitis, both allergic and nonallergic, is not only associated with but is a risk factor for the development of asthma.[3,7–9,19] In fact, it has been shown that management of allergic rhinitis (AR) at a young age with allergen-directed immunotherapy might prevent the development of asthma in later life.[70–72] Disease severity is also linked. Individuals with severe persistent forms of rhinitis are more likely to have symptomatic asthma than patients with intermittent forms of rhinitis.[3,10] In addition, support for the inter-relationship between these two diseases comes from the fact that the treatment of AR has been found to improve asthma control.[16,17,55,66]

AR is clinically characterized by a symptomatic inflammation of the nasal mucosa accompanied by nasal congestion/obstruction, rhinorrhea, sneezing, itching of the nose, postnasal drip, chronic cough, and conjunctivitis.[20,31] While there is an association between rhinitis and asthma, regardless of the atopic status of the patient, the relationship between asthma and AR is even more dramatic. While AR is generally categorized in the United States based on time of exposure into seasonal, perennial or occupational, the ARIA guidelines, first published in 2006, suggest that AR should be divided into subgroups based on duration of symptoms and level of impairment.[20]

Epidemiology

AR and asthma affect about 30% and 7–8% of people, respectively.[8,33,53] Asthma is epidemiologically linked to both allergic and non-AR with the two diseases occurring together at a rate much higher than would be expected from the baseline prevalence data of these conditions alone.[26] The majority of patients with asthma also have rhinitis. While only one-third of patients with rhinitis have asthma, it is important to realize that rhinitis often precedes the development of asthma with up to 20% of patients with rhinitis developing asthma later in life. In general, patients with rhinitis have a threefold increased risk for the development of asthma.[3,7,9] This association is influenced by a variety of factors, including atopic status and

the severity of disease symptoms. In patients with rhinitis and high serum IgE levels the risk of developing asthma is even greater.[3] In addition, the prevalence of asthma among atopic patients varies with the type of antigen responsible for their sensitivities. In a study performed by Linneberg et al.[11] subjects with AR were skin tested to various inhalant allergens. It was found that patients with a positive skin test to seasonal allergens had a 10-fold increased risk for developing asthma while patients with a positive test for dust mite, a perennial allergen, had around a 50-fold increase in the likelihood of developing asthma when compared to their nonallergic counterparts.

Consistent with these observations, Prieto et al.[81] found that nonasthmatic patients with AR exhibit bronchial hyper-responsiveness when exposed to sensitized allergens. Similar to studies carried out by Linneberg et al.,[11] patients sensitized to dust mite had lower methacholine challenge thresholds when compared with patients sensitized to seasonal allergens such as pollen. This study implies that individuals sensitized to perennial allergens are at an even greater risk of bronchial hyper-responsiveness than patients sensitized to seasonal allergens and that stimulants presented to the nasal mucosa have effects at the distal bronchioles.

Irritants that trigger rhinitis also trigger asthma exacerbations. Inflammation of the nasal mucosa in AR disrupts the filtering capabilities of the nose and can result in inhalation of unfiltered irritants into the distal airways. Even in the absence of a local response, irritants presented to an isolated portion of the respiratory system will exert distal effects. At least two mechanisms can explain the communication between the nasal and bronchial mucosa: (1) a local inflammatory response to an irritant leads to the upregulation of inflammatory mediators and subsequent system wide inflammation in the airways and (2) neurogenic reflexes allow for a downstream response through activation of the parasympathetic system.[77, 78]

Nasal-Bronchial Reflex

Fontanari et al.[77] found that when cold air was presented to the nasal mucosa, airway resistance increased. This response was suppressed when the nasal mucosa was anesthetized. This study suggests that neuronal stimulation in the nose results in the release of cholinergic neurotransmitters that stimulate smooth muscle contraction and result in bronchoconstriction.[89]

Inflammatory "Cross-Talk"

At a cellular level, the inflammatory cell profile found in the nasal mucosa of patients with AR is similar to that seen in the bronchial mucosa of patients with atopic asthma. The most prominent feature is an infiltration of eosinophils and an increased number of mast cells, lymphocytes, and various cytokines. Both disease entities also demonstrate thickening of the epithelial basement membrane.[79,80]

Braunstahl et al.[13–15] showed that inoculation of an antigen in the nose results in upregulation of inflammatory mediators in the lungs and that inoculation of an antigen in the lung using a bronchoscope results in upregulation of inflammatory mediators in the nose. The upregulation of inflammatory mediators at a distal site from inoculation suggests that within the respiratory system there exists a system of inflammatory "cross-talk". This association is further exemplified by the observation that the nasal mucosa is inflamed in asthmatics even if they lack nasal symptoms. Moreover, rhinitis tends to be more severe in asthmatics than in their nonasthmatic counterparts.

Prevalence

Severity of rhinitis and asthma often parallel each other. Asthma patients with severe rhinitis have been shown to have a higher rate of nighttime awakenings and absences from work than asthmatics with less severe rhinitis.[10] In a study performed by Shturman-Ellstien et al.,[12] asthmatic patients were monitored during exercise with either patent nares or nares that were occluded with a nasal clamp. Patients with obstructed nares showed a 20% decline in forced expiratory flow when compared with < 5% reduction among patients allowed to exercise with patent nares. This relationship suggests the presence of neurogenic responses along the respiratory epithelium that uniformly affect the upper and lower airways, and may also reflect the lack of nasal conditioning of air delivered to the lower airways.

CRS AND ASTHMA

Underlying the unified airway model, the nose, paranasal sinuses, trachea, and primary and secondary bronchi are lined by a pseudostratified ciliated columnar epithelium.[26] These similarities support many of the common pathophysiologies seen in unified airway diseases. Some of the common histopathologic changes seen in patients with CRS and asthma include infiltration of eosinophils beneath the mucosal epithelium, an increase in macrophages and lymphocytes, and thickening of the basement membrane.[6,54] There is a complex interaction between a variety of cytokines and cellular mediators that helps to

explain these changes.[26,55–58,60] These findings are also seen in histopathology specimens from the respiratory bronchi of asthmatics.

The prevalence of asthma in individuals with rhinosinusitis is substantially higher than in the general population, with at least 50% of patients with CRS with nasal polyps having asthma.[55,56] The type of inflammation and the response to that inflammation are similar in both of these diseases. In fact, both CRS and asthma exhibit eosinophilic inflammation, goblet cell hyperplasia, subepithelial edema, submucosal gland formation, hypersecretion and epithelial damage, and thickening of the basement membrane.[26,48,57,59,93,94] In addition, the changes seen in airway remodeling, which occur as a result of chronic inflammation with tissue damage and repair, are also the same.

One of the reasons for the similarities seen in the upper and lower airway systems during an inflammatory response may be a result of late-phase reactants. These late-phase agents result in an upregulation of eosinophilic progenitor cells that work at the level of the bone marrow to cause a systemic increase in eosinophils. The proportion of these progenitors appears to correspond to the degree of airway hyper-responsiveness with levels decreasing as airway symptoms return to baseline.[26,55,62] In addition, the severity of asthma corresponds to the severity of rhinosinusitis. It has been demonstrated in a variety of studies that patients with more severe forms of asthma demonstrate more dramatic sinonasal pathology on CT imaging.[63,64]

More recently, *Staphylococcus aureus* superantigens have been implicated as a trigger to the Th_2 inflammatory cascade and eosinophilic inflammation in patients with CRSwNP and asthma. It has been observed that the prevalence of comorbid asthma in patients with CRSwNP was significantly higher in patients who had IgE antibodies to staphylococcal enterotoxins.[67,68,101]

Aspirin-Exacerbated Respiratory Disease

Another condition that has both upper and lower airway consequences is aspirin-exacerbated respiratory disease (AERD), also known as Samter's triad. The development of AERD has recently been noted to have a potential association with an initial viral infection, with progressive nasal congestion, rhinorrhea and anosmia occurring later. Traditionally, symptoms progress to chronic hyperplastic eosinophilic rhinosinusitis and subsequently the development of sinonasal polyps. Symptoms usually occur immediately upon medication use in sensitized individuals. After the onset of symptoms, disease progression continues

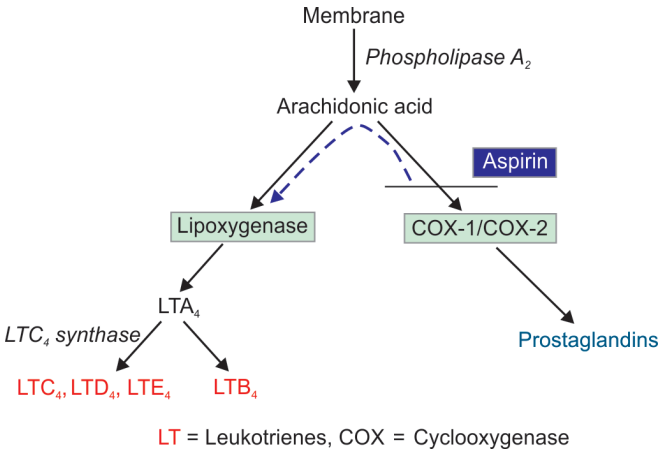

Fig. 15.1: The arachidonic acid cascade, demonstrating the generation of leukotrienes through the 5-OH-lipoxygenase pathway.

despite discontinuation of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).[74] Asthma may not present until 1–5 years after the presentation of initial symptoms but in aspirin-sensitive patients who develop asthma, 50% will have a chronic severe corticosteroid-dependent asthma.[26,69,73] A total of 70% of aspirin-sensitive patients will develop sinonasal polyps.[69,73,74]

While many questions regarding the pathophysiology of AERD remain unanswered, it is known that unlike type l hypersensitivity reactions AERD is not an IgE-mediated process but rather a result of an aberration in arachidonic acid metabolism. Through inhibition of the COX pathway, upstream metabolites are shunted to the lipoxygenase pathway with subsequent increased production of various proinflammatory metabolites such as cysteinyl leukotrienes A_4, B_4, C_4, D_4, and increased activity of leukotriene C_4 synthase[69,74] (Fig. 15.1). Histopathology specimens from patients with AERD exhibit a marked eosinophilia, with aspirin-sensitive patients exhibiting a fourfold greater number of eosinophils than aspirin-tolerant patients, and up to a 15-fold increase in eosinophils when compared to normal mucosa.[26,73] Similar to the inflammatory pattern described earlier for CRS, IL-5, RANTES, and eotaxin levels are elevated in individuals with AERD.[26,57]

All patients with aspirin sensitivity must be advised to avoid using NSAIDs, as there is a significant risk of death. While there are not any specific guidelines for the treatment of these patients, in individuals with mild asthma, drugs downregulating leukotriene function such as montelukast and zileuton, as well as inhaled asthma medications may be used.[73] Sinus surgery has been shown to not only improve sinonasal symptoms in aspirin-sensitive patients but also to improve asthma symptoms, pulmonary function scores, and medication usage.[75]

ASTHMA

Asthma is a chronic inflammatory disorder of the airways characterized by the influx of inflammatory mediators, mainly mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells, that results in reversible airway obstruction and bronchial hyper-responsiveness. In advanced cases of asthma, chronic inflammatory airway remodeling can occur, with irreversible injury to the respiratory mucosa. In individuals with asthma, airway inflammation results in symptoms of wheezing, breathlessness, chest tightness, and coughing.[32,34]

Epidemiology

Asthma affects about 8% of people in the United States and about 50% of people with asthma have had an exacerbation within the previous year.[33] Children have a higher prevalence of asthma than adults 9.6% and 7.7%, respectively. In childhood, boys have a higher prevalence than girls but with advancing age the prevalence ratio reverses with women having an increased prevalence compared with men.[33,99]

Asthma creates a significant impact on national productivity and health care costs. In 2008, children between ages 5–17 with at least one asthma attack in the previous year were reported to miss 10.5 million school days. In addition, employed adults with at least one asthma attack in the last year reported missing 14.2 million workdays. In 2007, asthma accounted for 13.9 million outpatient visits to private physicians, 1.75 million emergency room visits, and 456,000 hospital admissions. A total of 3447 deaths were due to asthma.[19] There is a geographic variability in asthma prevalence among children, with Greece and Italy having the lowest prevalence and Australia, New Zealand, Republic of Ireland, and United Kingdom having the highest prevalence.[39] While it is likely that some environmental exposure is at least partially responsible for this relationship, air pollution has not been found to be the primary cause associated with geographic differences in the prevalence of asthma or rhinitis in children or adults.[40,41,99]

Race and Socioeconomic Status

In the United States, the overall prevalence of asthma is highest in black individuals.[33] Asian adults are less likely to have been diagnosed with sinusitis or asthma in the last12 months when compared to black or white adults.[53] While the total prevalence of asthma in Hispanics appears to be low, individuals of Puerto Rican descent had the highest overall prevalence of asthma among any subgroup, but the overall prevalence of asthma in individuals of Mexicandescent was lower than any other subgroup including Asians. This observation suggests that genetics may play a role in asthma expression.[26,33] Prevalence also variesbetween socioeconomic groups with the prevalence of asthma being highest in low income families.

Risk Factors

There are many established risk factors for the development and exacerbation of asthma. As an example, passive tobacco smoke exposure is associated with increased wheezing in children, with more severe disease seen in children already diagnosed with asthma.[35] There is also a causal relationship between passive tobacco smoke exposure in adults with new onset asthma and asthma exacerbations.[36]

In addition, allergy is a well-known risk factor for asthma. Poletti et al.[52] analyzed dust samples from the homes of children hospitalized with asthma and children considered to be “stable asthmatics” (SA). He found that children hospitalized for asthma were significantly more likely to have been exposed to a sensitized allergen when compared with SA (OR = 2.9).

Obesity is an established risk factor for the development of asthma.[37] This relationship appears to be at least partially explained by the upregulation of proinflammatory cytokines by adipocytes. Two mediators currently implicated in this relationship are adiponectin and leptin. Adiponectin has systemic anti-inflammatory properties and functions by inhibiting proinflammatory cytokines TNF-α and IL-6 and upregulating anti-inflammatory signals such as IL-10 and IL-1 receptor antagonist. It has been observed that levels of adiponectin are decreased in obesity.[86] Leptin is a hormone produced by adipocytes and is a member of the IL-6 cytokine family that has proinflammatory activity.[87]Alterations in these mediators as a result of increased adipose tissue predispose for a proinflammatory state. This helps to explain why obese patients are more likely to have hyper-responsive airway disease.

In addition, there is an association with respiratory viral infections such as respiratory syncytial virus and childhood wheezing.[38] Further, unstable asthmatics are more likely to have a positive nasal viral culture than stable asthmatics.[52] As discussed earlier, rhinosinusitis, allergic and non-AR are also risk factors for the development

of asthma.[3,7–9,99] The association between CRS, rhinitis and asthma is even stronger in patients with both CRS and rhinitis when compared with either disease alone.[99] Moreover, a variety of environmental factors have also been implicated. There is a known association between respiratory symptoms such as dyspnea on exertion, breathlessness, and cough with air pollution.[41] Other environmental factors that increase asthma risk include moisture damage at work and home and occupational rhinitis.[97,100] In fact, the risk of asthma has been shown to be as high as seven times that of controls, among farmers with occupational rhinitis.[100]

Pathophysiology

While bronchoconstriction was once the focus of asthma pathophysiology, it has become increasingly clear that inflammation is the underlying mechanism for bronchial hyper-responsiveness, airflow limitation, and the respiratory symptoms experienced by individuals with asthma. This paradigm shift has implications in the diagnosis, management, and prevention of this disease.

Acute airway obstruction, which is a defining feature of asthma, is a result of contraction of bronchial smooth muscle. Muscle contraction can occur as a function of a complex interaction between resident inflammatory cells, such as mast cells and alveolar macrophages and the influx of inflammatory mediators such as eosinophils, lymphocytes, neutrophils, and basophils. These inflammatory cells secrete mediators such as histamine, leukotrienes (LTC_4, LTD_4, LTE_4) prostaglandin D_2, and platelet activating factor, which act on bronchial smooth muscle to cause muscle contraction.[32,60]

In addition to inflammation-induced bronchospasm, the smooth muscle lining the airways is under neuroregulatory control. Through either direct stimulation of the vagus nerve or as a result of a secondary response to a stimulus, parasympathetic activation results in bronchoconstriction. Neuromediators such as substance-P and calcitonin gene-related peptide (CGRP-LI) appear to play an important regulatory role and are known to influence histamine release from mast cells and to regulate airway smooth muscle tone.[28,29,60] Mediators such as histamine and bradykinin also work to bind interendothelial junctions (IEJs) and integrin-extracellular matrix complexes located on the vascular endothelium. This process results in the unrestricted passage of proteins and fluid and explains the resultant mucosal edema seen in these patients.[60,61] In addition, excess mucus produced in asthma can block the lumen of distal bronchioles and contributes to airflow obstruction.[60]

There are two categories of T-lymphocytes, Th_1 and Th_2, with atopic patients having a skewed predilection for the Th_2 phenotype.[42,43,44] Th_2 cells secrete a series of cytokines including IL-4, IL-5, and IL-13. These cytokines, along with B and T lymphocytes and endothelial cells, result in the production of the chemokines RANTES and eotaxin, which facilitates the transendothelial migration and activation of eosinophils.[55–58,60] In addition, ICAM-1 and VCAM-1, which are endothelial adhesion proteins bind receptors on the surface of eosinophils, lymphocytes, and neutrophils and result in the migration of these inflammatory cells from the intravascular space into the airway. Mast cell degranulation results in release of vasoactive amines such as histamine, as well as triggering the production of newly formed mediators of inflammation such as cysteinyl leukotrienes. Eosinophils migrate to inflamed tissues and are responsible for the release of toxic basic proteins that cause epithelial damage and airflow obstruction.[60] It is this inflammatory cascade that results in the characteristic histological features of mucosal edema, submucosal gland, and bronchial smooth muscle hypertrophy, mucus hypersecretion and basement membrane thickening and fibrosis seen in asthma.[45–47,60]

In fact, eosinophilic inflammation is so characteristic of asthma that it is used to help differentiate asthma from other types of obstructive pulmonary diseases such as COPD. Asthmatics have higher eosinophils levels in both their blood and their sputum while the primary cell type in COPD patients is neutrophils. While neutrophils are not the primary granulocyte seen in most forms of asthmatic inflammation, they do contribute to airflow obstruction in both acute and chronic severe forms of asthma. While the extent and mechanism has not been fully elucidated, it is known that neutrophils produce lipid mediators, reactive oxygen intermediates, and proteases that contribute to airflow obstruction, epithelial damage and remodeling. Interestingly, it has been observed that in patients with sudden onset fatal forms of asthma or in an acute asthma exacerbation, the number of neutrophils exceeds eosinophils. This observation suggests that neutrophils may play an important role in the acute, severe forms of asthma and these increased levels are likely a result of an infectious agent that triggers these events.[50,51]

In addition, total serum IgE levels are indictors of asthma severity. It has been found that serum IgE levels are directly proportional to the level of bronchial hyperactivity.[95] Further, Guerra et al.[3] found that in patients who

have not yet been diagnosed with asthma, high serum IgE levels significantly increase the risk of developing asthma later in life.

Airway remodeling is a result of tissue injury and subsequent repair, and is characterized by mucosal edema, submucosal gland and bronchial smooth muscle hypertrophy, mucus gland and globlet cell hyperplasia, angiogenesis, collagen deposition, basement membrane thickening and subepithelial fibrosis in the lamina reticularis.[45–47,60] Studies comparing histopathology specimens of patients with CRS and asthma found that both disease entities exhibit similar changes of epithelial damage, thickening of the basement membrane with eosinophilic inflammation.[48,96] The similar histopathology observed in CRS and asthma further suggests that these disease entities are a result of one disease process as oppose to two separate entities.

ASTHMA AND ATOPY

There is a strong association between asthma and atopy, and patients with atopic asthma exhibit evidence of IgE-mediated sensitivity to airborne antigens.[3] This Th_2 polarized inflammatory response appears to be the link between allergy and atopy in these individuals.[82]

Diagnosis

Asthma is a diagnosis made based on a variety of symptoms in the presence of persistent or episodic, and at least partially reversible, airway obstruction.[32] The National Asthma Education and Prevention Program[32] published a list of key indicators that are suggestive of asthma (Table 15.1). History and physical examination and/or spirometry can also aid in making the diagnosis. Symptoms of breathlessness, cough, recurrent wheezing, and chest tightness are very common in asthma. These symptoms may be worse at night and often result in sleep disturbance. Inquiry as to the effects of seasonal changes, environmental exposures, cold exposure, and other irritants may reveal triggers for the exacerbation of their symptoms.

On physical examination, wheezing, coughing, and accessory muscle use may be appreciated, especially in more severe disease. Auscultation may reveal prolonged forced exhalation and expiratory wheezes. Percussion of the lungs may reveal hyper-resonant breath sounds as a result of air trapping.[26] In light of the association of asthma and rhinitis a thorough head and neck examination should be performed as discussed earlier.

Table 15.1: Key indicators of asthma

- History of any of the following:
  - Cough, worse particularly at night
  - Recurrent wheeze
  - Recurrent difficulty in breathing
  - Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  - Exercise
  - Viral infection
  - Animals with fur or hair
  - House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
  - Mold
  - Smoke (tobacco, wood)
  - Pollen
  - Changes in weather
  - Strong emotional expression (laughing or crying hard)
  - Airbone chemicals or dusts
  - Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient

National Heart, Lung, and Blood Institute: National Institute of Health; US Department of Health and Human services: Expert panel report 3: guidelines for the diagnosis and management of asthma. NIH publication no. 07-4051, National Institutes of Health; National Heart, Lung, and Blood Institute Bethesda, Md. 2007. Accessed March, 2013. http://www.nhlbi.nih.gov.libproxy.temple.edu/guidelines/asthma *Courtesy*: From National Institutes of Health (NIH).

While medical history and physical examination are important in the evaluation of patients with asthma, objective measures are helpful in order to confirm the diagnosis. There are a variety of pulmonary diseases that present with similar symptoms to those seen in asthma. The lack of confirmatory testing can prevent patients from getting appropriate treatment for their disease.

Diagnostic Testing

There are a variety of tests used to assess pulmonary function, some of which include lung volumes, spirometry, flow volume loops, diffusion capacity, and body plethysmography.[26] Body plethysmography is used to assess intrathoracic gas volumes at different intervals of the respiratory cycle, although it is not commonly used in routine asthma evaluation. Asthmatics exhibit an increased residual capacity due to air trapping and a decrease in vital capacity.

Peak expiratory flow (PEF) is a commonly employed test that assesses the maximal speed of exhalation. In asthmatics, the PEF rate will decrease as a result of bronchoconstriction and obstruction to airflow. PEF primarily reflects the physiologic function of the larger airways. Full spirometry and flow-volume loops are extremely valuable in the assessment of asthma. In cases where the diagnosis is not clear, especially in individuals with concomitant or a questionable diagnosis of restrictive airway diseases, other obstructive pulmonary diseases, vocal fold dysfunction or central airway obstruction, ancillary testing may prove valuable.[32]

Lung function abnormalities may be categorized as either obstructive or restrictive. Spirometry can be used to differentiate the two and is performed by having the patient take a maximal inspiration followed by a maximal exhalation into a spirometer. Forced vital capacity (FVC) is the maximal volume of air that can be exhaled, and forced expiratory volume in the first second (FEV_1) is the volume of air that can be forcibly exhaled in the first second of exhalation. In obstructive disorders such as asthma FEV_1/FVC ratio will be decreased from normal, while in restrictive diseases the FVC and FEV_1 are proportionally reduced resulting in a normal or even increased FEV_1/FVC ratio. Flow-volume loops are also generated (Fig. 15.2). Flow volume loops are a graph of airflow versus volume. In obstructive diseases total lung capacity (TLC) and residual volume (RV) are increased as a result of air trapping, resulting in a shift of the curve to the left with decreased PEF. In addition the graph may be more concave as a result of mucus plugs or collapsed airways. In restrictive patterns of disease TLC and RV are decreased resulting in a shift of the curve to the right. Spirometry is also used to confirm reversibility of airflow obstruction, which is a pathognomonic feature of asthma. Reversibility is demonstrated on spirometry by a change in FEV_1 of ≥12% from baseline after inhalation of a short acting β2-agonist.[32] Spirometry should be performed during the initial assessment and repeated every 1–2 years to monitor airway function and sooner if symptoms or treatment changes.[32] In the pediatric population, diagnosis of asthma is more challenging, as spirometry cannot be readily used until around age 5.[32]

Diffusing capacity (DC) is another means of differentiating asthma from other obstructive pulmonary diseases. The study tests the lung's ability to transfer carbon monoxide. Diffusion is affected by surface area, capillary membrane thickness, circulating capillary blood volume, hemoglobin concentration, smoking, and altitude. In diseases such as emphysema, in which the lung parenchyma is affected, the diffusion capacity will be decreased. In contrast, asthma does not affect lung parenchyma and therefore the diffusion capacity should be normal.[83]

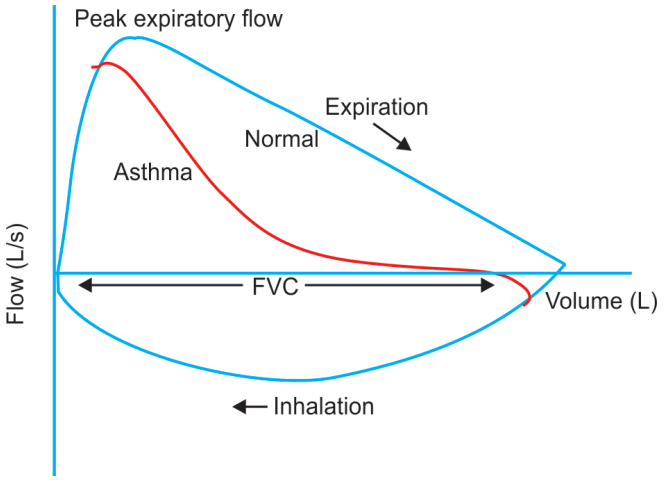

Fig. 15.2: Flow-volume loop in pulmonary function testing. (FVC: Forced vital capacity).

There are a variety of stimuli that trigger reversible bronchoconstriction in patients with asthma. Bronchoprovocation is used to assess airway hyper-responsiveness (AHR) and is commonly performed using methacholine or histamine. The provocative agent is serially increased until there is a 20% decrease in the FEV_1; this is considered the provocative dose. While patients with asthma have AHR, so do individuals with a variety of other diseases such as AR and chronic obstructive pulmonary disease (COPD); a positive bronchoprovocation test does not diagnose asthma but a negative test excludes asthma as a diagnosis.[32]

Fractional exhaled nitric oxide (FeNO) measurement can also be used to assess the presence of active airway inflammation in the lungs, as well as to assess the effects of medical therapy on airway inflammation at followup. This NO measurement is not widely used in clinical practice in the United States, but is commonly employed in Europe and elsewhere.

Severity

Asthma severity, which reflects the intensity of the disease, is most accurately assessed prior to treatment, although in many cases patients are already being treated when they present. Asthma severity is based on clinical parameters, including the number of nighttime awakenings, the frequency with which a short acting β2-agonist is needed for

symptom control, the level with which symptoms cause functional impairment and the results of pulmonary function testing (Table 15.2).

Asthma Control

Asthma is a dynamic disease that requires close observation. Asthma control is different from asthma severity.[84] While the patient's subjective impression can be used to evaluate asthma control, it cannot be the only means. It has been shown that both patients and health care providers generally overestimate asthma control, causing patients to frequently be undertreated.[88] This approach can lead to asthma exacerbations and an increased risk of asthma-related mortality.[26,88] In light of this observation, pulmonary function tests need to be performed at least every 1–2 years regardless of the subjective impression of disease management.

In addition, a variety of validated questionnaires have been developed in order to more accurately assess asthma control. Some examples are the Asthma Control Test (ACT),[88] Asthma Control Questionnaire (ACQ), Asthma Therapy Assessment Questionnaire (ATAQ),[90,91] and the Juniper Asthma Quality of Life Questionnaire (AQLQ).[92] These questionnaires help to assess the level of functional impairment and efficacy of treatment (Table 15.3). When assessing an asthmatic patient in the office, be sure to ask them about previous asthma-related hospitalizations and emergency room visits. In a study by Adams et al.[49] prior hospitalization in the last 12 months was one of the most significant risk factors for future visits to the emergency room and hospital admissions.

Table 15.2: Classification of Asthma Severity (Youths ≥ 12 years of age and adults)

Components of severity					
			Persistent		
		Intermittent	*Mild*	*Moderate*	*Severe*
Impairment	Symptoms	≤ 2 days/week	> 2 days /week but not daily	Daily	Throughout the day
	Night-time awakenings	≤ 2x/month	3-4x/month	> 1x/week but not nightly	Often 7x/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤ 2 days/week	> 2 days/week but not > 1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%		• Normal FEV_1 between exacerbations			
	Lung function	• FEV_1 > 80% predicted • FEV_1/FVC normal	• FEV_1 ≥ 80% predicted • FEV_1/FVC normal	• FEV_1 > 60% but < 80% predicted • FEV_1/FVC reduced 5%	• FEV_1 < 60% predicted • FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year (see note)	≥ 2/year (see note)		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1			

National Heart, Lung, and Blood Institute: National Institute of Health; US Department of Health and Human services: Expert panel report 3: guidelines for the diagnosis and management of asthma.
Courtesy: From National Institutes of Health (NIH).

Table 15.3: Classification of asthma control (youths ≥ 12 years of age and adults)

		Well-controlled	*Not well-controlled*	*Very poorly controlled*
Impairment	Symptoms	≤ 2 days/week	> 2 days/week	Throughout the day
	Night-time awakening	≤ 2x/month	1–3x/week	≥ 4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting β2-agonist use for symptom control (not prevention of EIB)	≤ 2 days/week	> 2 days/week	Several times per day
	FEV_1 or peak flow	> 80% predicted/personal best	60–80% predicted/personal best	< 60% predicted/personal best
	Validated questionnaires			
	ATAQ	0	1–2	3–4
	ACQ	≤ 0.75	≥ 1.5	N/A
	ACT	≥ 20	16–19	≤ 15
		0–1/year		*≥ 2/year (see note)*
	Exacerbations	*Consider severity and interval since last exacerbation*		
Risk	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can very in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		

ACQ values 0.76-1.4 are indeterminate regarding well-controlled asthma. EIB exercise-induced bronchospasm; FEV_1 forced expiratory volume in 1 sec

National Heart, Lung, and Blood Institute: National Institute of Heath: US Department of Health and Human services: Expert panel report 3: guidelines for the diagnosis and management of asthma.
NIH publication no. 07-4051, National Institutes of Health; National Heart, Lung, and Blood institute Bethesda, Md. 2007.
Accessed March, 2013. http://www.nhlbi.nih.gov.libproxy.temple.edu/guidelines/asthma
Courtesy: From National Institutes of Health (NIH).

Asthma Management

The primary goals of therapy in asthmatic patients are downregulation of inflammation, symptom reduction, improvement in quality of life, and prevention of future exacerbations. Asthma management is a dynamic process, based not on the patient's disease severity at presentation, but on his or her current level of control.[85] Unlike many other disease processes asthma severity is not fixed, exacerbations are not uncommon and response to therapy is variable. Therefore, close follow-up with adjustment in therapy is imperative, necessitating careful monitoring by a physician and appropriate alterations in treatment.

Medications for the treatment of asthma are classified as either "controller" or "reliever" with each playing a different role in asthma management.[85] Controller medications include inhaled and systemic corticosteroids, inhaled long-acting bronchodilators (LABA), leukotriene modifiers (LTRAs), mast cell stabilizers, sustained-release-theophylline, and immunomodulators. These medications are used to mitigate inflammation in order to treat the underlying pathophysiology of the disease and to decrease future adverse outcomes. On the other hand, "reliever" or rescue medications including short acting bronchodilators (SABAs) and inhaled anticholinergics are used to treat the acute symptoms of bronchoconstriction including dyspnea, wheezing, and cough.

THE LARYNX

While it is known that patients with AR commonly experience associated symptoms of laryngitis, dysphonia and or cough, the role of allergen exposure and inflammation at the level of the larynx has not been fully elucidated. It appears that even in cases where there is not a gross change to voice quality, exposure to inhalant allergens can

cause inaudible changes to voice dynamics.[98] It has been suggested by Krouse et al.[21] that laryngeal symptoms in AR and asthma may be at least partially explained by the anatomic position of the larynx at the division between the upper and lower airway systems. This position causes the larynx to be exposed to mucus and mucopurulent drainage that traffic from both directions. While the exact mechanism has not yet been fully described, it appears that the symptoms of dysphonia and/or cough in patients suffering from AR could be at least partially explained by the increased production of secretions in both the upper and lower respiratory systems, as a result of system wide inflammation.[21]

Mechanism

In allergic, or type I hypersensitivity reactions, the inciting allergen binds to the IgE receptors on mast cells, which results in degranulation of mast cell and the subsequent release of histamine and other mediators. The concentration of mast cells in the larynx, however, is not uniform. Mast cell concentrations are highest in the epiglottis and subglottis with very few mast cells at the level of the vocal folds. Concurrently, concentrations of substance-P and CGRP-LI containing nerve fibers follow the variability in concentration of mast cells in the larynx.[27] This relationship is important because there appears to be a complex interaction between substance-P and CGRP-LI containing nerve fibers and mast cells. It is believed that these neuropeptides have a regulatory role on histamine release from mast cells.[28,29] This distribution pattern may explain why in anaphylactic reactions edema is more apparent in the supraglottis and subglottis with little to no effect at the level of the vocal cords.

Corey et al.[31] categorized allergic reactions of the larynx into acute (anaphylactic) or chronic laryngitis. Acute allergic reactions, also known as angioedema, are characterized by rapid upper airway edema in response to a sensitized antigen that may result in airway compromise. In addition, patients may present with systemic symptoms of itching, sneezing, congestion, and/or urticaria. Signs of acute laryngeal involvement, which include hoarseness, dysphagia, inspiratory stridor, accessory muscle use and cyanosis, require prompt attention and the potential need for securing an airway. The symptoms of chronic laryngitis are less severe. Patients will present with symptoms of hoarseness, dry cough, and or laryngeal irritation.[25,31] Visualization of the larynx may reveal mild edema of the vocal folds, erythema of the arytenoids, or pale arytenoids and viscid mucus bridging the vocal folds.[25,31]

It appears that inflammation in the larynx is not only a result of a system wide allergic process initiated in the nose or lungs, but can also be due to local effects of allergens on the larynx itself. A series of experiments was conducted by Krouse and colleagues looking at the effects of direct antigenic stimulation of the larynx using aerosolized dust mite antigen in skin prick positive patients[22,23] These studies demonstrated that increased exposure to inhalant allergen results in coughing, throat clearing, dyspnea, a decline in pulmonary function and increased production of mucus. It was unclear in these studies whether the mucus was produced from the larynx itself or as a result of expulsion of mucus produced in the lungs.

In a double-blinded crossover study, Roth et al.[24] examined the direct effect of allergens on the larynx. Results demonstrated that allergens presented to the larynx directly result in vocal impairment. Consistent with the histopathology in rhinosinusitis and asthma, the allergic inflammatory reaction experienced by these individuals increased eosinophil concentration at the level of the supraglottis.[30]

It also appears that other environmental factors such as pollutants and tobacco smoke can contribute to laryngeal symptoms. Tobacco smoke has been shown to increase mucin at the level of the supraglottis and subglottis.[30]

Diagnosis

Patients with allergic laryngitis may have associated symptoms of dysphagia, odynophagia, cough, and/or globus sensation. These same symptoms can be caused by a variety of diseases including various malignancies and laryngopharyngeal reflux (LPR). A thorough head and neck examination should be performed as well as direct visualization of the larynx in order to obtain the correct diagnosis.

TREATMENT CONSIDERATIONS IN THE UNIFIED AIRWAY

Treatment of rhinitis and CRS has been shown to improve asthma outcomes and it is therefore important to consider the concurrent management of these diseases in all asthmatic patients.[12,16–18,65] Avoidance of allergens has been shown to improve both rhinitis and asthma control and is therefore recommended in all atopic asthmatics.[4] Intranasal steroids are commonly employed therapies in the treatment of both rhinitis and rhinosinusitis. Watson et al.[17]

demonstrated that the use of intranasal beclomethasone improves asthma symptoms and can reduce bronchial hyper-reactivity. In a similar study by Stelmach et al.[16] use of intranasal steroids, inhaled steroids or a combination of the two improved both rhinitis and asthma symptoms. Treatment with a combination of intranasal and inhaled steroids reduced the number of emergency department visits, as well as the number of asthma-related work absences and asthma-related episodes of nighttime awakening.

Knowing that AR often precedes the development of asthma, early and aggressive management of rhinitis should be employed in order to potentially prevent the development of asthma in later life. In a randomized control trial by Moller et al.[70] the use of immunotherapy to birch and or timothy pollen in children with AR was shown to significantly prevent the development of asthma at 3 years (odds ratio (OR) = 2.52). Additional research is necessary to confirm long-term efficacy and elucidate information regarding the optimal dosage and duration of immunotherapy that provide the best control.

Treatment directed at one portion of the airway allows for concurrent treatment of a distal respiratory site. This effect is illustrated by the fact that medical therapy such as intranasal steroids not only provides control of sinonasal symptoms, but has also been shown to decrease bronchial hyper-responsiveness.[16,17,55,66] In addition, surgical management of rhinosinusitis has also been demonstrated to positively impact asthma control.[65,66] In a prospective study carried out by Dejima et al.[65,58] 75% of patients with asthma who underwent endoscopic sinus surgery for CRS noted a subjective improvement in their bronchial symptoms. Furthermore, patients with asthma exhibited a significant improvement in their peak flow and an overall decrease in the dose or frequency of their asthma medications.

Aspirin desensitization appears to have promising results for both the upper and lower respiratory symptoms associated with AERD, but more placebo control studies are needed. Patients treated with aspirin desensitization have been shown to have a decreased number of hospital admissions related to asthma, improvements in anosmia, a reduced number of sinus infections and sinus procedures, and decrease in the need for systemic corticosteroids.[69,76]

Management of comorbid conditions is also important in achieving adequate control in diseases of the unified airway. Early and effective treatment of rhinitis and rhinosinusitis in patients with asthma has been shown to improve asthma symptoms, reduce exacerbations/hospitalizations, and decrease the need for medications.[16,17,55,66]

While gastroesophageal reflux (GERD) is present in up to 80% of asthmatics, studies have not been able to consistently demonstrate that treatment of GERD improves asthma control.[102] In addition, cardiac diseases can contribute to symptoms of dyspnea and can affect pulmonary function. Beta-blockers are used to improve cardiac physiology can also cause smooth muscle contraction in the respiratory bronchioles and trigger asthma exacerbations. Obesity is a known risk factor for asthma and therefore weight reduction is recommended in these patients. Physicians should always assess compliance prior to adjusting medications. Adequate and correct use of inhaled and oral medications should be checked and verified before increasing the dose.

It can be difficult to differentiate inflammatory laryngeal findings from those seen with LPR. It is reasonable to place patients with laryngeal symptoms on a trial of reflux medications and assess for symptomatic improvement. If after a trial of reflux medications the diagnosis is still unclear it may be necessary to perform ancillary tests such as allergy testing, 24-h esophageal pH monitoring, and impedance probe monitoring.

CONCLUSION

An understanding of the "unified airway model" presents physicians with a global framework for diagnosing and treating patients with airway diseases. Asthma is clearly linked to rhinitis and rhinosinusitis both epidemiologically and biologically. Asthma is a common and potentially fatal chronic disease of the lower airways and the incidence of asthma has been increasing worldwide. In light of these observations, otolaryngologists need to familiarize themselves with the diagnosis and management of asthma. In addition, concurrent treatment of upper airway disease in these patients has been shown to improve asthma control and overall patient outcomes. When treating rhinitis it is important to consider the possibility of comorbid asthma, or in nonasthmatic patients, the risk of developing asthma over time. It has been shown that early and aggressive therapy of rhinitis may be preventative for development of asthma. In patients who have a clinical picture consistent with atopy there should be a consideration of allergen-directed immunotherapy. It is becoming increasingly apparent that asthma and rhinitis/rhinosinusitis are not two separate disease processes but rather different manifestations of the same underlying pathophysiology.

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SECTION 5

Disorders of the Nose

CHAPTER

Granulomatous and Inflammatory Diseases of the Nose and Paranasal Sinuses

16

Caitlin McMullen, Alexis H Jackman

OVERVIEW

Granulomatous diseases are a diverse group of diseases that share a common pathologic inflammatory feature of a granuloma. Although this pathologic entity has been variably defined, in general, the granuloma is an organized structure composed of inflammatory cells, primarily macrophages, which have been activated and fused together to form a multinucleated giant cell. Often granulomas are pathologically described as "epithelioid" as their appearance hints at the presence of epithelial cells, and the surrounding inflammatory cells are an admixture of lymphocytes, eosinophils, and fibroblasts and possibly a component of necrosis, depending on the particular etiology of the disease. Granulomas are formed as a chronic inflammatory response to a specific antigen: bacteria, fungi, or even immune system triggers. Irrespective of the cause, the immune system plays a critical role in the maintenance and persistence of disease.

Broadly granulomatous diseases can be divided into infectious and noninfectious etiologies. Although both groups are well known to occur in the nose and paranasal sinus, they are often misdiagnosed, especially in the mild, limited forms and early in the disease process, probably because many of their clinicopathologic findings overlap with chronic rhinosinusitis, neoplastic, and traumatic disorders. Furthermore, given the pathologic similarities among the various granulomatous diseases, it can be difficult to diagnose the particular etiology in some cases. This chapter will review the presentation, diagnosis, and management of granulomatous disorders of the nose and paranasal sinuses.

NONINFECTIOUS GRANULOMATOUS AND INFLAMMATORY DISEASES OF THE NOSE AND PARANASAL SINUSES

Sarcoidosis

First described in 1877 by English physician Sir James Hutchinson as a skin disorder, sarcoidosis is a disease with an unknown etiology affecting multiple organ systems. The etiology and immunopathogenesis of sarcoidosis are largely unknown. An exaggerated cell-mediated immune response to an unidentified antigen may result in the accumulation of inflammatory cells and the formation of granulomas. Symptomatic onset of sarcoidosis is generally within the third decade, and a slight female predominance exists.[1] Incidence varies globally with a relatively higher risk from those from Nordic countries.[2-4] African-Americans, who also tend to develop more severe disease, have approximately 10 times the prevalence of sarcoidosis.[1,5] In the United States, the annual incidence of sarcoidosis in African-American women is approximately 107 in 100,000 individuals, the highest among any other demographic groups.[6]

With sarcoidosis, the nose and paranasal sinuses may be the only site of involvement, the site of initial presentation of disease, or, more likely, it may be one of several organs affected in a disseminated disease process that can include the lungs, eyes, skin, heart, nervous system, and kidneys. Almost all patients have pulmonary manifestations of the disease, frequently presenting as dyspnea or dry cough.[7,8] The head and neck are affected in approximately 10–15% of patients, most commonly with cervical

lymphadenopathy, salivary gland enlargement, and ocular manifestations.[9-11] Rarely, the larynx and otologic structures may be involved.[12-14]

Sinonasal involvement often results in significant morbidity of the patient, with common symptoms being nasal obstruction, epistaxis, crusting, headache, facial pain, and anosmia.[15,16] Lupus pernio, the characteristic skin lesion of sarcoidosis, may result in raised, purplish lesions of the nasal tip and cheeks (Fig. 16.1). Anterior rhinoscopy and nasal endoscopy may reveal submucosal nodularity, which macroscopically represents a conglomeration of granulomas, as well as crusting, friable mucosa and synechiae (Fig. 16.2). Unlike the case with most inflammatory diseases of the nose, the inferior turbinates, a typical site of granulomatous proliferation, may not decongest after topical application of decongestant.[16-18] The granulomatous proliferation and subsequent fibrosis (Fig. 16.3) of mucus glands result in decreased secretion production, dryness, and crusting.

Laboratory studies may help exclude other diseases that present similarly, but tissue biopsy is most critical in confirming the diagnosis. A full panel of testing should be performed, including antineutrophil cytoplasmic antibodies (ANCAs), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), rapid plasma regain (RPR), and angiotensin converting enzyme (ACE), skin testing with purified protein derivative (PPD), and cultures to rule out tuberculosis. ANA and ACE are most frequently elevated at 30% and 60–80%, respectively. ACE levels may be used to monitor disease activity.[14] Histopathologic analysis of biopsy specimens reveals noncaseating granulomas, composed of epithelioid cells with fibrosis, multinucleated giant cells, and leukocytic infiltration (Figs. 16.4 and 16.5).[19]

Since the diagnosis of rhinogenic sarcoidosis can be difficult, various diagnostic criteria have been proposed.[17,20] These authors suggest that the patient should demonstrate the following: (1) radiologic evidence of sinusitis; (2) histopathologic confirmation of noncaseating granuloma;

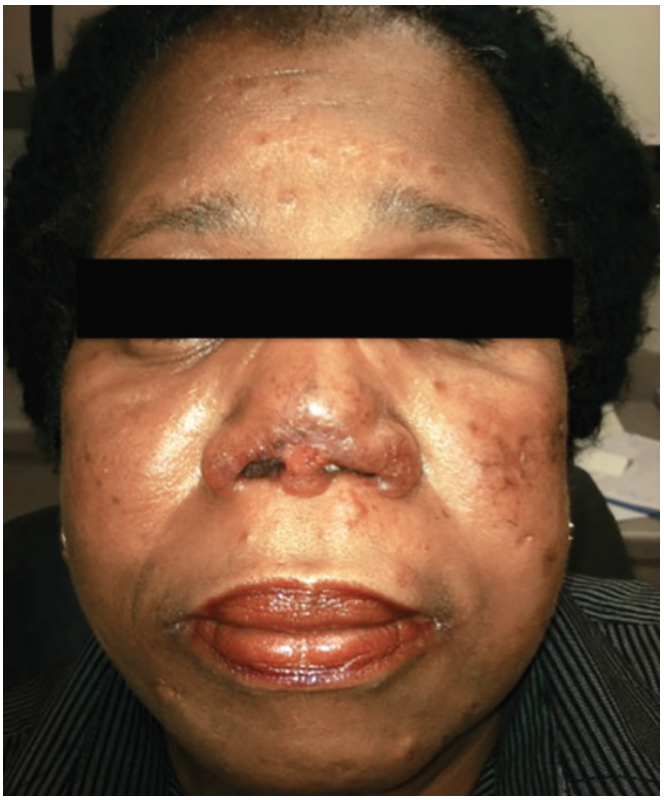

Fig. 16.1: The characteristic raised, purplish skin lesions of sarcoidosis, also known as lupus pernio, typically affects the nasal tip and cheeks.

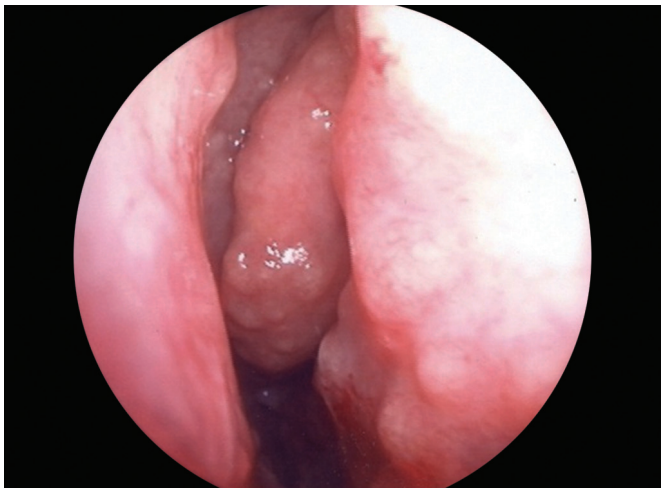

Fig. 16.2: Physical examination in sarcoidosis may reveal submucosal nodularity, which macroscopically represents a conglomeration of granulomas.

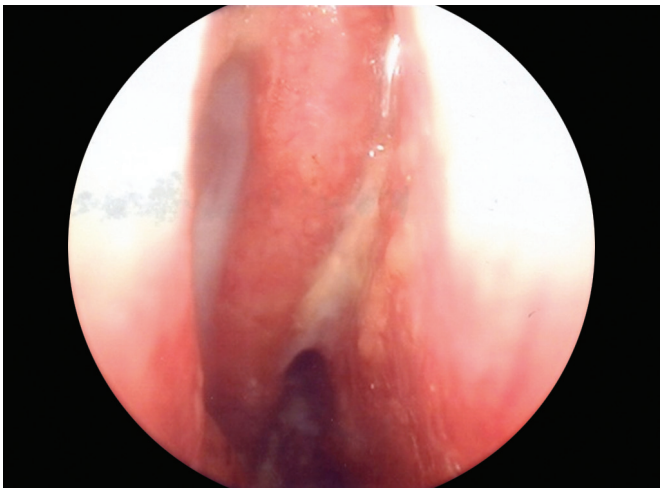

Fig. 16.3: The final stage of sarcoidosis affecting the nasal passages results in fibrotic changes to mucosal surfaces.

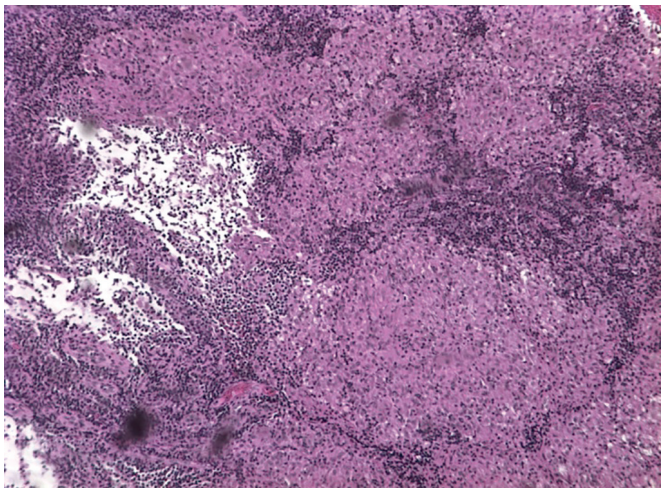

Fig. 16.4: Histopathologic analysis in sarcoidosis reveals noncaseating granulomas, composed of epithelioid cells with fibrosis, multinucleated giant cells, and leukocytic infiltration, evidenced in this specimen.

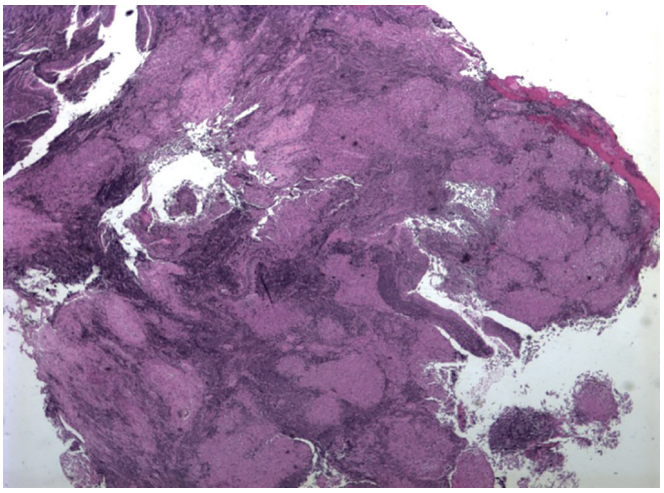

Fig. 16.5: Additional histopathologic specimen from a patient with sarcoidosis, demonstrating leukocytic infiltrates.

(3) the exclusion of other disease processes such as mycobacterial infection, fungal disease, or granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis); (4) symptoms not responsive to conventional sinusitis therapies; (5) physical examination findings consistent with rhinogenic sarcoidosis such as nodular mucosa; (6) elevated ACE; and (7) evidence of systemic sarcoidosis. These criteria are not widely accepted but provide a guide for the physician when confronted with a patient with suspected sinonasal sarcoidosis.

Corticosteroids are the mainstay of systemic therapy for sarcoidosis. Oral steroids may improve symptoms but may not affect the overall disease course.[21] Very mild and limited rhinologic disease may respond to topical corticosteroids, but the vast majority will require systemic corticosteroid. There is a very limited role for endoscopic sinus surgery in patients with rhinogenic sarcoidosis as long-term results are often disappointing.[17,22] The disease course tends to wax and wane, and may even spontaneously resolve in a significant number of patients. Mortality generally results as a complication of therapy for cardiac or pulmonary involvement of the disease process.[14]

"Idiopathic" Midline Destructive Disease: Nasal T and NK Cell Lymphoma

Destructive, progressive lesions of the midface and paranasal sinuses are rare and variously identified as polymorphic reticulosis, malignant granuloma, lethal midline granuloma, rhinitis gangrenosa progressiva, Stewart's syndrome, idiopathic midline destructive disease, and others. Immunohistochemical analysis of lesions has revealed the majority of these lesions to be manifestations of GPA, or natural killer (NK) cell or T-cell lymphomas, a form of extranodal non-Hodgkin's lymphoma.[23] Furthermore, these lesions may result from squamous cell carcinoma or chronic cocaine use in patients who may withhold this critical part of their history. Therefore, it is important to rule out alternative diagnoses (Table 16.1) with thorough history, physical examination, pathological, and laboratory testing.

Patients may present during a range of ages, predominately in males in their 60s. Patients are more commonly of Asian and Southern and Central American descent.[23] Symptoms include nasal obstruction, disfiguring facial lesions, nasal discharge, epistaxis, facial swelling, and recurrent fevers. Ulcerative nasal lesions progress aggressively through the nose and facial soft tissues, bone and cartilage, with symptoms related to local destruction such as cranial neuropathies from direct invasion. Physical examination most commonly demonstrates septal perforation, friable tissues, gray or yellow discoloration, and necrotic tissues. Diagnostic testing must include evaluation for HIV, GPA, and Epstein–Barr virus. Biopsy should be sent fresh in order to properly assess the tissue for lymphoma. Pathological specimens may reveal a significant amount of necrosis, inflammatory cell infiltrate, and the giant cell granulomatous reactions.[24] Due to the large amount of necrosis in tissue specimens, multiple biopsies may need to be performed prior to obtaining a satisfactory diagnosis. Imaging is useful to assess the extent of destruction but is not diagnostic in itself.

Table 16.1: Differential diagnosis of midline destructive diseases

Traumatic
Chronic cocaine use
Autoimmune
Granulomatosis with polyangiitis
Sarcoidosis
Allergic granulomatosis and angiitis
Neoplastic
Squamous cell carcinoma
Nasal T or NK cell lymphoma
Malignant salivary tumors
Infectious
Syphilis
Rhinoscleroma
Leprosy
Tuberculosis
Leishmaniasis
Fungal disease
Actinomycosis

Few prognostic factors exist, and despite chemotherapy and radiation patients have poor outcomes. Five-year disease-free survival is approximately 35% regardless of the treatment modality employed.[25] Targeted radiation and chemotherapy may slow disease progression, but unfortunately patients still frequently expire due to local invasion or disseminated lymphoma.[26]

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, is a rare granulomatous disease that results from clonal proliferation of Langerhans' cells, an immune effector cell. The exact pathophysiology is not known, but the disease is understood to be a neoplastic proliferation of a single clone of Langerhans precursor cells that accumulates in affected organs.[27]

Pediatric patients are primarily affected, with a slight male predominance. The clinical spectrum of LCH is extremely variable. Bones are most commonly affected but LCH can involve the skin, hypothalamus, thymus, gastrointestinal tract, lungs, central nervous system, liver, and other vital structures. Unifocal LCH, also known as eosinophilic granuloma, results in an isolated osteolytic lesion without constitutional symptoms. Hand–Schuller–Christian disease classically presents with lytic calvarial lesions, diabetes insipidus from pituitary involvement, and exophthalmos. In this multifocal form, patients may develop systemic symptoms such as fever, fatigue, and evidence of other organ involvement such as the temporal bone. Finally, the disseminated multiorgan form is referred to as Letterer–Siwe disease. This devastating form presents in children under 3 years and results in extensive morbidity, including blood dyscrasias, pulmonary infiltration, and lymphadenopathy.

In the head and neck, the mandible, maxilla, orbits, and temporal bone may be affected.[28] These lesions may be asymptomatic or present with swelling, localized discomfort, or pathologic fractures. Bony involvement of the maxilla may result in local obstructive symptoms if swelling and bony erosion compromise the nasal passages. Periorbital and facial swelling may be a presenting symptom. Nasal endoscopy may demonstrate a friable, fleshy mass within the nasal passages.[28,29]

Imaging may demonstrate lytic bony lesions without surrounding sclerosis and soft tissue masses. MRI can improve visualization of the lesion and its relationship to surrounding structures, and computed tomography (CT) can assess extent of bony erosion. In magnetic resonance imaging (MRI), lesions enhance significantly after contrast injection. They are intense on T2-weighted imaging without peripheral edema.[30,31]

Biopsy is essential for diagnosis. Tissue specimens reveal eosinophils, histiocytes, and Langerhans cells. Classic features of the Langerhans cell morphology include the Birbeck granule, visible with electron microscopy. Langerhans cells are elongated with a "coffee bean" appearance, resulting from the nucleus residing in a central groove. Immunohistochemical positivity for CD1a antigen and S-100 is characteristic. The combination of electron microscopy and immunohistochemical analysis is diagnostic.

Solitary lesions have an excellent prognosis. In some cases of isolated lesions, observation may be advocated as spontaneous regression may occur. Localized lesions may be treated surgically, or with low-dose radiation or intralesional steroid injection. A conservative approach with long-term follow-up is advocated. Multifocal or disseminated disease is managed with chemotherapy.[2-4,28,32]

Cholesterol Granuloma

A cholesterol granuloma is an expansile cystic lesion containing cholesterol crystals surrounded by giant cells and chronic inflammation. Although cholesterol granulomas most commonly occur in the petrous apex of the temporal

bone, they also may rarely present in the paranasal sinuses. Symptoms are due to mass effect of the lesion, related to its particular location. Patients may present with symptoms of chronic rhinosinusitis including facial pain, headache, nasal discharge, and nasal obstruction. Workup should include imaging to assess the extent of the lesion. MRI may be diagnostic and distinguish these lesions from mucoceles, as cholesterol granulomas are cystic and bright on both T1- and T2-weighted images. Areas of hemosiderin deposition may result in low signal intensity. CT may demonstrate bony erosion but is nonspecific in these cases.[1,5,33] Therapy is primarily surgical, but asymptomatic patients may be observed and followed with physical examination and serial imaging. Grossly upon surgical resection, lesions contain thick, "chocolate" colored material. Cholesterol granulomas as so named due to their histopathologic appearance. Histopathologically, granulomas form around cholesterol clefts, a product of lysed red blood cell (RBC) membranes and lipoproteins, admixed with giant cells and hemosiderin-laden macrophages. These characteristic histopathologic findings are diagnostic.

Autoimmune Granulomatous Diseases

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) formerly known as Wegener's granulomatosis, is a rare autoimmune disease that primarily affects the airway and kidneys. This necrotizing vasculitis primarily affects small and medium vessels, and is accompanied by an intramural granulomatous inflammatory reaction. The etiology of GPA remains elusive, but it is postulated that injury is a result of IgG-class antineutrophilic cytoplasmic antibody toward the enzyme proteinase 3 (PR3). The subsequent inflammatory cascade results in the granulomatous reaction and necrotizing vasculitis. The differential diagnosis of GPA includes nasal lymphoma, sarcoidosis, Churg–Strauss syndrome (CSS), and infectious processes such as syphilis**.**

The prevalence of GPA in the United States has been estimated to be 3 persons per 100,000.[6,34] Recently, increased testing for GPA and vigilance for the disease has been attributed to a perceived rise in incidence in some areas of the world.[7,8,35] Men are afflicted at a similar rate as women. The vast majority of patients are Caucasian, presenting at approximately the third to the fifth decades.[9,36]

The classic constellation of organ involvement is kidneys, lung, and upper airway, particularly the nose and paranasal sinuses. Systemic symptoms for GPA include fever, general malaise, anorexia, arthralgias, and weight loss prior to renal and airway symptom presentation. Renal disease is manifested by rapidly progressive proliferative glomerulonephritis. Pulmonary involvement results in cough, hemoptysis, wheezing, pleuritic chest pain, and dyspnea. As many organ systems are involved, a multidisciplinary approach is essential in GPA.

The majority of patients with GPA present with otolaryngologic symptoms, and over 90% of these patients experience rhinologic symptoms such as epistaxis, nasal congestion, nasal discharge, and crusting.[37-39] Physical examination should be thorough as GPA can have otologic, oral cavity, laryngotracheal, and salivary gland involvement. On nasal endoscopy, a variety of findings can occur such as mucosal erythema crusting, friable tissue, nasal stenosis, and/or septal perforation, which occasionally progress to saddle nose deformity (Figs. 16.6 and 16.7). Nasal lesions generally do not progress to palate perforation, which can be an important distinguishing factor from midline destructive disease as previously described. In the paranasal sinuses, radiographic findings in GPA are nonspecific, and CT findings can include mucosal thickening, mucocele, orbital mass, and bony destruction and sclerosis.

The American College of Rheumatology proposed a staging system that includes oral ulcers or nasal discharge, urinary sediment with RBCs, or more than five RBCs per high power field, in addition to granulomatous inflammation on biopsy.[40,41] These criteria are not necessarily

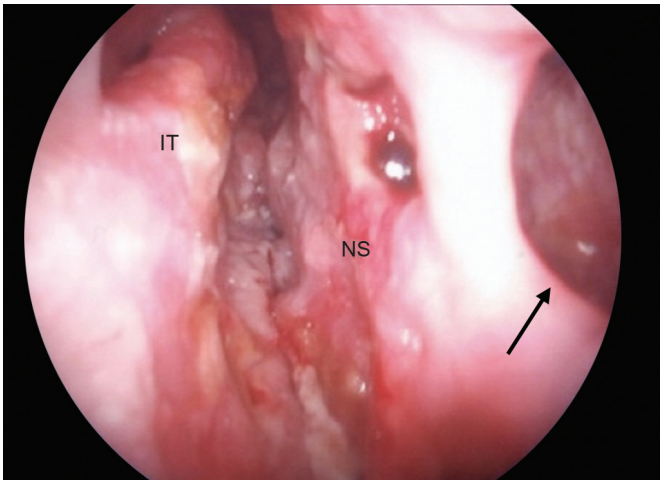

Fig. 16.6: Nasal endoscopic examination in granulomatosis with polyangiitis may reveal septal perforation (black arrow), erythema, crusting, friable tissue, and nasal stenosis.
(IT: Inferior turbinate; NS: Nasal septum).

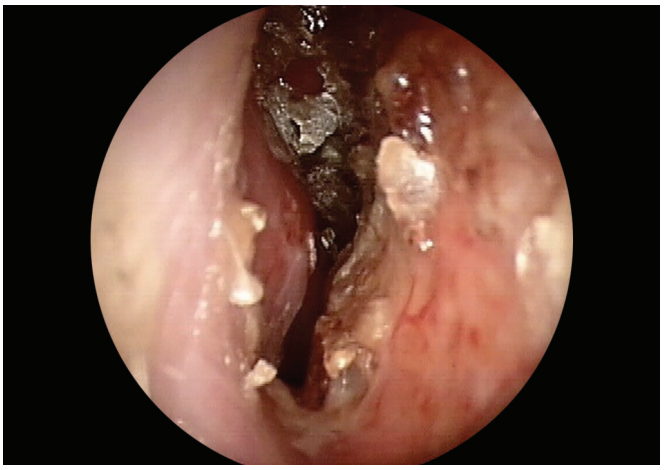

Fig. 16.7: Extensive nasal crusting is a feature of nasal involvement of granulomatosis with polyangiitis. Large crusts obstructing the nasal passage are visualized here.

sufficient for diagnosis and workup must therefore include imaging, laboratory testing, and histopathologic examination.

Initial laboratory testing should include complete blood count (CBC), basic metabolic panel, and urinalysis. These studies may reveal a normochromic, normocytic anemia, elevated plasma creatinine, leukocytosis, and/or thrombocytosis. Serologic testing for c-ANCA is essential in the workup and diagnosis of GPA, and it is highly sensitive for the disease. Indirect immunofluorescence is a sensitive initial test to demonstrate the characteristic cytoplasmic staining pattern (c-ANCA) in GPA. Subsequently, an enzyme-linked immunosorbent assay (ELISA) is performed to confirm c-ANCA positivity. Antibodies in GPA are directed against PR3 and myeloperoxidase (MPO), both present in neutrophils and monocytes. PR3 autoantibodies are present in up to 90% of ANCA-positive patients; however, sensitivity and specificity vary with disease activity, and ANCA may be positive in other autoimmune and bacterial diseases.[12,42]

Nasal mucosal biopsy may be helpful in confirming the diagnosis of GPA, but a negative biopsy does not rule out the disease. Tissue specimens from the nose or other involved organs may demonstrate intramural necrotizing granulomas, small- and medium-vessel vasculitis, extravascular necrosis, and microabscesses.[16,43]

Management of GPA should involve a multidisciplinary team. The mainstay of therapy is immunosuppression. Without therapy, patients rapidly progress and may survive a matter of months.[16-18,44] Relapses unfortunately frequently occur despite therapy. The role of surgery in GPA is limited. Functional endoscopic sinus surgery rarely results in long-term symptom relief, and is discouraged by some authors except in cases such as mucocele formation or orbital pseudotumor.[17,20,38,45] However, external nasal deformities may be surgically addressed after disease remission with satisfactory outcomes.[46]

Allergic Granulomatosis and Angiitis

Allergic granulomatosis and angiitis, or CSS, was first described in 1951 as a constellation of severe asthma, peripheral blood eosinophilia, granulomas, and systemic vasculitis.[21,47] This rare syndrome primarily affects medium-sized vessels and manifests in almost all organ systems. Its pathophysiology is unknown, and may be a result of an imbalance of T-cell effector populations.[17,22,48] It is also postulated that an inhaled antigen may trigger allergic reactions in certain, immunologically susceptible patients.[14,49]

The incidence of this rare disease in the United States is not exactly known, but varies from 2.7 to 14 persons per million across Europe.[50-53] The mean age of onset is highly variable. Men and women are equally affected. Organ systems that may be affected include the skin, heart, kidneys, gastrointestinal and nervous systems. However, the lungs, skin and paranasal sinuses are predominantly involved. Asthma usually precedes the vasculitic phase, and may become severe. This disease classically progresses in three phases: (1) asthma, followed by allergic rhinitis, polyposis and recurrent rhinosinusitis, (2) eosinophilic tissue infiltrates and eosinophilia, and finally (3) systemic vasculitis with granulomatosis.[23,54]

Patients may develop systemic symptoms such as fever, weight loss, fatigue, malaise and joint pain. Asthma and mononeuritis multiplex are the most common presenting symptoms. Pulmonary symptoms may mimic isolated asthma, and subsequent treatment for presumed asthma may mask CSS.[23,55] Skin lesions include palpable purpura and nodules. In rare cases, the orbit and central nervous system may become affected.

The otolaryngologist is frequently involved in the diagnosis and management of patients with CSS. Nasal symptoms are a prominent feature of the disease and occur in up to 60–70% of patients.[24,56,57] Sinonasal symptoms include obstruction, rhinorrhea, anosmia, thick crusting, and occasionally septal perforation. These may be the initial complaints prior to diagnosis. Nasal endoscopy reveals polyposis in 75% of patients, in addition to crusting in the nasal passages.[25,58]

Criteria have been developed for the diagnosis of CSS,[26,54,59] but generally clinical findings are adequate. A number of diseases including GPA and sarcoidosis may present similarly and must be ruled out. Useful laboratory studies in the evaluation of CSS include CBC with differential and sedimentation rate (ESR). Peripheral eosinophilia may be identified as well as an elevated ESR. Antineutrophil cytoplasmic antibodies are positive in one-third of patients, with the majority of those positive for MPO-specific ANCA.[27,60] Nose and paranasal sinus CT is nonspecific and may generally demonstrate findings consistent with polyposis and chronic rhinosinusitis.

If biopsy of the affected mucosal surface is performed, vasculitis and extravascular eosinophil granulomas may be visualized with eosinophilic and inflammatory cell infiltrates. However, histopathological findings are not pathognomonic. In accordance with the criteria determined by Masi et al. 2010, four of six criteria must be demonstrated: (1) asthma, (2) peripheral blood eosinophilia >10%, (3) peripheral neuropathy, (4) pulmonary infiltrates, (5) paranasal sinus disease and (6) extravascular eosinophilia on tissue analysis.[59]

Corticosteroids are the primary therapy but chemotherapeutic medications such as methotrexate may be added in severe cases. Functional endoscopic sinus surgery in CSS patients may temporarily relieve obstructive symptoms; however, nasal polyps frequently recur.

INFECTIOUS GRANULOMATOUS AND INFLAMMATORY DISEASES OF THE NOSE AND PARANASAL SINUSES

Bacterial Diseases

A number of bacterial organisms result in granulomatous inflammation of the nose and paranasal sinuses. The effects may be destructive, and early diagnosis is essential as most are treatable with antibiotic therapy.

Syphilis

Syphilis is an infectious process caused by the spirochete *Treponema pallidum*. This disease has been called a "great imitator" as its manifestations may resemble numerous other disease processes. Acquired syphilis progresses in four stages. The painless chancre of primary syphilis presents at the inoculation site from a few days until 3 months after exposure, and it may heal spontaneously. Secondary syphilis emerges as a consequence of treponemes circulating in the peripheral blood stream. Symptoms include fever, malaise, rash, arthritics, lymphadenopathy, and hepatitis. Latency follows secondary syphilis, which may persist for many years. If the patient remains untreated, tertiary syphilis may present in a subset of patients. Tertiary syphilis may have devastating affects on the vascular and central nervous systems and patients may develop gummatous lesions.

Head and neck manifestations are frequent in syphilis. The painless chancre of primary syphilis has been described in various locations throughout the head and neck, including the nasal passages, middle ear, larynx and throughout the upper aerodigestive mucosal surfaces. Regional adenopathy frequently accompanies the lesion. Secondary syphilis may frequently involve the oral mucosa and manifest as glottitis or patchy mucous membrane lesions, pharyngitis and laryngitis. Tertiary syphilis may present with cochleovestibular symptoms, including hearing loss, aural fullness, and vertigo.

Primary syphilis with sinonasal involvement may result in an ulcerative, scabbed appearance of the nasal vestibule and anterior septum. Secondary syphilis may present with symptoms similar to rhinitis. Thick discharge and nasal irritation may be observed. At this point, systemic symptoms or other organ involvement may be evident. Gummatous syphilis causes the classic saddle nose deformity from extensive destruction of the nasal septum. In congenitally acquired cases, purulent nasal discharge may present up to 2 weeks after birth. This discharge contains high numbers of spirochetes.[61]

Serologic testing is essential in confirming the diagnosis of syphilis. Histopathologic examination may reveal epithelial hyperplasia, plasma cell infiltrates in primary and secondary syphilis, and granulomatous infiltrates in tertiary syphilis.[62] In consultation with infectious diseases specialists, treatment primarily involves antibiotic therapy with penicillin G.

Mycobacterial Infections

Mycobacteriaceae are a genus of bacterium that are characteristically acid fast and aerobic in nature. Some of the mycobacterial species are associated with an immunocompromised state, although most can affect any immunocompetent individual. Nontuberculous mycobacteria include *Mycobacterium avium-intracellulare, chelonae, marinum, fortuitum,* and *kansasii. Mycobacterium tuberculae* is the causative agent in tuberculosis. In the United States in 2011, the incidence of tuberculosis was 3.4 per

100,000 persons, a 6.4% decline from the year prior. Despite a decline in overall incidence in the United States, the emergence of multidrug resistant strains has become a significant public health concern.[63]

Patients with tuberculosis may present with systemic signs that include weight loss, fatigue and diffuse lymphadenopathy. In extrapulmonary tuberculosis, the head and neck is occasionally affected including the cervical lymph salivary glands, skull base, temporal bone structures, oral cavity, larynx, and paranasal sinuses.[64] History must include travel, PPD status, exposure to affected individuals and previous treatment for mycobacterial infections. Patients with paranasal sinus involvement commonly report nasal obstruction, crusting, rhinorrhea and occasional epistaxis. Nasal endoscopic reveals ulceration, erythematous mucosal nodularity and grossly granulomatous appearing tissue.

Imaging may be helpful in certain circumstances. Chest radiography may reveal cavitary pulmonary lesions associated with tuberculosis. CT can assess the extent of paranasal sinus involvement. The appearance on CT, however, is nonspecific, and may demonstrate mucosal thickening, soft tissue masses, and sinus opacification. Diagnosis is ultimately based on histopathologic analysis of tissue specimens. Analysis of affected mucosal surfaces display caseating granulomas and may in some cases reveal the acid-fast bacteria. Patients with suspected disease should undergo tuberculin skin testing. Polymerase-chain reaction and ELISA-based testing are also available for disease detection. If clinical suspicion is extremely high without the characteristic histopathologic appearance, a positive response after 6–12 months of multidrug antituberculous medical therapy may be diagnostic as well.

Lupus vulgaris, also known as Hansen's disease, is caused by the bacterium *Mycobacterium leprae*. This disease is rare in the United States. The nose is an important portal of entry for this bacterium, and is therefore frequently affected.[65] Depending on the host immune response, nasal symptoms of leprosy may include epistaxis, gross nasal deformity and destruction. Patients may complain of anosmia and nasal obstruction. Upon nasal endoscopy, friable, granulomatous intranasal lesions involving the septum with associated crusting. In the early stage, yellowish discoloration of the mucosa, nodules or pale plaques may be visualized involving the septum and inferior turbinates. As the disease progresses, the mucosa becomes thickened, resulting in purulent nasal drainage that contains a high concentration of the organism. This disease has a predilection for neural invasion, resulting in decreased nasal sensation. Late stage leprosy is characterized by dryness, crusting and septal cartilage destruction. This disease is very slowly progressive, but once the diagnosis is confirmed, broad antibiotic treatment should be initiated to prevent disfigurement.[66]

Rhinoscleroma

Rhinoscleroma, a chronic granulomatous process, is caused by the gram-negative bacilli *Klebsiella rhinoscleromatis*. Rhinoscleroma is rare in the United States but endemic in other parts of the world, such as Mexico, Central and South America, Eastern Europe, Southeast Asia, and Egypt. In the head and neck, rhinoscleroma primarily affects the nasal passages. Nasal symptoms vary in severity, from chronic rhinitis, crusting, anosmia, nasal discharge, to extensive nasal deformation. The disease presents in three distinct clinical stages: the atrophic stage, the granulomatous stage, and finally the sclerotic stage. Patients initially present with mucopurulent, bloody nasal discharge, and crusting. The subsequent granulomatous stage presents with epistaxis, nasal obstruction, and anosmia. Physical examination at this point may reveal granulomatous nodules and extensive crusting. These nodules are eventually replaced with fibrotic tissue formation in the sclerotic phase, resulting in extensive scarring and deformity. The nasolacrimal duct may also be affected by stenosis. The middle and inferior turbinates are the most commonly affected sites in the nasal passages. Atrophic mucosa and nodularity may be visualized on nasal endoscopy. Lesions may extend to involve the palate, nasopharynx and larynx.

Radiographic appearance may be similar to sinonasal tumors and fungal processes. No specific serum laboratory testing is indicated. Diagnosis is made through histopathologic analysis of tissue specimens. Biopsied tissue, sent for pathology and culture, demonstrates the presence of the bacteria. Culture of crusts or nasal discharge is not sufficient for diagnosis. Pathology findings include granulomatous lesions, necrosis, inflammatory infiltrates and Mikulicz cells, a cell that is particularly characteristic of the disease.[67] Antibiotic therapy must be aggressive as this hearty bacterium is difficult to eradicate, and patients frequently recur. Surgery may be indicated for reconstructive purposes after treatment.

Actinomycosis

Actinomycosis is a chronic granulomatous infection caused by the filamentous anaerobic bacterium *Actinomyces israelii*, part of normal oral flora. This infection

typically presents in immunocompetent individuals after inoculation via trauma to healthy mucosal tissues. In the head and neck, actinomycosis presents most commonly as a mass lesion with cervicofacial involvement or mandibular osteomyelitis. Actinomycosis of the paranasal sinuses typically presents as a unilateral lesion with nonspecific symptoms associated with chronic sinusitis including facial pain, headaches, postnasal drip, congestion, rhinorrhea and bloody nasal discharge. In extremely rare cases, infections may become invasive, resulting in bony midface or skull base destruction (Fig. 16.8).[68] Nasal endoscopy reveals necrotic tissue, thick purulent material, and swollen mucosal surfaces. Imaging reveals opacification of the affected sinus and focal calcifications without bony erosion. Diagnosis may be made by the identification of sulfur granules in nasal discharge and biopsy specimens. Actinomycosis is susceptible to numerous common antibiotics including penicillin, tetracyclines, macrolides, clindamycin, and cephalosporins.

Fungal Diseases

Fungal infection should be considered in all patients with a history of chronic rhinosinusitis, in particular for patients who fail to respond to typical antibacterial therapy. The clinical spectrum tends to vary depending on the host immune response. The natural history of fungal sinusitis may be acute or chronic, noninvasive or invasive. Nongranulomatous forms of fungal sinusitis include allergic fungal sinusitis, sinus mycetoma, and fulminant invasive fungal sinusitis, which are described in other sections of this text. Certain fungal infections, however, may result in granulomatous disease in the sinuses: both invasive and noninvasive types. Nasal endoscopy with biopsy, including normal tissue, is essential to distinguish these various forms of fungal sinusitis.

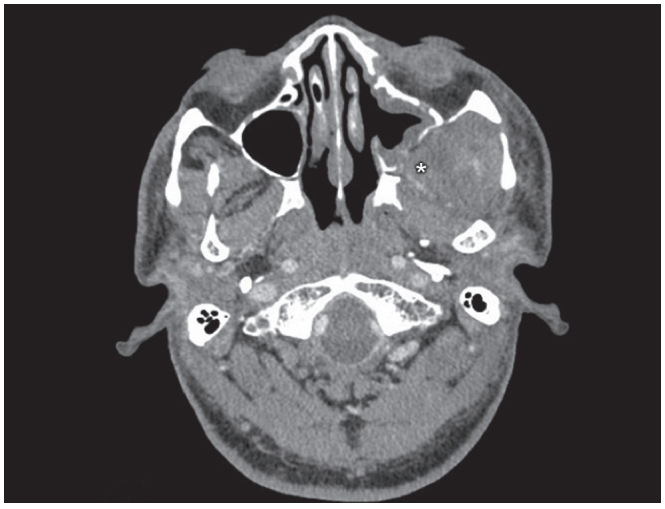

Fig. 16.8: Actinomycosis of the paranasal sinuses may rarely extend to surround structure. This computed tomography demonstrates bony erosion of the posterior wall of the maxillary sinus (asterisk), with resultant involvement of the infratemporal fossa.

Aspergilus flavus is the causative agent in granulomatous invasive fungal sinusitis (GIFS). This form of fungal sinusitis is typically, but not exclusively, found in patients from the Sudan, Northern Africa, and Southeast Asia. Also known as primary paranasal granuloma, GIFS progresses slowly. However, without treatment, lesions are aggressive and invade local structures including the brain and orbits. The clinical presentation is similar to that of chronic invasive fungal sinusitis. Symptoms may include facial swelling, unilateral proptosis, palatal erosion, headache, cranial neuropathies, and evidence of intracranial disease such as altered mental status and seizures. In certain cases, disease can progress to mycotic aneurysms, cavernous sinus thrombosis, and internal carotid artery rupture. Physical examination may reveal mucosal edema, soft tissue masses, and polyposis. The radiographic appearance of GIFS is similar to that of chronic invasive fungal sinusitis, with mucosal thickening, sinus opacification, and soft tissue masses eroding into bone and adjacent structures. The imaging appearance is similar to malignant processes, and therefore biopsy is essential for diagnosis. The characteristic feature, noncaseating granuloma, is demonstrated on histopathologic examination. Specimens may also demonstrate giant cells, fibrosis and necrosis, and inflammatory infiltrates.[69] Treatment involves a combination of surgery and antifungal therapy.

Other fungal organisms may cause granulomatous sinus disease including *Histoplasmosis capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis,* and *Coccidioides immitis.* The immunocompromised patient is particularly susceptible to these infections. In addition to sinus disease, constitutional symptoms such as fever and anorexia frequently occur. With hematogenous dissemination, other head and neck structures such as cervical lymph nodes are typically affected. Biopsy of lesions are helpful in diagnosis but should be examined cautiously, as the pseudoepitheliomatous hyperplasia demonstrated on pathologic specimens can erroneously be attributed to squamous cell carcinoma. Typically, these species are not angioinvasive and antifungal therapies are effective.

Histoplasmosis, caused by a dimorphic fungus, is most common in the Midwestern United States.[70] Transmission results from the inhalation of spores contained in bird or

bat droppings. The elderly, very young, and immunocompromised patients may develop disseminated disease, but most patients will not develop clinical sequelae after exposure. The nose and paranasal sinuses are rarely affected, but in some cases may be the presenting symptom. Patients may report nasal obstruction, painful lesions, nasal vestibule ulceration, septal perforation, extensive crusting, and destruction of nasal structures may be found on physical examination.

Cryptococcus neoformans is an opportunistic organism primarily affecting immunocompromised patients. Inhalation of spores contained in infected pigeon droppings is the main mode of transmission. The lungs, skin, and central nervous system are characteristically involved. While rare, nose and paranasal sinus involvements have been reported, and patients with late-stage HIV are at particular risk of developing multisinus disease. Nasopharyngitis and nasal ulcerations have been described as presenting symptoms.[71,72] Culture, biopsy, and polymerase chain reaction testing for the cryptococcal antigen are all useful methods of diagnosis.

Blastomycosis in a fungal disease caused by the dimorphic fungus *Blastomyces dermatitidis* and is endemic in the Southeast and Midwest United States.[70] Presentation is similar to many other types of fungal infection, mycobacterial, or neoplastic processes. Typically, a rash appears as a verrucous nodule with erythema and central crusting. The nose, in particular the nasal vestibule, may be involved in a small subset of patients. Patients may develop nasal swelling, crusting, obstruction, and erythema. Diagnosis may be made from tissue or sputum identification of *B. dermatitis,* a thick-walled yeast.[73] Similar to histoplasmosis, immunocompromised and elderly patients are at high risk of disseminated disease, but the majority of patients remain asymptomatic. Coccidioidomycosis may result in verrucous skin lesions, lymphadenopathy, and laryngeal granulomas. Granulomas may also form within the nasal passages resulting in obstructive symptoms. In certain cases, symptoms may resolve without treatment, but antifungals are effective for prolonged or severe disease.[74]

Parasitic Diseases

Leishmaniasis

Leishmaniasis is a tropical disease originating in Latin American nations and transmitted through the bite of a sand fly. Mucosal, cutaneous and visceral forms exist all caused by various subspecies of *Leishmania*. Mucosal leishmaniasis is caused by the parasite *Leishmania braziliensis, donovani,* or *infantum*. Lesions appear long after the initial infection. In the head and neck, leishmaniasis may progress to destroy structures including the larynx, pharynx, and facial skin, and lesions may masquerade as a malignant process.[75] Mucosal leishmaniasis commonly affects the nose and paranasal sinuses. Epistaxis and rhinorrhea are the most common initial complaints, in addition to coryza, headache, nasal obstruction, and facial pain. Montenegro skin testing and histopathological examination of biopsy specimens demonstrating the offending organism confirm the diagnosis. Characteristic Leishman–Donovan bodies, or protozoan forms of *Leishmania*, are visualized within affected human cells. Treatment with Pentostam (sodium stibogluconate) and amphotericin B are effective, but a small subset of patients can recur. Surgery can be effective for cutaneous lesions.[76,77]

TRAUMATIC CAUSES OF GRANULOMATOUS AND INFLAMMATORY DISEASES OF THE NOSE AND PARANASAL SINUSES

Giant Cell Reparative Granuloma

Giant cell reparative granuloma is a rare, benign, proliferating lesion that affects the maxilla, mandible, cranial bones, and rarely the paranasal sinuses. The etiology of this lesion is believed to be intraosseous hemorrhage after direct trauma to the area. Young adults are primarily affected with a slight predilection for females. Patients with paranasal sinus involvement may present with nasal obstruction, epistaxis, nasal discharge, or proptosis. On physical examination, an intranasal mass may be visible. Imaging is nonspecific but may reveal an expansile lesion with focal cystic or hemorrhagic areas, and bony destruction may be present.[78] The differential diagnosis of this lesion includes Brown tumors and aneurysmal bone cysts. Histological examination of tissue specimens reveals lymphocytic infiltrate, macrophages, osteoclastic giant cells with fibroblastic stroma.[79] Surgical excision is the mainstay of treatment, and incomplete resection may result in recurrence. Antiangiogenic chemotherapy or radiation therapy may be helpful in nonoperative and extensive, recurrent cases.[80]

Cocaine-Induced Midline Destructive Disease

Chronic cocaine use may result in significant, progressive destruction of the midfacial structures. The vasoconstrictive and inflammatory effects of repetitive exposure to cocaine and its contaminants may result in extensive tissue destruction. If a patient is not forthcoming about their history, this lesion may be confused with a number of other disease processes, including midline lymphomas, GPA, and squamous cell carcinoma. Patients may present with symptoms such as hyposmia or anosmia, facial pain, epistaxis, and nasal obstruction. Physical examination is revealing in these cases. Diffuse ulcerative lesions, crusting and extensive necrosis of both the septum and turbinates may be present. This process can extend inferiorly into the palate and superiorly to skull base. Imaging may reveal the extent of disease and destruction but is generally nonspecific. Biopsy may also be relatively nonspecific, with fibrosis, necrosis, inflammatory infiltrate, and microabscesses on histopathological examination.[81]

NONGRANULOMATOUS INFLAMMATORY DISORDERS OF THE NOSE AND PARANASAL SINUSES

Relapsing Polychondritis

Relapsing polychondritis (RP) is a rare condition that primarily affects the cartilaginous structures, including the ear, nasal cartilages, larynx, bronchi, and joints. The range of ages at which patients present is from childhood to the sixth decade.[82] The exact etiology is unknown, but the majority of patients demonstrate antibodies to type II cartilage in the acute phase of disease, supporting an autoimmune pathogenesis.[83] Patients frequently have additional coexisting vasculitic or autoimmune diseases.

Patients with RP most commonly present to an otolaryngologist, as characteristic symptoms predominantly affect the ears, nasal cartilages, and upper airway. Auricular chondritis, typically bilateral, may be a presenting symptom, as evidenced by sudden-onset auricular erythema and tenderness. The cartilage may eventually collapse after a symptomatic period of approximately 2–4 weeks. Painful, tender joints frequently occur and may affect all joints. Rarely, the cochlea and vestibular structures may be affected, resulting in sensorineural hearing loss, vertigo, and tinnitus. Involvement of the ocular structures results in keratitis, conjunctivitis, scleritis, or uveitis. The nasal cartilages are affected in approximately 60% of cases, resulting in the eventual collapse of the nasal septum and sadly nose deformities. Patients may report hyposmia, crusting, epistaxis, and congestion. Airway involvement results in significant morbidity for the patient. They may present with stridor, cough, dyspnea, and voice changes. Patients develop difficulty breathing as a result of chondromalacia and stenosis of the tracheobronchial tree or larynx. Destruction and scarring may reduce the caliber of the tracheobronchial tree to a pinpoint lumen.[84] The disease may progress to cardiac involvement with valvular disease and aortic aneurysms.

CT may be useful in assessing the extent of airway compromise, but clinical examination is sufficient for diagnosis. Classically, CT findings include collapse of the nasal cartilages, abnormal calcifications of the nasal, and auricular cartilages as well as tracheobronchial narrowing.[85] Laboratory testing is nonspecific, but a CBC may reveal anemia and an elevated sedimentation rate. Biopsy of affected tissues may reveal a loss of basophilic staining of the cartilage matrix, perichondral inflammation, cartilage destruction, and replacement by fibrous tissue.[86] Cardiac evaluation with echocardiography is essential in suspected cardiac involvement.

Early stage diagnosis is critical, as the disease may progress to life-threatening complications and permanent deformity. In 1976, McAdam et al. proposed the following diagnostic strategy for patients with suspected RP (Table 16.2). In order to diagnose a patient with RP, they must have at least three of the following symptoms: recurrent bilateral auricular chondritis; nonerosive inflammatory

Table 16.2: Criteria for the diagnosis of relapsing polychondritis[82,86]

More than three of the following clinical signs:
Recurrent bilateral auricular chondritis
Nonerosive inflammatory polyarthritis
Nasal cartilage chondritis
Cochlear/vestibular damage (SNHL, tinnitus, vertigo)
Updated criteria:
More than three diagnostic criteria without histologic evidence
More than one clinical signs with positive histologic evidence
Chondritis in two or more separate anatomic locations with response to steroids and/or Dapsone

polyarthritis; nasal cartilage chondritis; ocular inflammation; tracheal, bronchial or laryngeal chondritis; cochlear/vestibular damage demonstrated by sensorineural hearing loss, tinnitus, or vertigo.[86] McAdam et al.'s criteria were purely clinical and did not account for histopathologic confirmation. Damiani et al. updated the McAdam criteria in the following manner: (1) at least three or more diagnostic criteria without histologic evidence, (2) one or more McAdam signs with positive histologic evidence, or (3) chondritis in two or more separate anatomic locations with response to steroids and/or Dapsone.[82]

For mild disease such as isolated involvement of the auricular cartilages, nonsteroidal anti-inflammatory medications may suffice. Dapsone and glucocorticoids have been shown to be effective anecdotally. Doses may be tapered to an effective maintenance dose or increased for flares. Surgical repair of saddle nose deformity during quiescent disease is controversial, but repair with bone grafts have been reported to improve nasal airflow.[87] Prognosis is variable, but 5-year and 10-year survivals have been reported to be 74% and 55% from all causes of death, respectively. Approximately 10% of these patients died specifically from respiratory tract involvement of RP. Saddle nose deformity and anemia at diagnosis may be poor prognostic signs.[88]

Lobular Capillary Hemangioma

Lobular capillary hemangioma (LCH), also known as pyogenic granuloma, is a vascular lesion that can occur in the nose and paranasal sinuses. Despite its name, this lesion is not a granulomatous disease but inflammatory in nature. LCH is a benign lesion associated with previous nasal trauma and hormonal factors such as pregnancy. Patients usually present with unilateral epistaxis, epiphora, nasal obstruction, or purulent rhinorrhea. Nasal endoscopic examination reveals a pedunculated, polypoid mass within the nasal cavity frequently emanating from the septum (Little's area) or the inferior turbinate. Radiographic studies are extremely helpful in assessing the lesion and potentially determining the diagnosis. CT demonstrates an intranasal mass without bony erosion, most frequently arising from the inferior turbinate with intense enhancement.[89] In addition to the nasal passages, lesions may also be found on the lip, tongue, and oral mucosa. Treatment involves surgical excision, which usually can be accomplished transnasally with electrocautery for hemostasis. Local recurrence of the lesion after resection is rare, and may be more likely in older patients.[90,91]

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CHAPTER

17 Fibro-Osseous Lesions of the Paranasal Sinuses

James Phillips, Bradford A Woodworth

BACKGROUND

"Fibro-osseous lesions" of the craniofacial skeleton is a general term that is used to describe a subset of neoplasms that exhibit expansive, disorganized growth of mesodermal tissue.[1] In the sinonasal tract, the most common lesions are fibrous dysplasia (FD), ossifying fibroma, osteoma, and osteitis deformans (Paget's disease).[2] Although these tumors resemble each other, lying along a continuum from least to most bony content, they may also be regarded as distinct clinical entities.[3] They are benign and slow growing, and often found incidentally on imaging obtained for unrelated reasons.[4] Frequently, they may be managed expectantly with observation and serial imaging to determine the rate of growth. However, over time symptoms may arise from the space-occupying compression of surrounding structures. These may include compromise of the skull base, compression of the orbit or optic canal leading to visual disturbance, or postobstructive chronic sinusitis symptoms such as headache.[5-7] Intracranial complications such as mucocele, meningitis, abscess, cerebrospinal fluid (CSF) leak, or pneumatocele can occur when dura is breached.[3] Because of their cancellous, fragmented nature, pathological diagnosis of fibro-osseous lesions is notoriously difficult to obtain from preoperative biopsy.[2] A great deal of diagnostic information must be gleaned from the appearance of the preoperative imaging as well as the location of the lesion.

Currently, there are no accepted medical treatments for sinonasal fibro-osseous lesions, although some evidence exists that bisphosphonates such as pamidronate, alendronate, and zoledronic acid may have efficacy in the treatment of osteitis deformans (Paget's disease) and bone pain from FD.[8,9] Gross total resection of isolated lesions is typically curative, with very few cases reported regarding recurrence. However, as with any surgical treatment of the skull base, the deformative and functional consequences of resection should be weighed against the progression of disease.[3,6,10] Also, the benefit of exposure with open techniques must be considered against the advantage in the decreased morbidity of endoscopic approaches.[4] These decisions are made on a case-by-case basis, determined by the location and size of the lesion as well as the individual skill set of the treating surgeon.

CONSIDERATIONS FOR INDIVIDUAL FIBRO-OSSEOUS LESIONS

Osteoma

Although they are relatively rare, osteomas are the most common benign lesion of the paranasal sinuses with a reported incidence between 0.014% and 0.43%.[3,5,7,11,12] The vast majority of these lesions arise from the frontoethmoid region with as many as 80% originating from the floor of the frontal sinus.[13] Within the frontal sinus, they may be located either medial or lateral to the parasagittal plane created by the lamina papyracea in near equal number.[14] This distinction is important in considering the ability to perform an endoscopic versus open resection.

The etiology of osteoma is unknown, but the prevailing theories involve faulty development, exposure to trauma, or reaction to chronic infection.[3] A developmental explanation is based on the idea that embryonic stem cells can

become trapped at the suture lines of the craniofacial skeleton where the endochondral and membranous bones meet. The rests of osseous or cartilaginous precursors may then slowly proliferate unchecked as the individual matures. In the traumatic theory, osteomas are considered the result of a hyperactive inflammatory response in response to trauma of the facial skeleton—even minor, otherwise clinically insignificant fractures. A high preponderance of osteoma patients has a history of facial trauma or iatrogenic disturbance of the bone (e.g. Caldwell-Luc sinus procedure). An aberrantly vibrant subperiosteal healing response could increase the production of bony osteomas. Finally, the infectious theory of osteoma creation arises from the notion that chronic stimulation of an immune response in the bone of sinuses with chronic sinusitis leads to formation. Causation is difficult to demonstrate in this instance, however, as osteomas may frequently present with postobstructive chronic infection.

Osteomas are typically smooth and lobulated in appearance and covered by the sinus mucosa.[3,7,12] Histologically, they are divided into three groups: the eburnated type, the mature type, or a mixture between the two.[12] Eburnated osteomas are very dense and lack haversian canals. They are thought to arise from the membranous elements of bone. The mature type, or osteoma spongiosum, is thought to develop from more cartilaginous tissue and is softer in consistency. Both histologies contain dense lamellar bone with little medullary space.

Radiographically, osteomas are best demonstrated by plain films or computed tomography (CT). They appear as dense, radio-opaque masses that are homogenous and well circumscribed (Fig. 17.1). This is in contrast to other pathological bony processes, which may have a lytic or moth-eaten appearance.[3] The surrounding bone will appear thinned but not invaded by the lesion.

In counseling patients found to have an osteoma, clinicians must remember its association with Gardner's syndrome—the triad of colorectal polyps, skeletal abnormalities (e.g. osteomas), and supernumerary teeth.[3] These patients have a 100% risk of malignant transformation of colon polyps, and so a thorough family history and patient review of associated gastrointestinal complaints (e.g. abdominal pain, rectal bleeding, and diarrhea) should be recorded.

Decisions on surgical intervention should be driven by the patient's symptoms and potential compromise of surrounding neurovascular structures. For tumors discovered incidentally by imaging obtained for unrelated reasons, informing the patient of the tumor and undergoing a period of observation is a reasonable course of action. If there are no contraindications, the individual may be reimaged with CT at initial intervals of 6 months to 1 year. However, lesions presenting with chronic obstructive sinus symptoms should be considered candidates for surgical resection. Headache or facial pain and pressure localized to the involved sinus can be indicative of a symptomatic lesion.

Asymmetric fluid-level densities in the involved side proximal to the obstruction from trapped mucus or presence of a mucocele with thinning of the surrounding normal bone are potential CT imaging findings. Even without

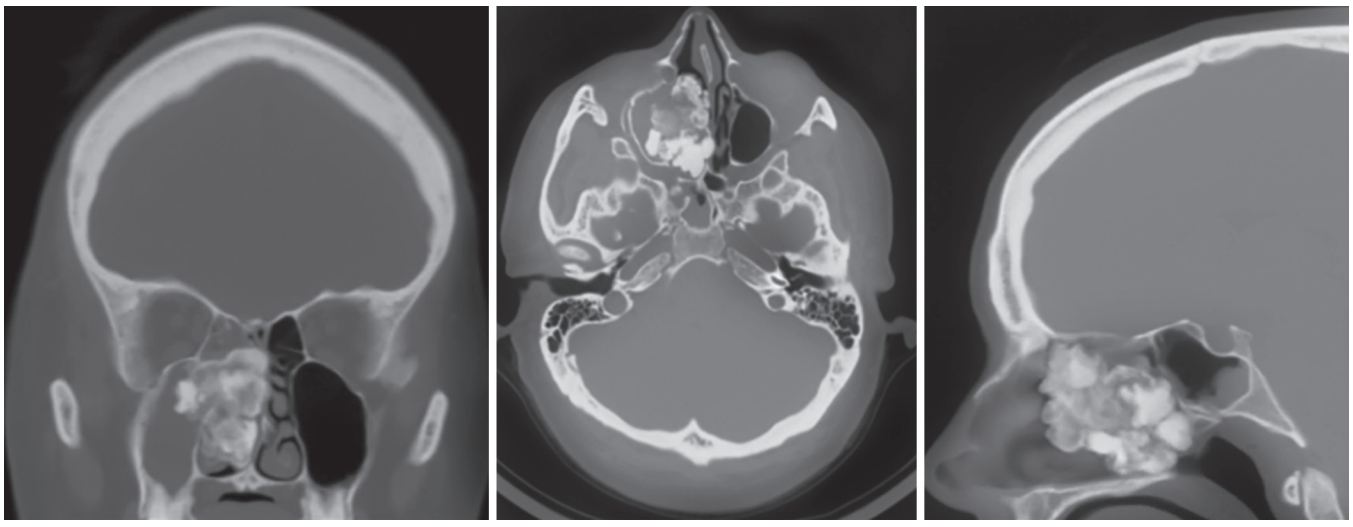


Fig. 17.1: Coronal, axial, and sagittal computed tomographic imaging of an osteoma, mature type of the ethmoid sinuses. This patient was also diagnosed with Gardener's syndrome.

associated mucosal thickening, patients may experience chronic pain from constant pressure and bony remodeling. Development of mucopyoceles or suspicion of neurovascular compromise are indications for magnetic resonance imaging (MRI) to better delineate the involvement of surrounding soft tissue structures such as the dura and the orbit.[13,15] Sequelae can be catastrophic to the patient, and the urgency of surgical intervention is elevated in this situation. CT is also invaluable for surgical planning regarding endoscopic, open, or combined techniques. The position of the base or stalk of the tumor can be compared to certain aspects of the patient's anatomy, such as the native size of the frontal recess, to predict the feasibility of a particular approach.[11]

Fibrous Dysplasia

Fibrous dysplasia is a developmental deformity of bone (rather than a true neoplasm) in which there is an abnormal proliferation of bone-forming mesenchyme.[6,16] First described by Von Recklinghausen in 1891, FD may affect any aspect of the craniofacial skeleton, but the maxilla and the mandible are the most common. In the sinonasal tract, FD most commonly affects (in descending order) the frontal, sphenoid, and ethmoid bones.[16] It may be characterized into two clinical groups: polyostotic (multiple bones affected) and monostotic (one or more lesions within a single bone). The polyostotic type may be a component of McCune–Albright syndrome, which is accompanied by precocious puberty and café-au-lait spots.[3] In Mazabraud syndrome, FD presents with soft tissue myxomas, which are often intramuscular.[17] Most craniofacial FD is monostotic, but when the diagnosis is made, a skeletal imaging survey should be performed to search for lesions at other sites. FD typically becomes symptomatic in younger patients with 75% of diagnoses made in patients < 30 years.[18] Like osteomas, FD can become disfiguring or also cause compressive symptoms. Although very uncommon, some lesions do undergo malignant transformation (around 0.5%) with patients who have McCune–Albright syndrome at the greatest risk (closer to 4%).[19,20] This should be suspected when there is rapid growth acceleration of a known FD lesion leading to more pronounced compressive symptoms.

Histologically, FD is characterized by the replacement of medullary bone with abnormal fibrous tissue that has variable cellularity and density according to the level of the progression of the disease.[6] Irregular trabeculae of bone intermix with normal bone, thus blurring the margins between normal and pathologically involved tissue. Microscopically, this appearance has been classically described as similar to Chinese calligraphy. In the earlier phase of disease, pronounced osteogenesis is appreciated in the midst of thin osteoid connecting trabeculae rimmed with osteoblasts.[21] The stromal fibroblastic element is proliferative and hypercellular, creating an osseous–collagen woven pattern. Later, the woven bone is replaced with lamellar bone resulting in the trabeculated mosaic pattern.

Multiple theories regarding the pathogenesis of FD have been proposed, including infectious and traumatic etiologies. However, the current understanding is primarily that FD arises from a missense mutation in the coding of the G_s alpha subunit protein, which couples the cell signaling molecule cyclic adenosine monophosphate (AMP) to hormone receptors. This results in increased adenyl cyclase activity and higher intracellular concentrations of cyclic AMP.[22,23] These molecular changes result in defective cellular proliferation. G_s alpha subunit mutations have also been found in up to 40% of pituitary tumors leading to acromegaly.[21] The mutations in FD are felt to be postzygotic, leading to somatic mosaicism. This theory explains why some bones are affected in patients with polyostotic FD while others are not.[21]

On CT, the appearance of FD lesions varies according to the stage of progression. Initially, they are radiolucent and difficult to distinguish from normal bone, but with further calcification, lesions may appear as an expanded bony growth with a "ground-glass" appearance, depending on the degree of metaplastic bone formation. FD does not exhibit well-delineated margins and typically blends into the normal appearing surrounding bone on CT. While CT best demarcates the extent of disease, MRI has a role in the analysis of the surrounding soft tissue structures such as the orbit, dura, and cranial nerves when compressed by growth of the mass.[24,25]

As with osteomas, surgical resection of FD lesions should be dictated by patient symptoms while also considering the low potential for malignant transformation. Complete resection is usually definitive, but the involvement of the facial skeleton and skull base may be extensive, thus limiting intervention to a partial resection. The most common complaints leading to an attempt at surgical excision are skeletal deformities leading to structural issues such as vision changes and proptosis or dental malocclusion.[20,26] Obstructive sinonasal symptoms and compression of cranial nerve ostia leading to neural deficits are

less common. CT and MRI imaging can reveal alteration of normal bony architecture. Because lesions are difficult to distinguish from normal bone in the surgical field, intraoperative CT may be a useful adjunct to demonstrate residual disease.

Ossifying Fibroma

More commonly found in the mandible, ossifying fibromas (OF) are infrequently found in the paranasal sinuses.[27] However, because of the capability for local destruction, they are considered a more aggressive fibro-osseous lesions and complete excision is recommended.[3] Typically painless, an OF leads to cortical expansion of the affected bone. Several variants exist including cemento-ossifying fibroma, psammomatoid ossifying fibroma, or juvenile-aggressive ossifying fibroma. The cause of OF is unknown, but it is felt to be related to the periodontal ligaments of the teeth because of their capacity to produce cementum and osteoid material.[27,28] Histologic examination of the lesion demonstrates islands of osteoid material rimmed by osteoblast-forming lamellar bone.[19] The surrounding stroma appears as a parallel and whorled arrangement of collagen and fibroblasts. Most tumors present as single focal lesions, but the gigantiform cementoma subtype is typically multifocal.[21]

Notoriously difficult to diagnose endoscopically, OF is best differentiated from FD via radiographs (Figs. 17.2A to C). Unlike FD, which has ill-defined borders, OF is well circumscribed.[27] In early stages, the lesion appears radiolucent since the osseous element is noncalcified.[21] As the matrix calcifies in more progressive lesions, OF assumes a round or ovoid shape with an opaque eggshell rim. The nonhomogenous rate of calcification of the central matrix dispersed with less dense areas of fibrous tissue classically appears as "ground glass". This central area may enhance with administration of intravenous contrast.[27]

Ossifying fibromas (OF) assumes three distinct or mixed histological patterns.[21,29] The ossifying form may be indistinguishable from FD as there is a trabeculated pattern of osteoid rimmed by osteoblasts in the midst of hypercellular stroma. The cementifying form contains osseous trabeculae among cemental structures, which resemble the cementicles of the normal periodontal ligament.[30] Lastly, the storiform pattern is composed of streaming fibroblastic stroma in a pinwheel configuration with areas of calcification that resembles dystrophic bone. Clinically, the histology does not seem to change the behavior of the tumor. All tend to grow slowly.

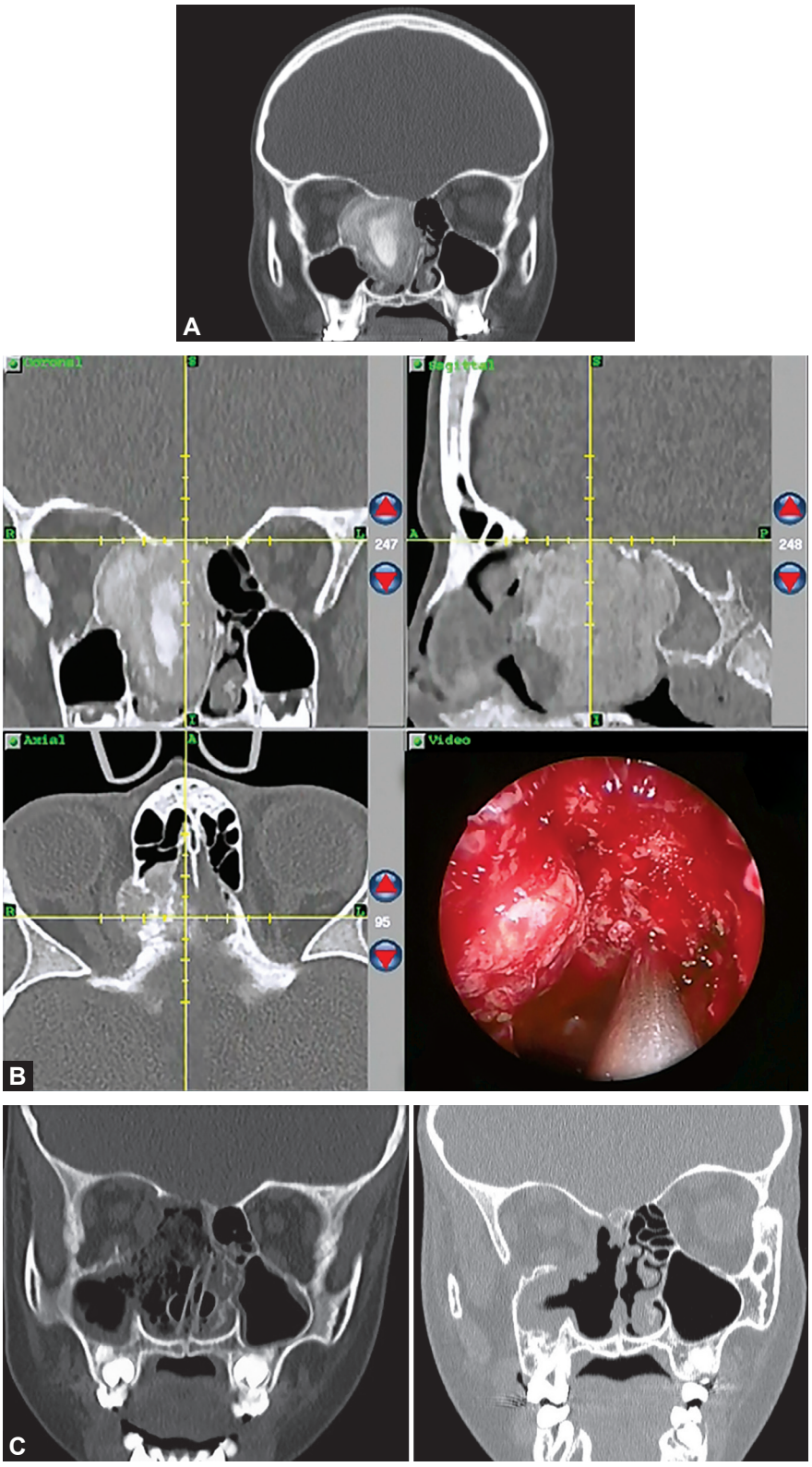
The term juvenile ossifying fibroma may be used to describe two separate clinical entities, trabecular juvenile ossifying fibroma (TrJOF) and psammomatoid juvenile ossifying fibroma (PsJOF), although they are often confused as the same pathological process.[31-35] As the moniker implies, both tend to affect younger patients with greater frequency. TrJOF occurs predominantly in the maxilla and mandible and has a more aggressive rate of expansion. Microscopically, TrJOF is composed of a cell-rich fibrous stroma containing bundles of cellular osteoid and bone trabeculae without osteoblastic rimming.[36] It is unencapsulated and has a characteristically loose structure. Males and females are affected equally with only 20% of patients >15 years of age. Pain is rarely a presenting symptom, but if the maxilla is affected, the patient may experience nasal obstruction or epistaxis.

Unlike TrJOF, PsJOF affects predominantly extragnathic craniofacial bones, particularly the periorbital frontal, and ethmoid bones. These lesions are constituted of a cellularly dense stroma with psammoma bodies, multiple small uniform ossicles.[32,37] Like TrJOF, they may grow more aggressively than other fibro-osseous lesions, although this may be due to aneurysmal bone cyst formation. Orbital extension may result in proptosis, visual disturbance, and even blindness.

Once the diagnosis is suspected from radiologic evaluation, total resection is generally recommended due to the locally destructive nature of OF. This is particularly true in cases of the juvenile-aggressive form.[38] However, some centers advocate the validity of a "wait-and-scan" approach in nonjuvenile cases, similar to the option for expectant management of other fibro-osseous lesions.[39] Adequate resection can be accomplished through curettage and enucleation, but recurrence is more common. Radiotherapy is contraindicated due to the poor radiosensitivity of OF and the increased potential for malignant transformation.[38]

Osteitis Deformans (Paget's Disease)

Osteitis deformans is used to describe the pathologically rapid turnover of bone throughout the skeleton, leading to dysplasia.[21] Although the classic form is a disease of the elderly, Juvenile Paget's disease is recognized as a similar process affecting younger patients. As affected areas undergo frequent remodeling, progressive skeletal deformities result. At the skull base, the foramina of the cranial nerves can become compromised causing functional deficits such as deafness. In the paranasal sinuses,



Figs. 17.2A to C: (A) An ossifying fibroma of the right ethmoid cavity. Note the expansile nature of the lesion against the orbit and skull base. (B) Triplanar image-guided computed tomographic (CT) scans with endoscopic view shows the tumor is resected to the dura. (C) Immediate (left) and 2 years (right) postoperative coronal CT scans demonstrating complete resection with no recurrence.

obstructive phenomena result from the stenosis and closure of the natural mucus outflow tracts.

While the cause of classic osteitis deformans is unknown, there does seem to be a genetic preponderance. The disease is prominent in the British Isles and New Zealand. While calcium and phosphate levels remain normal, alkaline phosphatase levels are markedly elevated, consistent with the high rate of bone turnover.[21] In Paget's disease and similar bony syndromes with pagetoid features, the regulatory pathway of osteoclastogenesis, osteoprotegerin/TNFRSF11A or B/RANKL/RANK, is found to be defective.[40] Nuclear material and viral particles of the paramyxovirus that causes measles have also been observed in osteoclasts, leading to the theory that Paget's disease may be due to a chronic infectious process of the bone. This relationship has not been definitively identified.

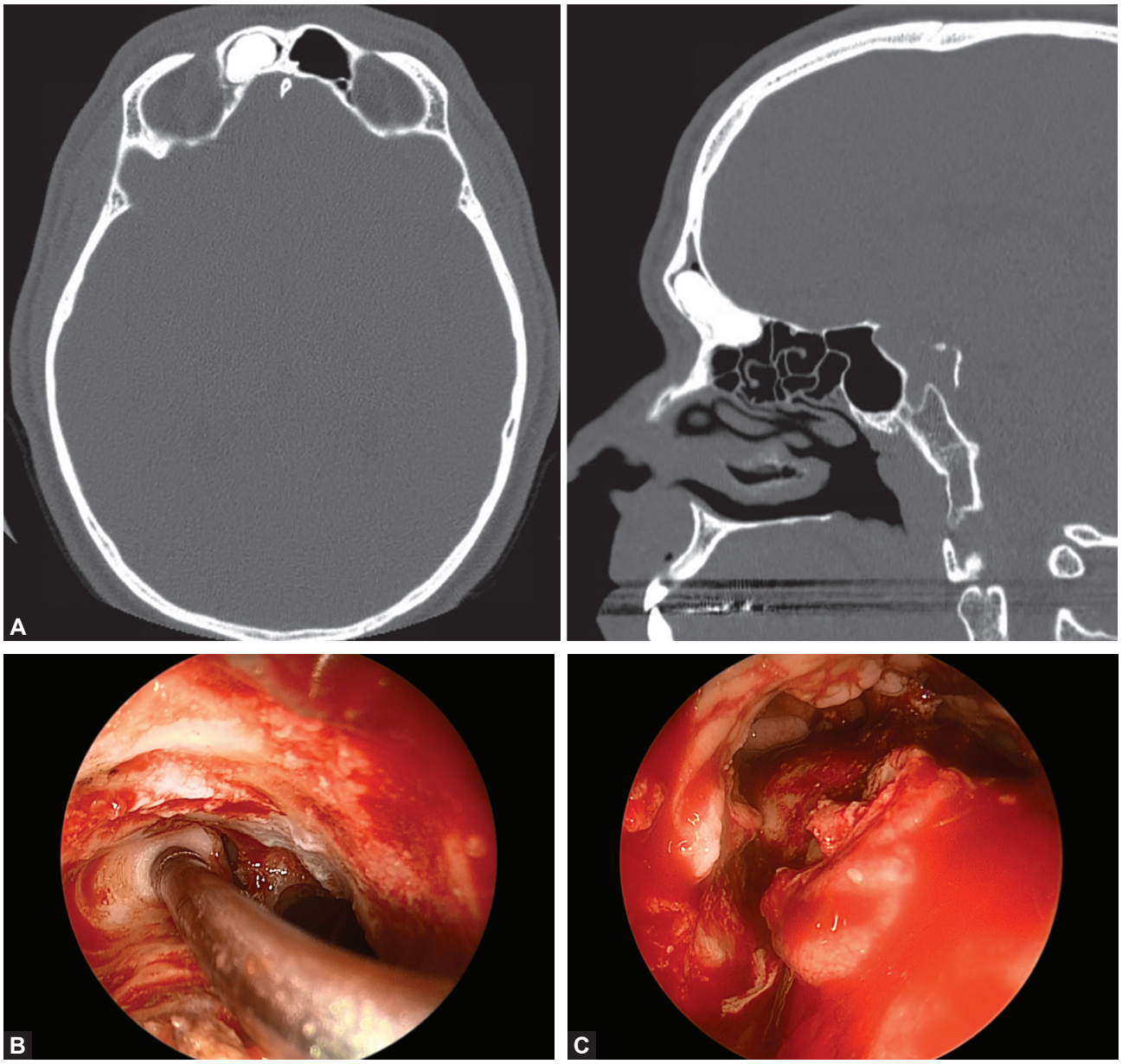
Radiographs of the calvarium may reveal radiolucent "coin-shaped" lesions from the decreased bone density of involved areas in early stages of the disease. With progression, larger areas of diffuse sclerosis develop (classically described as a "cotton wool" appearance). Microscopically, a woven pattern of osteoid between osteoblasts and osteoclasts is demonstrated. The osteoclasts are often abnormally enlarged and have multiple nuclei.

Initially, treatment of Paget's disease is centered on medical management with bisphosphonates (pamidronate, alendronate, and risedronate), which have been shown to reverse many of the abnormalities of lesions.[41] Operative intervention is warranted when lesions become a structural imposition to normal sinonasal physiology or when neurovascular compromise can be addressed without significant morbidity. CT will demonstrate postobstructive fluid opacification of the sinuses consistent with chronic sinusitis/mucocele formation or narrowing of neural foramina.

The juvenile form of the disease is often associated with facial deformity, bowing of the extremities, and above average height.[42] It is inherited in an autosomal recessive pattern and presents in infancy or early childhood. Otherwise, the radiological and histological appearance of diseased bone is very similar to the adult-onset form.

SURGICAL TECHNIQUES

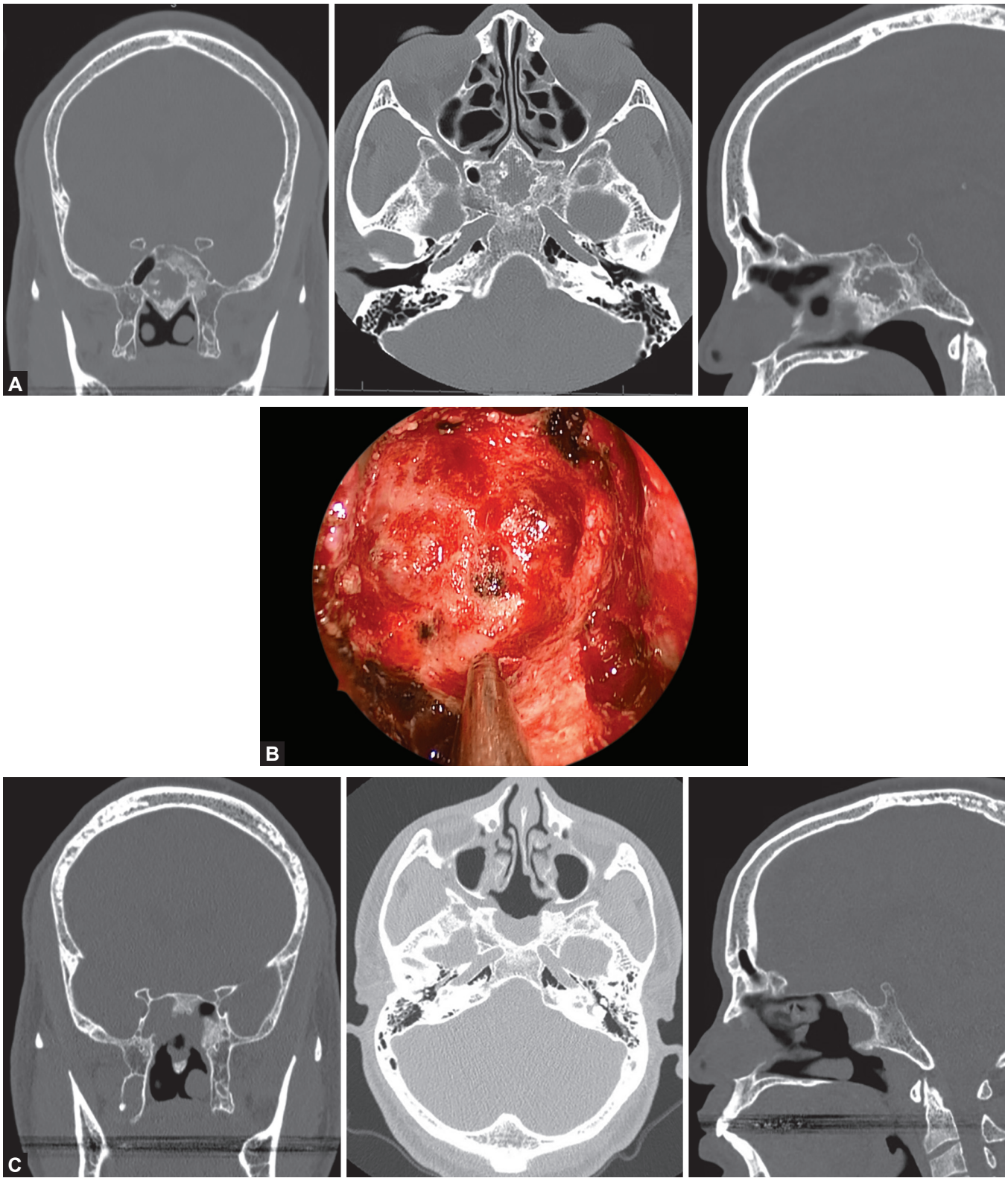
The endoscopic surgical approach to the resection of fibro-osseous lesions of the paranasal sinuses is dictated by the location of the neoplasm. By their nature, these tumors alter the bony anatomy of the paranasal sinuses—sometimes dramatically. Landmarks can be altered in shape or location. For this reason, intraoperative CT image guidance is invaluable. Lesions of the maxillary and ethmoid sinuses are well exposed and addressed through routine endoscopic sinus techniques. Endoscopic approaches to these lesions commences with traditional endoscopic sinus surgery, including uncinectomy, ethmoidectomy, and, if indicated, sphenoidotomy and frontal sinusotomy. The paranasal sinus boundaries are skeletonized, and mucosal sparing techniques are used. Powered instrumentations, such as the microdebrider and the endoscopic drill, are useful adjuncts for the identification, reduction, and extirpation of larger tumors.[3] The completeness of resection may be evaluated in real time with intraoperative CT imaging. Potential violations of the skull base must be anticipated from pre-operative imaging evaluation, and the surgeon must be prepared to repair injuries in the usual fashion to prevent postoperative CSF leak. Beyond the basic maneuvers involved in endoscopic sinus surgery, surgical treatment of fibro-osseous lesions typically require the application of expanded endonasal techniques. FD and osteomas often involve the extreme reaches of the frontal bone or the skull base, and special attention to some of the surgical maneuvers utilized to address these lesions is worthwhile. Regarding the frontal sinus, a determination must be made whether a lesion is best addressed via an endoscopic, open, or combined approach (Figs. 17.3A to C). In general, the parasagittal plane defined by the lamina papyracea is recommended as the limit of purely endoscopic resection.[12,14,43] In these instances, a coronal approach with an osteoplastic flap is a reasonable approach for the far lateral regions of the frontal sinus. However, although the frontal sinus is considered the most difficult area to address using endoscopic techniques, the accumulation of experience and the development of frontal-specific instruments have allowed an increasing number of far-lateral fibro-osseous lesions to be treated in this fashion. A Draf IIB or III (endoscopic modified Lothrop procedure) should be considered for far lateral access to the frontal sinuses in select instances. This involves the drilling of the floor of the frontal sinuses bilaterally, resection of a superior window of the nasal septum, and removal of the frontal intersinus septum. Management of frontal sinus CSF leaks created during removal may be addressed endoscopically with proper equipment and expertise, while novel techniques to improve frontal sinus patency, such as the Draf III mucosal



Figs. 17.3A to C: (A) Axial and coronal computed tomographic images of a typical frontal sinus osteoma. (B) Intraoperative view of osteoma resection. An angled endoscopic drill is used to core out the central aspect of the lesion so that the remnant may be fractured inward and removed. (C) Postresection image of the defect.

grafting technique, may also be employed.[44-46] Importantly, traditional open techniques, such as osteoplastic flap and even cranialization procedures will be necessary in certain cases.

For lesions of the central skull base, the pterygopalatine and trans-sphenoidal approaches are useful expanded endonasal techniques. Because FD frequently involves the clivus or tuberculum sellae, access may be provided through the initial creation of a wide sphenoidotomy (Figs. 17.4A to C). The optic tract and carotid artery are then identified and the dysplastic bone is resected with endoscopic drills or bony punches as necessary.[47] More laterally, exposure to the pterygopalatine and infratemporal fossae is facilitated by an endoscopic medial maxillectomy followed by removal of the posterior maxillary wall. The internal maxillary artery and its branches are identified and ligated as necessary. The neural structures including the vidian and infraorbital nerves as well as the



Figs. 17.4A to C: (A) Preoperative axial, coronal, and sagittal computed tomographic (CT) imaging of a fibrous dysplasia involving the clivus causing persistent headaches. (B) Intraoperative view after resection of FD through a wide sphenoidotomy. (C) Postoperative CT imaging confirms the completeness of resection. This patient has had complete resolution of his headache for 18 months postoperatively.

sphenopalatine ganglion can be preserved. The pterygoid plates may be identified and resected if indicated.

Although the majority of fibro-osseous lesions can be adequately resected via an endoscopic approach, an open approach (e.g. Caldwell-Luc) for tumor that extends deeply into the maxilla in a lateral or anterior fashion may provide the greatest chance for complete resection. Sublabial and extended Caldwell-Luc approaches provide access for maxillectomy without the presence of an external incision. Tumors with superior extension may require a lateral rhinotomy approach. Although incisions can be placed inconspicuously, this necessitates a scar on the facial skin. Involvement of the cranial base may require a craniofacial resection. This may be accomplished in conjunction with an endoscopic approach, an open craniotomy, or a combination of these techniques. The benign histology of fibro-osseous lesions renders approaches involving facial incisions to a last resort.

Surgical resection for fibro-osseous tumors of the paranasal sinsuses is typically definitive as recurrence rates are low when resection is complete. A recent clinical series reporting the outcomes of a large series of endoscopically resected osteomas showed no evidence of recurrence at a mean follow-up time of 52 months.[48] The outcomes of the radical resection of other fibro-osseous lesions are similar. However, complete resection may not be possible or indicated, depending on the extent and location of the disease. Some cases of FD may involve large portions of the cranial vault and facial skeleton making complete resection unfeasible. Furthermore, the size and extent of a tumor often dictates a piecemeal resection, increasing the risk for recurrence from residual tumor. Ossifying fibromas (OF), in particular, have recurrence rates reported as high as 30–56%, although an exact determination of outcomes is difficult because of the rarity of the lesion.[36] The primary reason for high OF recurrence is the tendency for rapid expansion and local bone invasion compromising the ability to obtain clearance of the bony margins. The juvenile form tends to be more aggressive.[33] Despite this propensity for local recurrence, the tumor does not metastasize and the incidence of malignant transformation is very low.

Follow-up after resection is accomplished with surveillance endoscopy (an obvious advantage with endoscopic resection) or intermittent reimaging of the paranasal sinuses if necessary. Initially, this occurs at an interval of a few months but can be extended to annual visits if there are no concerning findings. More reliable patients may be cautioned regarding concerning symptoms that may arise during the surveillance period and asked to return should problems occur.

CONCLUSION

Benign, fibro-osseous lesions of the paranasal sinuses present unique treatment challenges. The pathological bone expansion and remodeling can be ill-defined and infiltrative on radiological evaluation. Histologically, each entity may be considered to lie along a spectrum of mesodermal-derived lesions with varying levels of fibrous or bony content—often in dysfunctional and disorganized patterns. Furthermore, classification of separate disease entities may be subtle and inconsistent between various lesions. Regardless, fibro-osseous tumors frequently require removal once they become symptomatic. Expanded endonasal sinus and skull base surgical techniques have allowed the ability to remove the majority of fibro-osseous lesions with low patient morbidity, but open techniques are still necessary in select cases.

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CHAPTER

18

Benign Neoplasms of the Nose and Paranasal Sinuses

Brian Thorp, Kenneth Rodriguez, Brent A Senior

INTRODUCTION

Benign tumors of the nasal cavity and paranasal sinuses represent a wide spectrum of distinct histopathologic entities. Although globally uncommon, these tumors are frequently seen in high-volume rhinology practices and deserve specific focus as lack of identification or misdiagnosis can lead to poor patient outcomes. Often, these tumors will present with common, nonspecific complaints such as epistaxis or unilateral nasal airway obstruction. Thorough history taking as well as comprehensive examination with nasal endoscopy are crucial in the workup of these tumors. Imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or angiography can be helpful in diagnosis, surgical planning, and surveillance. Malignant lesions and fibro-osseous lesions are discussed separately in this text but remain important in the differential diagnosis.

INVERTED PAPILLOMA

Inverted papilloma (IP) was originally reported by Ward in 1854.[1] In 1855, Billroth described two cases of papillomatous growths in the nasal cavity characterizing them as "villiform cancers".[2] Further characterization followed and in 1935 Kramer and Som published on 86 cases and were the first to distinguish IP from inflammatory polyps.[3] In 1971, Hyams subdivided the pathology into inverted, fungiform, and cylindrical.[4] Throughout its history IP has been called >50 different names. This complex history of nomenclature has led to confusion about what specifically constitutes IP versus other similar variants. Three morphologically distinct papillomas arise from the mucosa that lines the nasal cavity and paranasal sinuses now termed exophytic, inverted, and oncocytic papillomas. Collectively, this group is called schneiderian papillomas.[5]

Exophytic papillomas account for 18–50% of all schneiderian papillomas and more commonly occur in men and in individuals between 20 years and 50 years of age. These lesions most commonly arise from the nasal septum with 4–21% originating from the lateral nasal wall. Paranasal sinus involvement is rare as is malignant degradation. Oncocytic (cylindrical cell papilloma) accounts for 3–8% of schneiderian papillomas. This lesion exclusively occurs on the lateral nasal wall or in the sinuses. Malignancy occurs in 4–17%, typically squamous cell carcinoma (SCC).[5]

The incidence of IP has been derived from numerous series and from a population standpoint occurs in 0.6–1.5 per 100,000 people.[6-12] IP represents approximately 0.4–4.7% of all sinonasal tumors and 47–79% of all schneiderian papillomas.[5] IP usually affects patients in the fifth and sixth decades of life.[13] Symptoms are nonspecific and include unilateral nasal obstruction, epistaxis, nasal drainage, and sinusitis.[14,15] IP has a male:female ratio ranging from 2:1 to 5:1. The overwhelming majority of cases are unilateral with no side predilection, although bilateral lesions can occur in up to 4.9% of patients.[16-18] Weissler et al. found in a review of 223 patients with IP, 9% were bilateral (most due to direct spread through the septum) and 12% were multicentric. There are no significant racial differences.[19] IP usually originates from the middle meatus or lateral nasal wall but involves at least one paranasal sinus 82% of the time.[13,18] They can arise from the septum in 8% of patients.[20] IPs have been reported in the oropharynx, posterior pharyngeal wall, hypopharynx, nasopharynx, lacrimal sac, and middle ear/mastoid.[21-26]

Malignancy Risk

Diagnosis and prompt treatment of IP is critical given its association with SCC. A review of 1390 IPs published in 2009 showed that IP was associated with carcinoma in 150 cases or 11%.[5] In another large analysis published in 2010, the authors subdivided patients into those with carcinoma in situ (14/414, 3.4%), synchronous (163/2297, 7.1%), and metachronous carcinomas (74/2047, 3.6%) with metachronous lesions being defined as development of cancer in the resection bed of IP after initial tumor resection.[27] Although the most common malignancy associated with IP is SCC, verrucous, mucoepidermoid, spindle cell, clear cell, and adenocarcinoma have also been reported. There does not appear to be a correlation between the number of local recurrences of an IP and the subsequent development of carcinoma.[5] There is, however, a bias in regard to the actual malignancy rates, which have been reported as high as 53%, but these data are often from tertiary centers reflecting more difficult situations and hence potentially higher rates of cancer.[28,29]

Pathophysiology

Grossly, IP appears to be exophytic and polypoid and is typically pink to gray in color. It may be sessile and diffuse but more frequently emanates from a discrete pedicled site despite draping over large areas of mucosa. The underlying mucosa remains normal and does not need to be resected along with the tumor (Fig. 18.1).[4] IP originates from ciliated respiratory mucosa of the sinonasal tract. Diagnosis is established via biopsy. The characteristic microscopic feature is digitiform proliferation of squamous epithelium into the underlying stroma. Its name derives from the inverted (endophytic) growth of the epithelium into the stroma respecting the basement membrane.[15]

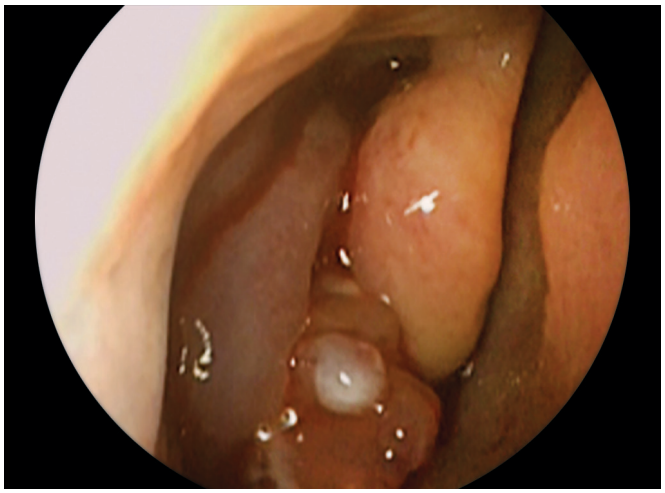

Fig. 18.1: Endoscopic image of an inverting papilloma emanating from the right middle meatus.

Although the exact cause of IP remains uncertain, recent interest has grown into whether human papillomavirus (HPV) is a causative factor in IP with conflicting opinions. Jenko et al. performed a study to investigate the frequency of HPV infection in patients with IPs without carcinoma (n = 68), IPs associated with SCC (n = 5), and controls (n = 47). HPV DNA was found in 20 (30.3%) patients with IPs, in 3 (60%) patients with IPs with SCC, and in 6 (13%) patients from the control group. The frequency of HPV infection in the study group was significantly higher (p = 0.032) than in the control group. However, the presence of HPV DNA was not a significant risk factor for associated SCC (p = 0.32). They conclude that since HPV type 11 was the predominant genotype in all groups, it may represent incidental colonization.[30]

In a meta-analysis published in 2012, Syrjanen and Syrjanen concluded that variability in HPV detection rates in sinonasal papillomas can be explained by their histological types and not by HPV detection method or geographic origin of study, and none were significant.[31]

Overall, the data remain controversial concerning the role of HPV infection in IP formation and possible role in malignant degeneration with no clear consensus presently available.

Of note, recurrent respiratory papillomatosis (RRP) is known to be caused by HPV, especially types 6 and 11.[5] It is the most common benign neoplasm of the larynx among children.[32,33] Infection in children has been associated with vertical transmission during vaginal delivery from an infected mother. There are histologic similarities between RRP and exophytic schneiderian papillomas. Both tend to be mainly squamous lesions with an exophytic/papillary architecture with the main difference being the presence of mucocytes (goblet cells) and intraepithelial mucous cysts in exophytic IP, but these features are not usually seen in RRP. Respiratory and/or transitional type epithelium is much more commonly seen in exophytic IPs, and the degree of surface keratinization is usually greater in RRP.[5]

Staging

Unlike SCC, there is no generally adopted staging system for IP. While it is clear that standardized staging allows for greater clarity in reading the literature, it also assists in

Table 18.1: Krouse staging system for inverted papilloma (2000)

Stage	*Criteria*
T1	Confined to nasal cavity
T2	Ostiomeatal complex region, ethmoid, or medial maxillary involvement (with or without nasal cavity involvement)
T3	Any wall of maxillary sinus but medial, frontal sinus, or sphenoid with or without T2 criteria
T4	Any extrasinus involvement or malignancy

Source: Adapted from Krouse.[34]

Table 18.2: Han staging system for inverted papilloma (2001)

Stage	*Criteria*
Group I	Limited to nasal cavity, lateral nasal wall, medial maxillary sinus, ethmoid sinus, and sphenoid sinus
Group II	Extension lateral to medial maxillary wall with or without group I criteria
Group III	Extension into frontal sinus
Group IV	Extension outside sinuses

Source: Adapted from Han et al.[13]

promoting consistency in clinical practice. Similarly, being able to stratify risk for recurrence based on reliable staging is essential for improved patient outcomes. Many systems have been proposed including those of Krouse, Han, and most recently Cannady, each with specific advantages and disadvantages. Krouse's system emphasized tumor extension beyond the maxillary sinus as an important prognostic factor and included malignancy (Table 18.1).[34] Han's system did not include malignancy and placed medial maxillary, lateral nasal wall, ethmoid and sphenoid tumors into an early stage group and frontal sinus disease or extension beyond the medial maxillary sinus a higher stage (Table 18.2).[13] Cannady's system is based on the recurrence risk centered on location (Table 18.3).[35] In the event of pathological discovery of SSC, the primary tumor, regional lymph nodes, and distant metastasis (TNM) staging system as found in the American Joint Committee on Cancer (AJCC) staging manual should be used (Table 18.4).[36]

Table 18.3: Cannady staging system for inverted papilloma (2007)

Stage	*Criteria*
Group A	Inverted papilloma confined to the nasal cavity, ethmoid sinuses, or medial maxillary wall
Group B	Inverted papilloma with involvement of any maxillary wall (other than the medial wall), or frontal sinus, or sphenoid sinus
Group C	Inverted papilloma with extension beyond the paranasal sinuses

Source: Adapted from Cannady et al.[35]

Management

With its tendency to recur and its association with malignancy, thoughtful and comprehensive management in all phases of treatment is essential. Management begins with comprehensive history and physical examination with focus on nasal endoscopy. Facial sensation, baseline vision, and sense of smell should all be evaluated prior to surgical intervention. Imaging with a non-contrast computed tomography (CT) of the paranasal sinuses may help differentiate tumor with its characteristic calcifications and define the exact location and extent of the tumor, whereas CT with contrast may demonstrate slight enhancement.[37] Coronal and sagittal reconstructions help determine the relationship of the lesion with the orbital and cranial base (Fig. 18.2). Bony changes, including bowing near the mass, are common CT findings, while dehiscence may be seen particularly in the region of the skull base. Focal hyperostosis is an important feature to identify, often reflecting the point of origin of the tumor.[15,37-39] MRI can assist to differentiate tumor from postobstructive secretions while also helping to differentiate invasion of tumor into adjacent structures (Fig. 18.3). IP is isodense on T1-weighted images and iso to hyperdense on T2-weighted images. Contrast can lead to heterogeneous enhancement.[40]

Complete surgical excision with aggressive clearance of the anatomic origin of the lesion has been recognized as key to management of these tumors for several decades. The exact surgical approach for IP has evolved as advances in surgical techniques and technology have allowed for increasingly less invasive surgeries while achieving the goal of complete excision. Early approaches involving simple polypectomy and/or Caldwell-Luc resulted in unacceptably high rates of recurrent disease, leading to the development and standard application of open approaches such as the lateral rhinotomy and midfacial degloving in the 1970s and 1980s. Noting the benefits of these open procedures, Weissler et al. identified a recurrence rate of 71% for closed intranasal procedures compared with 29% for open procedures in 1986.[14] However, since the 1990s, endoscopic techniques have proven an effective alternative to more extensive open approaches. Initially, described in 1992, Waitz and Wigand compared endoscopic

Table 18.4: American Joint Committee on Cancer staging system

Stage	*Criteria*
Maxillary sinus	
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease with tumor invading anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid, or frontal sinuses
T4b	Very advanced local disease with tumor invading any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus
Nasal cavity and ethmoid sinus	
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease with tumor invading any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid, or frontal sinuses
T4b	Very advanced local disease with tumor invading any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V_2), nasopharynx, or clivus

Source: Adapted from AJCC.[36]

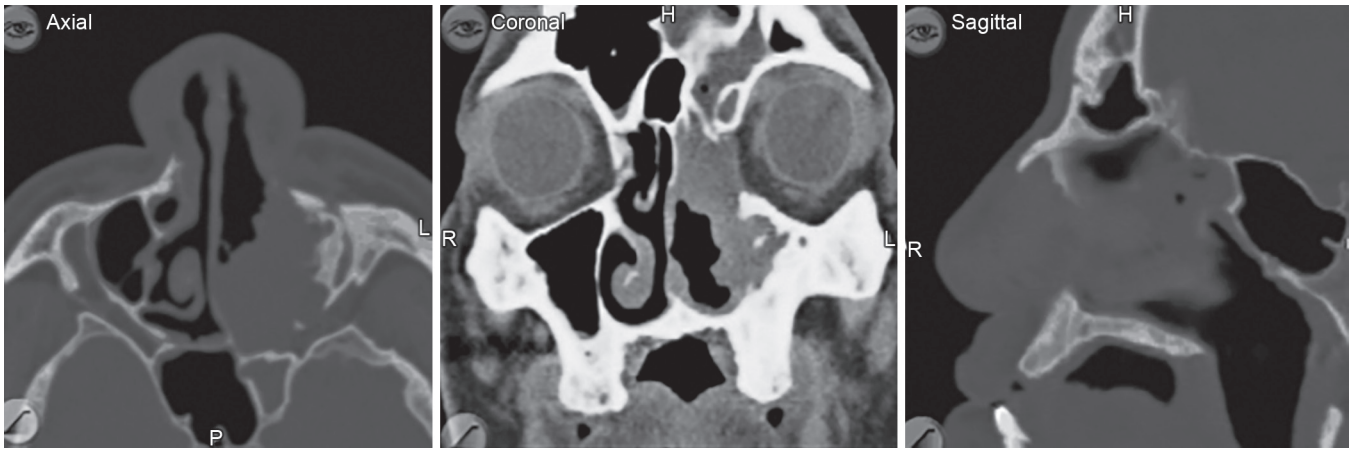

Fig. 18.2: Computed tomographic imaging of an extensive, recurrent left-sided sinonasal inverting papilloma with extension to the skull base and frontal recess. Note the dehiscent left lamina papyracea.

resection of smaller IPs to traditional open procedures of more extensive tumors and noted similar recurrence rates of 17% versus 19%. While a selection bias was noted, some have argued that this bias has persisted in the literature with most series comparing endoscopic and open techniques being skewed by tumor size.[41] However, Busquets and Hwang helped to more fully validate endoscopic techniques by performing a large meta-analysis in 2006 of treatment outcomes for IP. They divided the literature into two groups: pre (1970–1995) and post (1992–2004) endoscopic periods. Without consideration of tumor size, they found a significantly lower recurrence rate in the endoscopic era compared with the nonendoscopic era (15% vs 20%, $p = 0.02$). Moreover, and most significantly, endoscopically treated patients were found to have a significantly lower recurrence rates compared with nonendoscopically treated patients (12% vs 20%, $p < 0.01$). Furthermore, recurrence rate for nonendoscopic treated patients in the

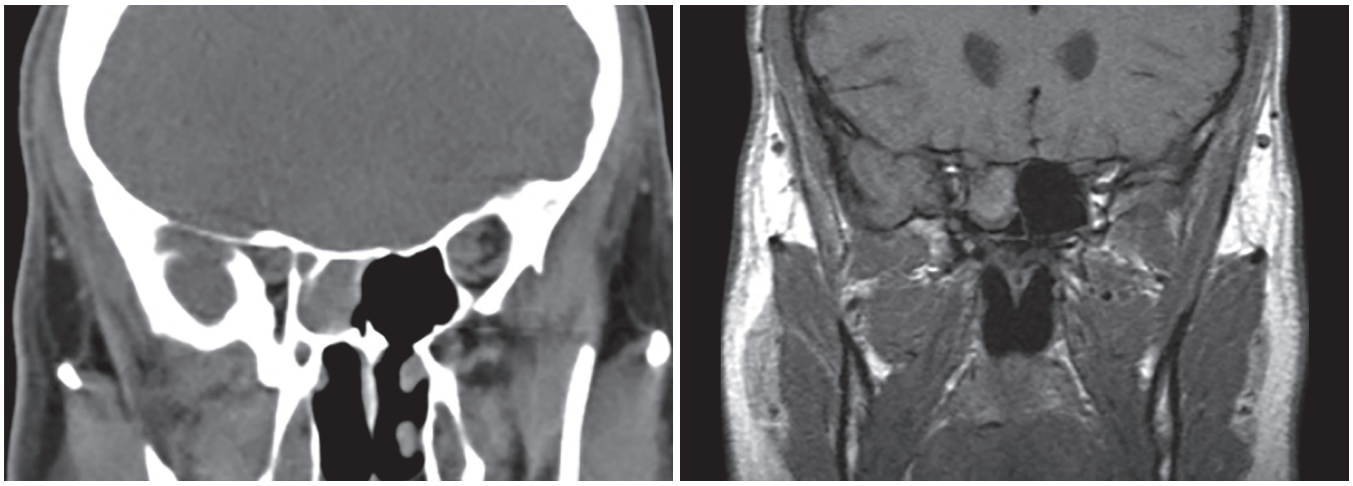

Fig. 18.3: Preoperative computed tomographic imaging and magnetic resonance imaging of an isolated right sphenoid inverting papilloma.

endoscopic era was found to be equivalent to that of the nonendoscopic patients in the pre-endoscopic surgery era (20% vs 19%, $p = 0.78$).[42]

Identification of the site of origin is critical to the complete surgical resection of IP. IP is found to originate in the ethmoid region in 48%, the maxillary sinus in 28%, the sphenoid sinus in 7.5%, the frontal sinus in 2.5%, the inferior turbinate in 2.5%, and the septum in 2.5%.[19] Endoscopic en bloc resection of tumor may, in some cases, be possible. More commonly partial debulking of the tumor is needed to allow clear identification of the site of attachment. As with any other sinus surgery, mucosal preservation of uninvolved sites should be attempted. At the site of origin, however, it is essential that the adjacent mucosa and underlying bone be removed or thinned with a drill to clear the deep margin.[43,44] IP involving the lamina papyracea or cranial base deserves special mention as it represents a difficult clinical entity. If there is a recurrence at these sites after bone removal, the tumor will be present directly on periorbita or dura greatly increasing morbidity of further resection. There is no clear clinical answer for these situations. Debulking of recurrent tumor when the patient becomes symptomatic while leaving the periorbita or dura intact and close follow-up of pathology results is one option. Any aggressive features such as new facial numbness, vision changes, or any signs of intracranial extension should be evaluated to ensure malignancy is evaluated and, if present, handled appropriately.

Tumor resection needs to be tailored to each individual surgical case. Krouse, using his staging system, recommended that T1 tumors be resected endoscopically. T2 and T3 lesions can be treated endoscopically, with external approaches employed if visualization is limited, whereas T4 tumors may benefit from an extranasal approach.[34] Frozen sections at the time of surgery can help ensure clear margins. After resection, patients require long-term surveillance in the form of nasal endoscopy, and if clinically indicated, serial imaging studies. Although the majority of recurrences occur within the first few years after surgery, delayed, long-term recurrence is possible.

Radiotherapy is rarely used for histologically benign IPs given that surgical excision is curative. Historically, there has been an association of malignant transformation in patients with papillomatosis in the picture of prior radiation therapy.[45] More recent publications do not support that association. Indications for radiation include inoperability due to the extent of disease, medical comorbidities resulting in an unacceptably high risk for perioperative medical complication, incomplete resection, history of multiple recurrences, or malignant degeneration within the specimen.[46] In a recent review, Strojan concluded that for histologically benign IPs, radiotherapy is safe and is indicated when the risk of tumor recurrence after surgery is increased, either due to subtotal resection or a history of recurrent disease, and in inoperable tumors.[47]

CONCLUSION

The IP represents pathology that must be considered in the differential of any nasal or sinus tumor. Comprehensive management requires a thoughtful, stepwise approach. The point of origin should be carefully sought. Although the etiology is debated, complete resection, either through

an endoscopic, combined, or open approach, is the standard of care. Malignant degeneration should be staged through the AJCC guidelines and managed accordingly. Radiation can be considered in select cases. Close follow-up is mandatory.

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Juvenile nasopharyngeal angiofibroma (JNA) represents a rare, complex clinical entity whose vascular characteristics and propensity for local extension require aggressive surgical excision within the complex anatomic environment of the sinonasal tract, nasopharynx, and skull base. Emerging techniques have resulted in shifts in preoperative analysis, treatment, and surgical resection.

Initially described in 1906 by Chaveau, JNAs are histologically benign and almost exclusively affect males in the second decade of life.[48] These highly vascular tumors represent 0.05% to 0.5% of upper aerodigestive tract tumors with recent population studies indicating an overall incidence of 0.4 cases per million inhabitants per year.[49]

The median age at diagnosis of patients with JNA is approximately 15 years, but this can range widely with reports of older men in the recent literature.[49,50] Interestingly, rare reports in female patients are known.[51-53] Such a finding should prompt comprehensive genetic analysis with karyotyping and fluorescence in situ hybridization (FISH) analyses. Although a comprehensive review of the molecular and genetic alterations found in patients with JNA is outside the scope of this chapter, it should be noted that evidence of autosome and allosome genetic alteration favor oncogene activation and loss of chromosome Y activity.[54-56]

As described by Mills et al., JNAs histologically demonstrate a connective tissue stroma with mesenchymal matrix harboring a complex array of blood vessels ranging widely in size from small capillaries to large vascular channels.[57] It is this dense vascular network that results in the tumor's propensity to bleed often resulting in spontaneous epistaxis. Moreover, in-office biopsy is contraindicated when this entity is suspected given its vascular nature.

Despite its benign denotation, JNAs display aggressive local extension and must be managed in the complex milieu of the skull base, nasopharynx, and sinonasal tract. Originating in the region of the sphenopalantine foramen, these nonencapsulated tumors spread via direct extension through existing fissures, foramina, and ostia with the capacity for osseous erosion. A thorough understanding of this anatomy highlights the potential routes of spread, which include the nasopharynx, nasal cavity, paranasal sinuses, pterygopalatine fossa, infratemporal fossa, orbit, skull base, and/or intracranial space. Of note, dural remodeling without invasion can be seen in advanced tumors.[58-60]

Clinical manifestations directly result from the histologic characteristic of this disease entity in the setting of local and aggressive extension. Common symptoms include nasal obstruction and epistaxis occurring in approximately 90% and 60% of patients, respectively. Depending on the tumor burden, other potential clinical manifestations include nasal discharge, pain, sinusitis, facial deformity, diplopia, hearing impairment, and otitis media.[49, 60,61]

The complex surrounding anatomy and potential for local extension necessitates contrasted CT and MRI in any suspected case of JNA (Fig. 18.4). In concert these studies reveal important information regarding the local osseous and soft tissue anatomy critical for treatment planning and staging. In some cases, axial CT imaging may reveal expansion of the pterygopalatine fossa with anterior bowing of the posterior maxillary wall, classically termed the "Holman–Miller sign", a finding that is pathognomonic for this disease process.[60-62] In addition to these studies, angiography provides further diagnostic and therapeutic advantages, allowing identification of feeding vasculature and preoperative embolization, typically performed 24–48 hours prior to scheduled resection to allow tumor devascularization and potential shrinkage (Fig. 18.5). These advantages have led to the frequent integration of embolization into the treatment plan with a multitude of studies suggesting decreased intraoperative blood loss and transfusion need.[63-66] It has also been hypothesized that recurrence rates are improved with preoperative embolization.

Classically, JNAs derive blood supply from the ipsilateral external carotid artery via the internal maxillary artery branches and the ascending pharyngeal artery as well as from the ipsilateral internal carotid artery via the ophthalmic artery. Contralateral contributions have been demonstrated in approximately 40% of patients with both distinctly lateralized and bilateral disease burden, originating from both the external and/or internal carotid systems.[67] Occasional contribution from the posterior circulation is also seen, particularly in recurrent tumors, making it imperative that all vessels be imaged preoperatively.

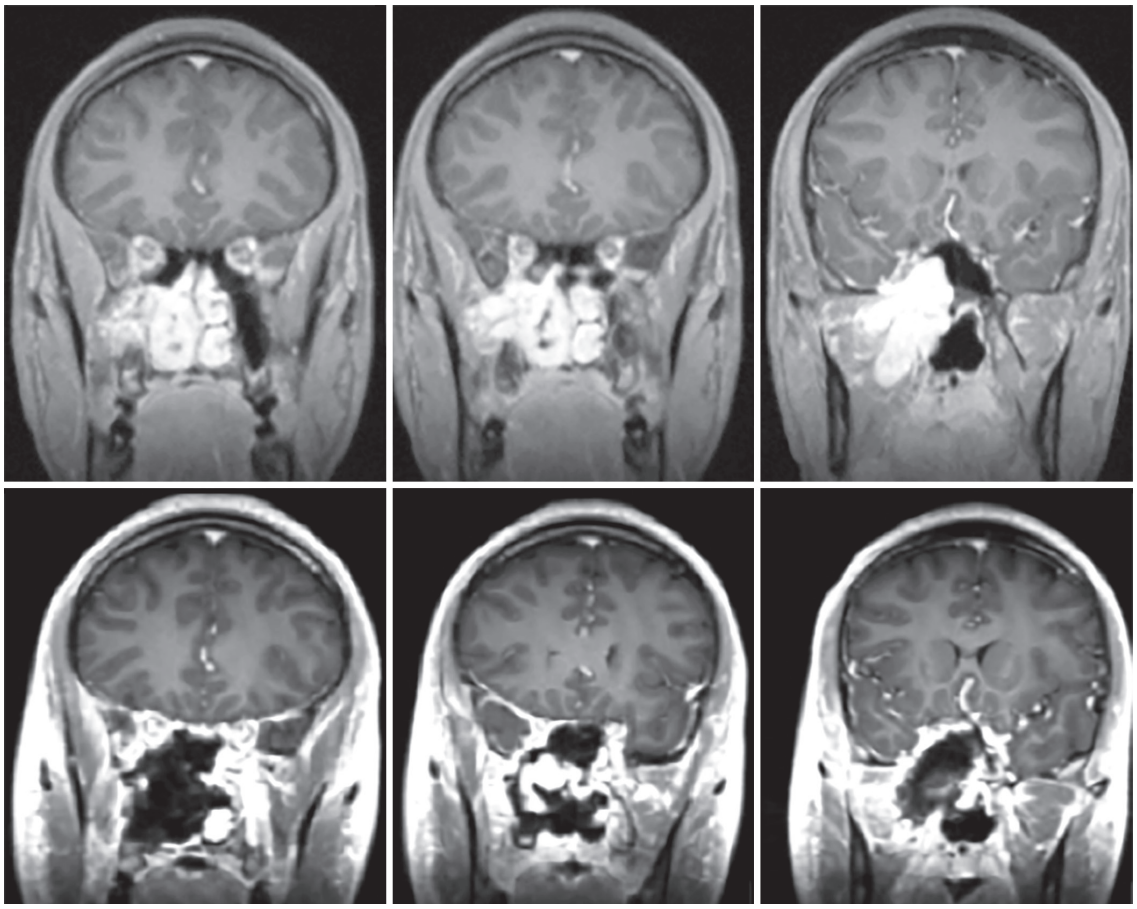

Fig. 18.4: Preoperative and postoperative magnetic resonance imaging from an extensive, recurrent right-sided juvenile nasopharyngeal angiofibroma.

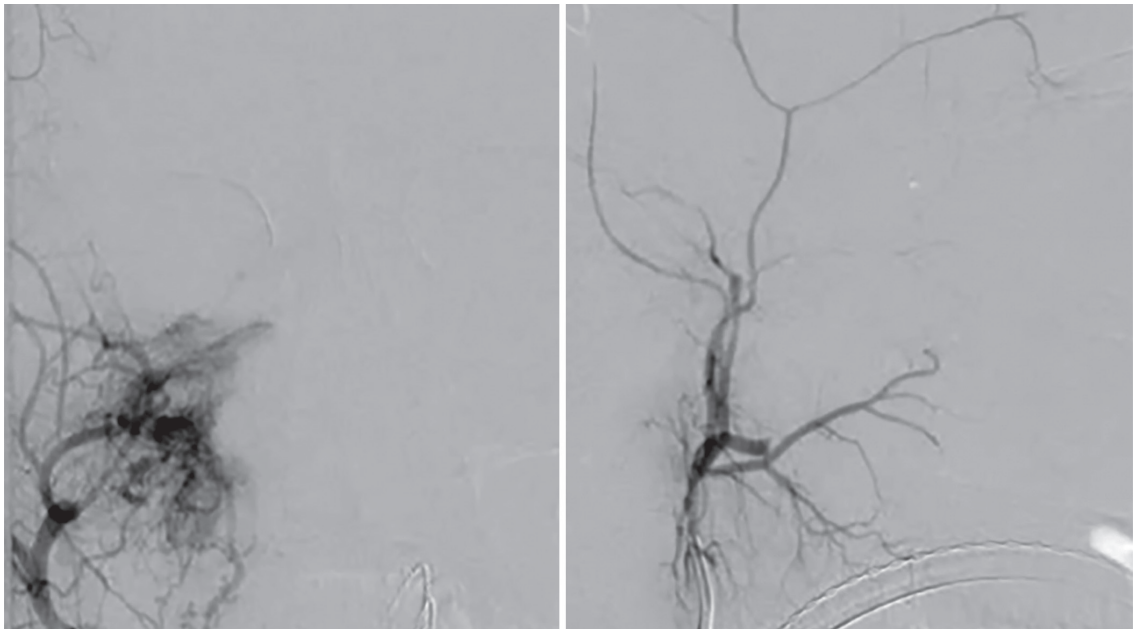

Fig. 18.5: Pre-embolization and postembolization angiography images from an extensive, recurrent right-sided juvenile nasopharyngeal angiofibroma.

Table 18.5: University of Pittsburgh Medical Center (UPMC) staging system for angiofibroma

Stage	*UPMC staging system*
I	Nasal cavity, medial pterygopalatine fossa
II	Paranasal sinuses, lateral pterygopalatine fossa; no residual vascularity
III	Skull base erosion, orbit, infratemporal fossa; no residual vascularity
IV	Skull base erosion, orbit, infratemporal fossa; residual vascularity
V	Intracranial extension, residual vascularity; M, medial extension; L, lateral extension

Source: Adapted from Snyderman et al.[74]

A multitude of staging systems have been introduced and subsequently revised to describe tumor extent and provide clinical risk stratification for recurrence rates, morbidity, and mortality. Examples include Sessions et al., Fisch, Chandler et al., Andrews et al., Radkowski et al., and Onerci.[68-73] With the continued technological advances in rhinologic and skull base surgery, many of these staging systems may no longer fully approximate the risk stratification for which they were initially intended, which has led to the recent development of the University of Pittsburgh Medical Center (UPMC) staging system. Incorporating residual vascularity following preoperative embolization androute of cranial base extension with emphasis on tumor relationship to the intracranial internal carotid artery, the UPMC staging system was found to strongly correlate with intraoperative blood loss, need for transfusion, need for multiple operations, residual tumor burden, and recurrence. It should be noted that while designed utilizing data from endoscopic resections, the UPMC staging system is not influenced by surgical approach (Table 18.5).[74]

The evolution of staging systems detailed above has paralleled surgical advances, which have shifted from traditional external approaches to largely endoscopic techniques. While careful preoperative surgical planning is required to determine the appropriate surgical approach or combination of approaches, it is clear that the role of endoscopic intervention is expanding with multiple reports indicating comparable or improved intraoperative blood loss, reduced occurrence of complications, and reduced rates of recurrence with decreased operative time and hospital length of stay. Regardless of approach, the treatment goal remains complete surgical excision.[50, 60,61,75-77]

Although surgical therapy is regarded as the treatment of choice, many advocate for the utilization of radiotherapy in the primary, concurrent, or salvage settings. Studies indicating comparable control and recurrence rates with primary radiotherapy have been reported, and also highlight the potential for radiation-specific morbidity, including growth retardation, hypopituitarism, cataracts, radiation keratopathy, malignant transformation, induction of malignancy, osteoradionecrosis, osteomyelitis, or temporal lobe necrosis.[78,79] Additional adjuvant therapies such as chemotherapy and hormonal therapy have been suggested with no clear data supporting routine usage or consideration in the treatment algorithm.

Overall, surgical therapy remains the treatment of choice in the primary and recurrent settings with adjuvant therapies reserved for cases in which the disease burden or patient fitness is not amenable to surgical intervention.

HEMANGIOMA

Hemangiomas are rare, vascular tumors of the sinonasal tract that most commonly involve the nasal vestibule and nasal septum with reports of paranasal sinus origin (Fig. 18.6). These lesions are classified as either cavernous or capillary based on the predominant vessel size with the majority of the capillary type. Histologically, diffuse vascular proliferation in the absence of inflammatory infiltrate, atypia, or endothelial proliferation is seen. Recurrent spontaneous epistaxis and nasal obstruction are frequently seen and given the vascular nature of these tumors significant bleeding with manipulation can occur. Therefore, in suspected cases, biopsy should be performed in the operative theater setting.

Contrasted CT and MRI is important in diagnostic evaluation and treatment planning. As with JNA, angiography allows diagnostic and therapeutic advantages including preoperative embolization.[80,81] Surgical excision remains the mainstay of therapy with shifts in approach paralleling that of JNA with recent reports indicating safe endoscopic resection.[82]

PYOGENIC GRANULOMA

Pyogenic granuloma or granuloma gravidarium is a benign, vascular tumor that most commonly affects multiparous females in the second and third trimesters between the ages of 20 and 50 years with a prevalence of 0.5% to 5%. Although the pathogenesis is not fully defined, it is clear

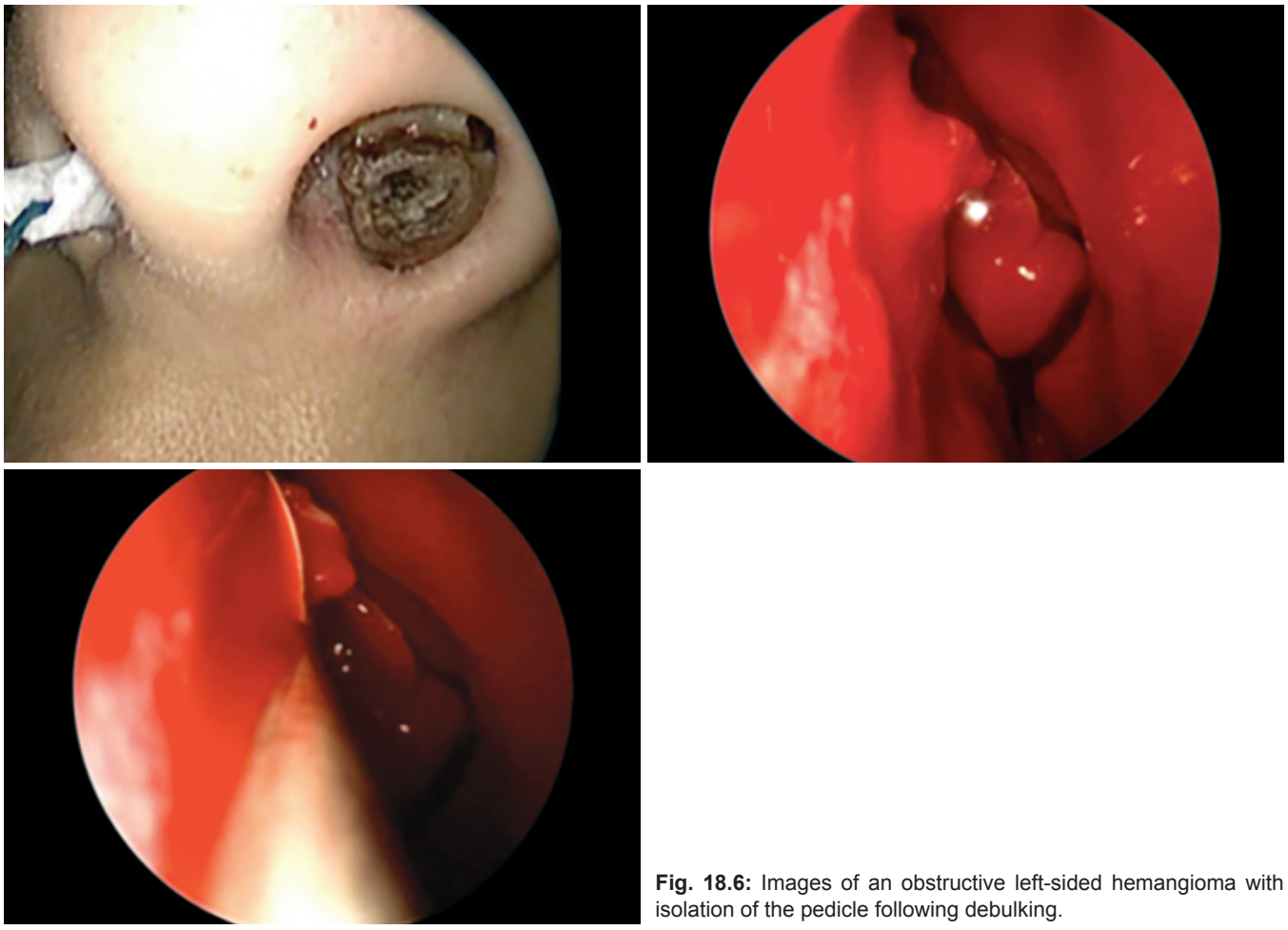

Fig. 18.6: Images of an obstructive left-sided hemangioma with isolation of the pedicle following debulking.

that hormonal influence and/or external trauma play a role. Solitary, erythematous lesions most frequently occur in the oral cavity but have also been described in the nasal cavity. Lesions of the nasal cavity classically present with recurrent epistaxis and nasal obstruction. While these lesions may resolve postpartum, surgical excision is employed in symptomatic patients, nonpregnant females, male patients, patients with persistence after pregnancy, and lesions exhibiting rapid growth and/or boney remodeling of adjacent facial bones.[83-85]

BENIGN SALIVARY GLAND NEOPLASMS

Pleomorphic adenoma of the minor salivary glands of the nasal mucosa is exceedingly rare with few documented reports in the literature. Nasal obstruction is most commonly seen with symptoms related to tumor burden. Treatment is achieved with complete surgical excision.[86,87]

HAMARTOMAS

Hamartomas are defined as benign masses of disorganized mature cells of any tissue type. Sinonasal hamartomas are rare but becoming more commonly recognized with the respiratory epithelial adenomatoid hamartoma subtype described by Wenig and Heffner in 1995 being seen most commonly.[88] Although initially thought to originate in the nasal cavity and olfactory cleft, recent reviews suggest a higher predilection to paranasal sinus origin. In addition, an association with allergic rhinitis, chronic rhinosinusitis, and nasal polyposis has been noted with symptoms similar to these entities. Although management of these benign lesions is conservative with complete excision curative, it is imperative to distinguish hamartomas from other entities to avoid unnecessary or inadequate interventions.[89] Preoperative imaging is strongly recommended for both its diagnostic value and benefits with therapeutic planning (Fig. 18.7).

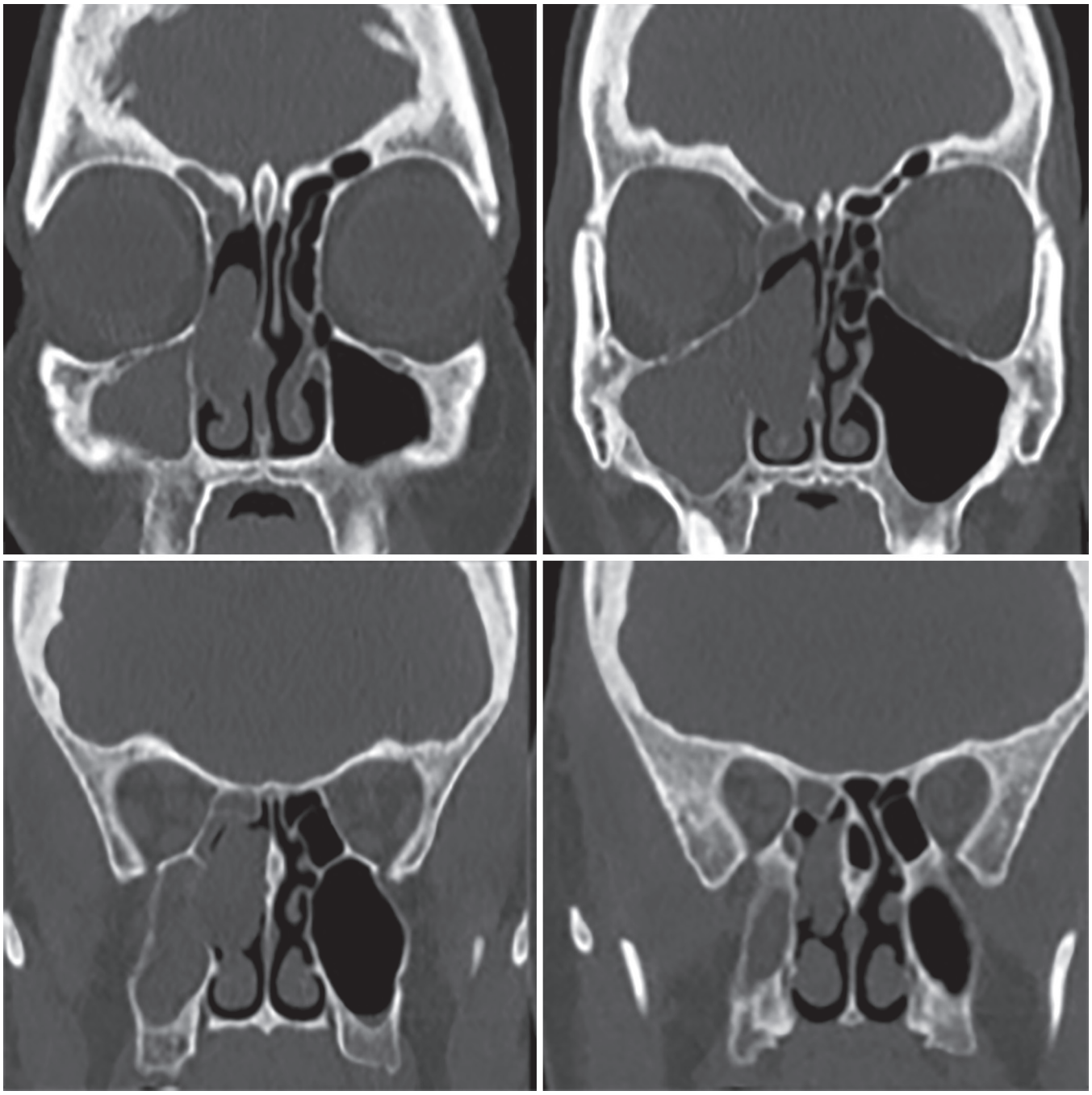

Fig. 18.7: Computed tomographic imaging of a patient with a right-sided respiratory epithelial adenomatoid hamartoma.

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CHAPTER

19

The Nose and Sleep Disorders

Steven Y Park, Samuel N Helman

INTRODUCTION

Nasal congestion is commonly found in snorers and patients with obstructive sleep apnea (OSA)[1,2] and is also a strong risk factor for having OSA.[3,4] Nasal resistance can predict snoring severity,[5] and nasal resistance is higher in snorers with OSA compared with snorers without OSA.[6] Chronic nasal congestion is also known to produce adenoid facies, typified by an open mouth posture and an elongated, narrowed face.[7-9]

There are many anecdotal historical reports of mouth breathing and diminished health. In 1889, Hill advocated for treating nasal congestion to lower the number of "stupid children."[10] George Catlin, an American painter during the Civil War era, observed in his book "Shut Your Mouth to Save Your life" that native American Indians who were nasal breathers were healthier, less prone to infectious diseases, and had broader facial features.[11]

Although treating nasal congestion can alleviate sleep-related breathing disorders, overall results in the research literature are mixed. This chapter will describe the physiologic interaction between sleep and sinonasal function, review the diagnostic testing and treatment options of nasal disorders as they relate to sleep function, and summarize the research investigating the relationship between treatment for nasal disorders and OSA.

CRANIOFACIAL ANATOMY AND NASAL PHYSIOLOGY

Human infants are born obligate nose breathers until about 2 to 6 months of age when mouth breathing occurs in addition to nose breathing. This transition is facilitated by laryngeal descent, as the epiglottis, which overlaps the soft palate in newborns, separates away from the soft palate during this time period.[12] It has been proposed that traditional infant feeding methods such as breastfeeding and eating foods that are hard in consistency promote optimal dental formation and arch widening. Corruccini found that communities in the United States that transitioned from hard foods to softer foods produced children with a significantly higher rate of malocclusion.[13] Bottle feeding is also thought to promote malocclusion in the dental literature.[14] It has been suggested that the epidemic of malocclusion in Western, developed societies parallels the rise of sleep-related breathing disorders.[15]

Malocclusion, by definition, is associated with dental crowding and narrowed dental arches. Underdeveloped upper and lower jaws produce crowding of the soft tissues, such as the tongue, turbinates, and nasal septum. Adults with a deviated nasal septum are found to have more craniofacial abnormalities.[16] Another study using cephalometric measurements in 98 children with deviated nasal septums showed significantly increased total facial height, retrusive positioning of the maxilla and mandible, and increased rates of class II malocclusion.[17]

There are numerous conflicting explanations for the origins of a deviated nasal septum. Nasal birth trauma from passing through the birth canal is widely implicated as a major cause of septal deflection, whereas others contradict this explanation.[18] Patients with high-arched palates, dental crowding, and retrognathia are also more likely to have nasal congestion. Since nasal sidewall width

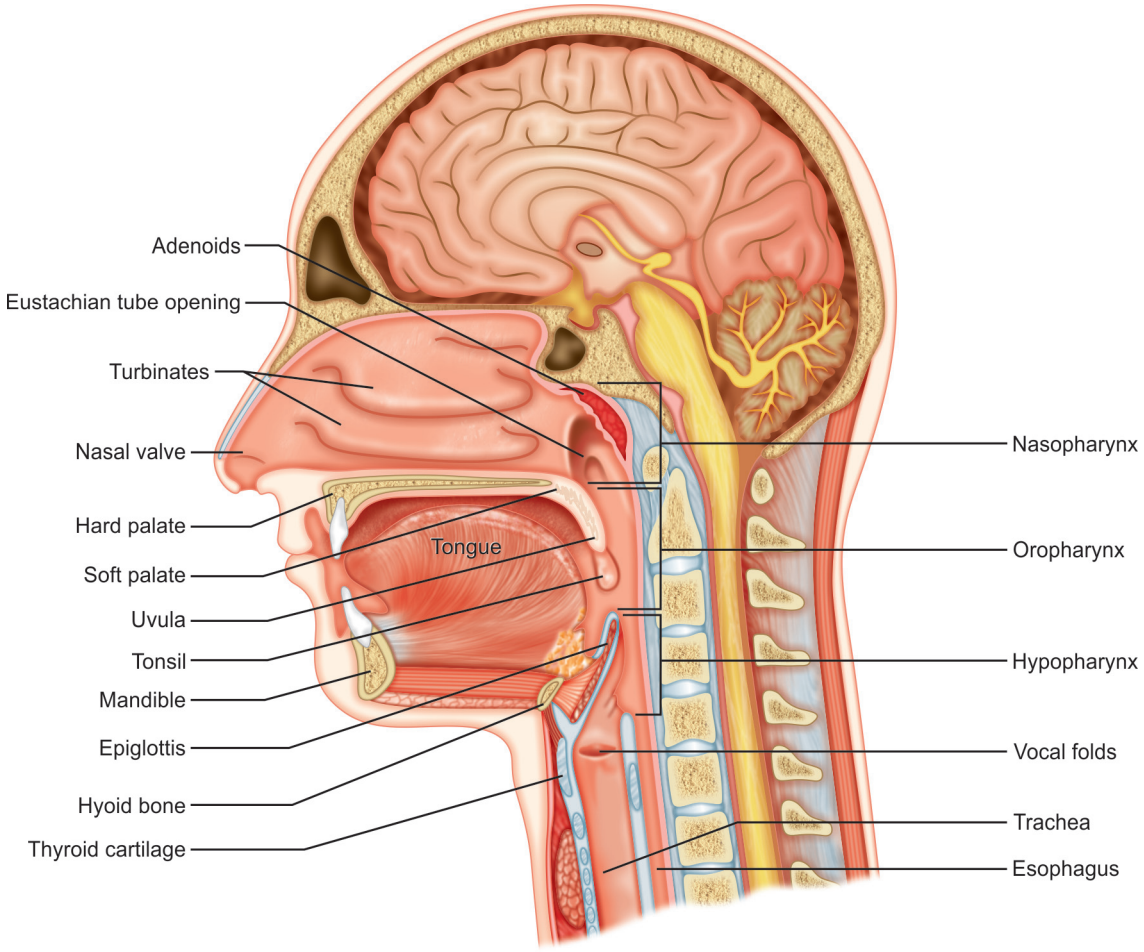

Fig. 19.1: Nasal sidewall anatomy.

is directly related to maxillary intermolar distance, having a high-arched hard palate will also produce a diminished nasal cavity cross-sectional distance. Rapid maxillary (palatal) expansion has been shown to significantly improve nasal cavity cross-sectional volume and lower resistance.[19,20] In addition, due to lack of nasal floor descent, septal buckling or deflections are more likely.

Turbinate Anatomy and Physiology

The nasal turbinates are wing-like, bony structures surrounded by erectile vascular tissue and a mucous membrane covering. They line the lateral nasal sidewalls, in three or sometimes four parallel pairs (Fig. 19.1). Proposed functions of the nasal turbinates include promoting laminar airflow, humidification, filtration, heating, and even an antimicrobial effect from nitric oxide (NO) production.[21]

The turbinates are also regulated by the autonomic nervous system, with alternating congestion and decongestion about every 2 to 4 hours in succession. This is not considered pathologic and overall, nasal resistance does not change. However, in the presence of anatomic narrowing anywhere else in the nose, any degree of turbinate swelling can predispose to symptomatic unilateral or bilateral nasal congestion.

Turbinate vascular constriction is regulated by the sympathetic nervous system, whereas cholinergic parasympathetic stimulation causes vasodilatation, with subsequent erectile engorgement of the veins and cavernous sinusoids. Assuming a recumbent position (especially the lateral position) can cause additional engorgement of the turbinates, leading to nasal congestion. Exercise increases sympathetic discharge, causing vasoconstriction and lowered nasal resistance. Similarly, sympathomimetic

medications such as oxymetazoline diminish nasal congestion due to vasoconstriction. Many antihypertensive medications, due to their antisympathetic properties, can cause vasodilatation of the turbinates, with resulting nasal congestion.

NASAL ANATOMY AND FLOW DYNAMICS

The nasal valve is bounded by the septum medially, the inferior turbinate inferolaterally, and the upper and lower lateral cartilages. It is further subdivided into the internal and external nasal valves. The lower two thirds of the external nose is composed of the paired upper and lower lateral cartilages (Fig. 19.2). The nasal alae are stiffened during inhalation by the action of the dilator nasalis muscle, which is an accessory muscle of inspiration. Depending on an individual's anatomic configuration, ethnic origins, and internal nasal factors, the soft tissue envelope of the lateral nostrils can collapse to various degrees. Significant collapse during nasal inspiration can lead to subjective and objective nasal congestion. Rhinoplasty, which can sometimes weaken the lower lateral cartilages (cephalic trim, etc.), can predispose to nasal valve collapse many years later. Therapeutic options for nasal valve collapse include various over-the-counter nasal dilator devices and surgical procedures.

There are numerous other medical reasons potentially responsible for nasal congestion, including nasal polyps, chronic sinusitis, adenoid hypertrophy, upper respiratory tract infection (URI), allergic rhinitis, or nonallergic, or vasomotor rhinitis. In patients with vasomotor rhinitis, there is a relative dysfunction of the sympathetic nervous system.[22] Woodson et al. found that patients with mild OSA had significant autonomic nervous system abnormalities with decreased adrenergic function.[23] It is presently unclear whether OSA precedes autonomic dysfunction or vice versa.

In addition to the medical etiologies for nasal congestion, other factors such as gravity, hormonal status, and weather changes can also significantly affect nasal airflow patency. Lastly, a number of different medications, especially the alpha antagonists (which attenuate sympathetic activation), are associated with chronic nasal congestion (*see* Table 19.1).[24]

The nasal valve is the most narrowed point in the human upper airway, with the smallest cross sectional area. This creates the highest level of airway resistance. Overall,

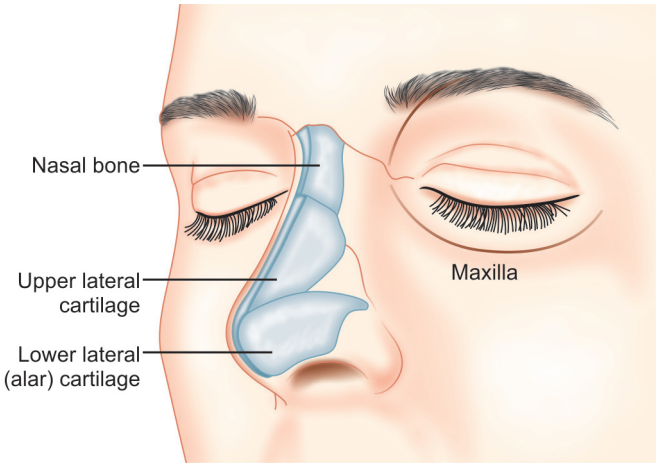

Fig. 19.2: External nasal anatomy.

the nose accounts for about 50–60% of total airflow resistance in the upper airway.[25,84] Nasal airflow resistance is highly dynamic, being affected by nasal anatomy, the nasal cycle, body position, the environment, and various other vasomotor factors.

According to Poiseuille's law, resistance is defined by $R = (8\mu l)/(\pi r^4)$, where R = resistance, l = length of pipe, μ = the dynamic viscosity, and r = the radius of the pipe. According to this formula, even small changes in the radius of the channel can result in large degrees of change in resistance.[25] This model can be applied to nasal airflow and has significant implications for sleep-disordered breathing.

The human upper airway can be described as a Starling resistor (Fig. 19.3), where along a hollow tube, partial obstruction at the inlet (the nose) produces a suction force with negative intraluminal pressures and a collapsible downstream segment (the oropharynx). This effect is exacerbated in the supine sleep position, when nasal resistance is at its highest.

The nose has two types of potential narrowing or collapse: static and dynamic. The geometric volume and configuration of the internal nasal structures can be seen as a static structure (septum, sidewalls, turbinates). However, these dimensions can change slowly from minutes to hours due to edema or vascularity of the turbinates and the mucous membranes of the septum. The nasal valve, which is composed of epithelial skin, cartilage, and mucous membranes, is a dynamic structure, influenced by the volume of airflow and rigidity of the nasal sidewalls. Allergies and an URI can promote nasal congestion and exacerbate airflow resistance, collectively increasing the likelihood of nasal valve collapse.

Table 19.1: Causes of nasal congestion

Structural causes	
Deformities	Space occupying masses
Nasal bones and cartilages	Neoplasm (carcinoma, papilloma, fibroma, etc.)
Nasal septal bones and cartilage	Polyps
Turbinate bones and concha bullosa	Encephalocele
	Foreign body
	Sarcoidosis
Infectious causes	
Rhinosinusitis	
Viral, bacterial, fungal	
Polyps	
Necrotizing (ozena)	
Allergic causes	
Inhalant allergy	
Food allergy	
Nonallergic rhinitis	
Vasomotor reactions	
Drug induced	Recumbency
Antihypertensive	Nasal cycle
Nose drop/spray abuse	Compensatory turbinate hypertrophy with septal deformity
Cocaine abuse	
Birth control pills	Vascular atony of chronic allergic or inflammatory rhinitis
	Rhinitis of nonairflow
Pregnancy and premenstrual "colds"	Laryngectomy
	Choanal atresia
Hypothyroidism	Adenoid hypertrophy
Anxiety and emotional stress	Etc.
Inhalant irritants	
Dust, smoke, tobacco	
Chemical fumes	
Weather changes	

Source: Adapted from Papsidero and Fairbanks.[25]

Any degree of nasal congestion, whether due to internal nasal pathology (deviated septum, turbinate hypertrophy, allergic rhinitis, URI, foreign body, nasal polyps, adenoid hypertrophy, etc.), or from external malformations (nasal valve collapse or even reading glasses), can increase downstream airflow, leading to circumferential retropalatal or oropharyngeal narrowing, palatal fluttering and snoring, or tongue base collapse.

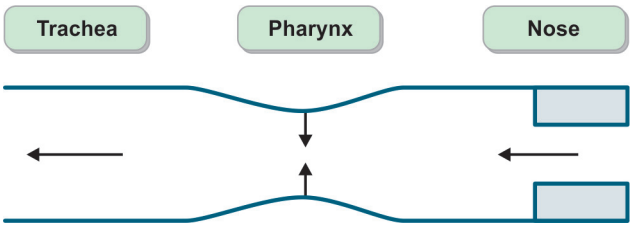

Fig. 19.3: Starling resistor model. Obstruction at the inlet (nose) produces forces that manifest downstream in the collapsible pharynx.
Source: Adapted from Georgalas.[84]

NASAL OBSTRUCTION AND SNORING

Despite the prevalent lay public's view that snoring comes from nasal obstruction, the offending vibrations in fact originate from the uvula and soft palate. With heavy snoring, other soft tissues, such as the tonsils, epiglottis, and tongue base can also vibrate. Numerous studies have shown that snoring by itself without any significant levels of OSA can be detrimental. For example, snoring during infancy has been strongly associated with behavioral problems later in childhood.[26] Acoustic vibrations from snoring have also been associated with a higher rate of carotid artery atherosclerosis.[27]

NASAL OBSTRUCTION AND OBSTRUCTIVE SLEEP APNEA

Nasal packing after surgery was found to worsen sleep quality and cause sleep disturbed breathing.[28,29] Occlusion of nasal breathing in normal individuals has been shown to significantly increase obstructive apneas and sleep fragmentation.[7,30-32] Snoring can be explained by Bernoulli's principle, which states that as the flow of liquid or air increases through a tube, the pressure inside the tube decreases.[33] Since the human upper airway is essentially an elongated tube with multiple points of potential collapse (nose, oropharynx, hypopharynx), the first point of air entry (the nose) can profoundly impact downstream upper airway collapsibility. Snoring and apneas can potentially occur when negative intrathoracic pressures present against an upstream resistance and compliant upper airway.[34]

Nasal congestion is often associated with mouth breathing. Although this may seem to alleviate upper airway obstruction and to normalize breathing, the opposite is seen.[25] Olsen et al. demonstrated that open-mouth posture creates an unstable lumen by producing a posterior-superior displacement of the genioglossus muscle.[31]

Mouth breathing is associated with up to 2.5 times higher total resistance.[35] NO is normally produced in the nasal and sinus cavities and is a potent vasodilator in the lungs, reducing ventilation–perfusion mismatch, and improving overall pulmonary oxygenation.[36] Obstructed nasal breathing can inhibit this important process.

The nasopulmonary reflex is well known within the medical literature.[37,38] There is evidence suggesting that receptors in the nasopharynx may affect upper airway muscle tone. White et al. blocked nasal and nasopharyngeal receptors with 4% lidocaine in 10 male subjects.[39] These patients were found to have a fourfold increase in sleep-disordered breathing events, with equal amounts of obstructive and central events. Minute ventilation was found to be greater during nasal breathing compared with oral breathing, suggesting that nasal breathing stimulates breathing.[40] Another study found that vasoconstriction of the nasal mucous membranes with phenylephrine had no relationship to upper airway muscle activity.[41] All these studies taken together suggest that nasal breathing increases ventilation by stimulation of receptors in the nose, and that dilating the nasal airway has no effect on upper airway patency. However, occluding the nose in even normal subjects may decrease upper airway patency and trigger sleep disordered breathing.

Allergic rhinitis has been strongly associated with OSA. McNicholas et al. found that people with seasonal allergic rhinitis had significantly higher rates of nasal resistance, sleep fragmentation, and obstructive apneas during the allergy season compared with periods when patients were asymptomatic.[42] Similarly, subjects with nasal congestion due to allergy are 1.8 (odds ratio) times more likely to have moderate to severe sleep disturbed breathing compared with controls.[32] This may explain the high rates of fatigue and sleep complaints in people with allergic rhinitis.

NASAL OBSTRUCTION AND UPPER AIRWAY RESISTANCE SYNDROME

Upper airway resistance syndrome (UARS) is described as frequent sleep-related upper airway resistance and flow limitation that causes arousals but not meeting the criteria of apnea or hypopnea on polysomnography. This can lead to fragmented sleep and excessive daytime sleepiness (EDS).[43] Guilleminault studied EDS patients using an esophageal pressure transducer, finding increasingly negative inspiratory pressures with diminished oral and nasal airflow.[44]

The UARS episodes are generally short, with electroencephalographic arousals and immediate reduction in upper airway resistance. Negative intrathoracic pressure is thought to stimulate upper airway mechanoreceptors, leading to these arousals.

Bahamman et al.[45] studied the effect of external nasal dilators (Breathe Right, sleep position, and sleep stage on UARS. Treatment significantly reduced stage I sleep and desaturation time, but did not change any other sleep parameters, including arousals. In this study, sleep position and sleep stages were found to have significant association with sleep-disordered breathing in UARS.

NASAL OBSTRUCTION AND FACIAL GROWTH IN CHILDREN

Allergic rhinitis and adenotonsillar hypertrophy are commonly seen in children, with both conditions potentially leading to nasal congestion. Adenotonsillectomy results in significant improvement of sleep-related breathing disorders ranging from 60% to 80%.[46,47] Similar to the adult literature, treating allergic rhinitis in children with nasal steroids lowers sleep-related breathing disturbances.[48] A switch from nasal to oral breathing has been shown to promote abnormal craniofacial growth patterns, with an elongated, narrow face with an open-mouth posture.[49] Occlusion of nasal breathing in monkeys during development resulted in downward and backward rotation of the mandible, upward and backward growth of the condyle, divergent gonial angle, and an anterior open bite.[50] Sometimes called adenoids facies, these children will also have a short upper lip, prominent upper incisors, a high-arched hard palate, and a head-forward posture.[51]

MEDICAL TREATMENT AND OUTCOMES

Decongestants

There are numerous anecdotal published reports of snoring or OSA resolution by using a nasal dilator strip, pill, or nasal spray. Undoubtedly, some of these over-the-counter options may work to various degrees, but none have been proven to help significantly on a consistent basis. The degree to which these options work may depend on the degree to which nasal congestion alters downstream pharyngeal collapsibility.

The most common over-the-counter options are nasal decongestants. Application of nasal oxymetazoline

in patients with OSA and severe nasal congestion resulted in reduced mouth breathing and reduced OSA severity, but it did not significantly alleviate OSA.[52] A randomized, placebo-controlled, cross-over trial on 12 patients found similar results, with significantly improved nasal resistance but did not produce clinically significant improvement in OSA.[53] A combination of oral pseudoephedrine and domperidone, a promotility agent, was found to significantly diminish snoring in the majority of patients compared with a placebo group.[54]

Nasal Dilator Strips

There are numerous over-the-counter options that stiffen or dilate the nostrils. Nasal dilatation devices can be applied internally or externally. The most commonly applied devices are external adhesive strips that lift up the nasal alar sidewalls. The Breathe Right brand is an externally applied adhesive strip that pulls open the nares. There are also a number of internally applied nasal valve stents or alar dilator devices. (Nozovent, Brez, Breathe with EEZ, Sinus Cones, etc).

Numerous studies have shown significant improvements in snoring intensity using various nasal dilator options. In one study, application of Breathe Right was found to significantly diminish snoring intensity and improve subjective sleep ratings, but only in stage I and II sleep. Snoring intensity remained the same in deep (slow wave) sleep and in rapid eye movement sleep.[55] Another study reported significant improvements in snoring intensity, mouth dryness, and the Epworth Sleepiness Scale (ESS).[56] Schonhofer et al. also reported significant improvements in snoring with application of Nozovent.[57] While Breathe Right strips were found to have no significant improvements in respiratory parameters as measured by polysomnography, one study did show significant subjective improvement in reported nasal breathing.[58]

Application of Nozovent (an internal nasal dilator) had no significant effect on sleep-related breathing parameters in two studies[59,60] but did show significant improvement in another study, with a mean decrease in the apnea index by 47% on average.[61] A Japanese study reported 72.2% improvement in snoring, and 16% of patients had significant improvements in sleep apnea using Nozovent.[62]

In another randomized placebo-controlled crossover trial of 10 patients, treatment of nasal congestion with external nasal dilator strips and topical decongestion (oxymetazoline) was associated with significant reduction in nasal resistance, mouth breathing, and sleep architecture, but there was only a modest reduction in OSA severity (12 points) with no significant difference between the treated group versus the control group.[63]

Anti-Inflammatory Agents

Treatment for allergic rhinitis with topical agents has also been described to treat OSA. Application of fluticasone was found to significantly lower the apnea hypopnea index (AHI) (10.7 to 5.8, $p = 0.04$) in a randomized, triple-blind, placebo-controlled, parallel-group pediatric cohort with adenotonsillar hypertrophy.[64] Intranasal corticosteroid application was found to significantly lower the AHI in treated versus control patients (11.9 vs. 20, $p < 0.05$) in an adult population by possibly lowering nasal resistance.[65] In this study, there was a strong correlation between change in AHI and nasal airway resistance. Application of intranasal budesonide significantly reduced the severity of mild OSA as well as adenoid hypertrophy in children.[66] One study found no significant change in the AHI or objective sleep parameters. Despite some studies that showed significant lowering of the AHI on polysomnography,[49] most patients still had significant residual OSA.

Treatment with montelukast and intranasal budesonide was found to significantly improve residual OSA after adenotonsillectomy in a pediatric population.[67]

SURGICAL TREATMENT AND OUTCOMES

Nasal Surgery and Snoring

Various studies report on the effect of nasal surgery on snoring, with some reporting reductions of snoring episodes in 50–70% of treated patients.[68-70] Most of these studies used subjective questionnaires or visual analog scales. In contrast, a Finnish study reported that snoring time and intensity did not improve significantly.[71]

Nasal Surgery and Obstructive Sleep Apnea

A number of studies report on the effectiveness of nasal surgery for the treatment of OSA. Friedman et al. studied 50 consecutive patients who underwent submucous resection (SMR) of the nasal septum, with or without SMR of the inferior nasal turbinates.[72] They found no significant

improvement in objectively measured sleep apnea parameters but did notice reduced continuous positive airway pressure (CPAP) levels after nasal surgery. In another study by Verse et al, 26 adults were prospectively studied and divided into simple snorers and those with OSA.[73] Polysomnography revealed a surgical response rate (>50% reduction in postoperative AHI and the final AHI <20) of 15.8% for the apneic group. As a whole, the AHI dropped from 31.6 to 28.9, which was not statistically significant. However, the number of arousals and the level of daytime sleepiness were significantly reduced. In addition, in four patients, the AHI was higher in the postoperative polysomnogram.

Series et al. studied 20 adults prospectively and also found no significant differences in respiratory parameters, despite increased time spent in REM sleep and lowered nasal resistance.[74] In four patients with normal posterior airway space and mandibular plane to hyoid bone distances, they noted normalization of respiratory parameters. A follow-up study on this finding enrolled 14 OSA patients (with normal posterior airway space and mandibular plane to hyoid distance), who underwent nasal surgery (septoplasty, turbinectomy, polypectomy). All but one had normalization of the AHI <10, and sleep fragmentation improved significantly from 23.9 (3.3/hour) at baseline to 10.6 (2.5/hour) arousals after surgery.[75]

Li et al. also found no significant improvement in polysomnographic parameters, but like other studies, they found significant improvements in the ESS and nasal resistance.[76] Of note, those with a lower body mass index, lower levels of daytime sleepiness, and lower tongue position had significantly higher success rates (50% vs. 3%; $p < 0.001$). In a different study, Li et al. found that despite significantly improved disease-specific and quality-of-life parameters, there was no statistically significant improvement in objective polysomnographic data.[77]

Surgical success rates from the literature vary from 0%- to 33%.[74-76,78,79] Unfortunately, different criteria for surgical success are often used, necessitating cautious interpretation of data in light of this issue.

Nasal surgery may offer significant quality-of-life improvements, but objective results are mixed. The choice of nasal procedures will depend on the patient's individual anatomic needs, as well as on the evaluation and recommendations of the surgeon.

Septoplasty with or without turbinate surgery can be offered to most people with chronic nasal congestion. However, one simple test to see if the patient will require nasal valve surgery is as follows: Have the patient use oxymetazoline 30 minutes prior to sleep for three nights. On the third night, have the patient use Breathe Right strips in addition to the oxymetazoline. For the next two nights, use the strips only. Depending on the patient's response when using only the decongestant spray versus nasal dilator strips or both, a reasonable decision can be made in deciding whether or not to add a nasal valve procedure to the intranasal procedures. If there is no clear advantage in using nasal dilator strips, the patient must be counseled that there is a small chance that nasal valve collapse may persist, and that a secondary procedure may be needed. The other option is to continue using nasal dilator strips.

Nasal Surgery and Nasal CPAP Adherence

Despite disappointing results with nasal surgery in treating OSA, nasal surgery can significantly improve subjective and objective nasal breathing measures, quality-of-life measures, as well as CPAP tolerance and compliance.[80] Nakata et al. reported on 12 patients who had nasal congestion and were intolerant of CPAP. All 12 patients became CPAP tolerant after nasal surgery. In five patients, where CPAP titration was performed, the average pressure dropped significantly from 16.8 to 12 cm H_2O. The ESS dropped significantly from 11.7 to 3.3, but there was no significant change in the number of apneic or hypopneic events. They concluded that increased nasal resistance is a determinant of CPAP intolerance.[81]

Nasal Surgery and Oral Appliance Therapy

Zeng et al. reported that increasing nasal resistance correlated inversely with oral appliance therapy treatment outcome.[82] Marklund et al. report that in their retrospective review of 630 subjects, women who reported subjective nasal congestion were less likely to respond to oral appliance therapy.[83]

Although there is currently no role for nasal surgery as a single modality for OSA, it is still useful to improve nasal breathing, as well as to improve CPAP and oral appliance adherence, and as part of multilevel surgery. Patients who do not respond to medical therapy for nasal congestion are obvious candidates for nasal surgery, but even those who do respond may wish to consider nasal surgery to avoid prolonged pharmacologic regimens.

PHYSICAL EXAMINATION OF THE NOSE AND UPPER AIRWAY

Mirror Test

In a newborn or an infant, placing a mirror underneath each nostril can reveal nasal patency when fogging is seen. This is a commonly performed procedure to test for choanal atresia.

Examination of the Internal Nasal Cavity

Direct visualization of the anterior nasal cavity can easily be performed using either a stainless steel nasal speculum or a lighted handheld instrument with a disposable nasal speculum. A rigid or flexible fiberoptic endoscope can provide much more useful information over a traditional view with the naked eye.

Before inspecting the internal nasal cavity, notation must be made of the configuration of the external nasal structures, including the presence of a dorsal hump, deviated dorsum or tip, and the positioning and collapsibility of the nostrils.

The Cottle maneuver is performed by placing both examiner's index fingers beside the patient's nostrils, and simultaneously pressing and lifting the cheek skin upward and outward. If the patient can inhale more freely through the nose, the test is called positive. Alternatively, two ends of a cotton-tipped applicator can be placed inside the nostrils and lifted outward.

Anteriorly, the nasal septum is usually midline, but in patients with OSA, it is often deflected to one or both sides. There can also be spurs at the bony-cartilaginous junction. Sometimes, the inferior part of the septum that normally rests on the maxillary crest has slid off to one side, sitting on the floor of the nasal cavity, while the middle part of the septum is severely deviated to the contralateral side.

Attention is next paid to the nasal turbinates. The color, any presence of edema, purulence, bogginess, or hypertrophy is noted. Sometimes there is polypoid degeneration of the polyps. The middle meati are next visualized for purulence, polyps, concha bullosa, and patency.

The nasal roof and the Eustachian tubes are then inspected for any obvious pathology. The presence and/or size of the adenoids are then noted. A nasopharyngeal examination can be performed using an endoscope or indirect mirror nasopharyngoscopy.

Nasal Endoscopy

The posterior soft palate and oropharyngeal structures are then visualized endoscopically to complete the remaining portions of the examination for snoring and OSA (📹 19.1). Briefly, the patient is examined upright and supine. The Mueller's maneuver (forceful inhalation through the nose while the examiner pinches the nostrils closed around the flexible endoscope) is performed to determine retropalatal collapsibility. The posterior airway space, and the position of the tonsils, tongue base, and epiglottis are noted in the sitting and supine positions. Many patients will have significant narrowing of the posterior airway space in the supine position, which can be significantly improved by having the patient advance the lower jaw forward with minimal jaw opening. Significant opening of the posterior airway space can potentially predict better outcomes with a mandibular advancement device. Minimal to no movement of the tongue base and epiglottis is a contraindication for oral appliance therapy.

DIAGNOSTIC TESTS

Options for Nasal Airflow and Resistance

There are a number of objective methods of measuring nasal obstruction, including nasal peak flow, rhinomanometry, and acoustic rhinometry. Depending on the clinical needs, any of the following options can be used for evaluating nasal obstruction in a patient with OSA.

Nasal peak flow testing, although inexpensive, is highly patient effort dependent, and results can vary widely. A modified peak flow device (inspiratory spirometer) is typically used. Peak flow correlates well with nasal resistance and is most useful in detecting large changes in nasal airflow.

Rhinomanometry uses pressure transducers to measure airflow and resistance in the nasal cavity. Placement of the posterior rhinomanometer properly in the oropharynx can be challenging for some patients. It can be a useful tool to measure airway patency before and after any medical intervention or surgical procedure.

Acoustic rhinometry uses reflected sounds in the nasal cavity to produce a two-dimensional cross-sectional area that approximates nasal volume. Nasal resistance cannot be measured easily with this option. Usually taking <10 seconds to perform, it can be easily administered, even to children.

Radiologic Imaging

Computed tomographic imaging and magnetic resonance imaging for nasal obstruction is a relative indication. Most cases of a simple deviated nasal septum can be easily diagnosed without any radiologic imaging, especially if a thorough endoscopic examination is performed. Patients with chronic sinusitis or nasal polyposis will usually require imaging to properly address these respective issues. Lateral soft tissue imaging can be helpful in younger children to evaluate for adenoid or lingual tonsillar hypertrophy.

MANAGEMENT STRATEGIES FOR NASAL CONGESTION AND OBSTRUCTIVE SLEEP APNEA

Nasal congestion is commonly seen in patients with OSA. Treatment always begins conservatively, by first implementing avoidance measures and then treating any underlying inflammatory factors such as allergic rhinitis or sinusitis. Having the patient follow a strict antireflux protocol can also complement therapy since reflux is potentially associated with OSA and even nasal congestion. Patients are strongly encouraged to avoid eating or ingesting alcohol within 3 to 4 hours of bedtime. Routine nasal saline irrigation is also encouraged. When appropriate, topical intranasal steroids with or without oral anti-inflammatory medications (steroid, antihistamine, or antileukotriene products) are considered. Allergy evaluation with appropriate avoidance measures and testing with possible immunotherapy should also be considered.

Patients with nonallergic rhinitis might also benefit from intranasal steroids, or a topically applied antihistamine. If rhinorrhea is a major symptom, ipratropium nasal spray can be helpful. Oral decongestants can also be considered in selected patients for short-term use but may be contraindicated in patients with hypertension or who are sensitive to the stimulant effects. Topical decongestants can also be used, but only for 3 to 5 days, due to the possibility of rebound nasal congestion. There should be a low threshold for nasal surgery when conservative options fail, for craniofacial and structural factors, as well as nonallergic nasal conditions often do not respond consistently to medical therapy. Antibiotics and oral steroids may be considered for patients with nasal polyps or chronic sinusitis.

Patients with chronic nasal congestion often struggle with CPAP. In addition to medical treatment of nasal congestion, optimal levels of humidification and correction of potential air leaks are important considerations.

The choice of nasal procedures will depend on the patient's clinical situation. Most people will undergo septoplasty with or without a turbinate procedure, but considerations for nasal valve surgery or functional endoscopic sinus surgery are always an option. Some patients will have hypertrophied tonsils and adenoids. Although adenotonsillectomy in adults is less effective for OSA than in pediatric patients, the decision for surgery must be made on a case-by-case basis.

If nasal surgery is being considered, the patient must be counseled that the procedure is unlikely to significantly alleviate OSA, and that the main purpose of the proposed procedure is to improve nasal breathing, and potentially to facilitate CPAP or oral appliance therapy.

If the patient rejects or is not a candidate for CPAP or oral appliance therapy, nasal surgery can be safely performed in conjunction with multilevel procedures, including simultaneous palatal and/or tongue base procedures. Proper anesthesia care and close monitoring by the operating team and nursing staff can minimize any risks when the patient undergoes multilevel sleep apnea surgery. If the nose is addressed in conjunction with other pharyngeal procedures, nasal packs and/or splints are discouraged to maintain nasal patency immediately after surgery and to have access to a nasal airway in case the need arises.

SUMMARY

Nasal obstruction and OSA frequently coexist. Physiologic pathways in which nasal obstruction can lead to or contribute to OSA include blocking the nasopulmonary reflex, Starling resistor model, reducing NO production and delivery, and shunting of breathing through an unstable oral airway.

Nasal steroids have been proven to improve objective scores and subjective sleep quality on sleep studies in patients with allergic rhinitis, but they are not to be considered a standard form of treatment for OSA.

Nasal surgery is not indicated as a primary mode of treatment for OSA, but for selected patients, it can significantly improve subjective and objective nasal breathing measures, as well as to improve CPAP and oral appliance tolerance and adherence. In some patients, it may also improve snoring severity and improve quality-of-life outcomes.

VIDEO LEGEND

Video 19.1: Nasal endoscopy during upper airway examination

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CHAPTER

20

Sinonasal Effects of Drugs and Toxins

Carrie E Flanagan, Sarah K Wise

INTRODUCTION

The sinonasal cavity and mucosa are exposed to numerous drugs and toxins. For rhinitis and rhinosinusitis, systemic and topical medications combat infection and inflammation. Medications for other conditions may result in undesired rhinologic symptoms and abnormalities. Daily habits and home or work environments can impact sinonasal health due to exposure to allergens, irritants, and carcinogens. Furthermore, the nasal cavity has become an area of intense research for drug and vaccine administration. Each of these topics will be addressed in this chapter.

MEDICATIONS FOR RHINITIS AND RHINOSINUSITIS

Treatment of rhinitis and rhinosinusitis involves various classes of medications. Several other chapters in this book discuss the management of infectious and inflammatory rhinologic conditions. Thus, the majority of these medications will be mentioned only briefly in this section. Please refer to Table 20.1 and other chapters of this text for additional information on oral and topical antihistamines, leukotriene inhibitors, topical and systemic decongestants, systemic antimicrobials and antifungals, topical antimicrobials and antifungals, xylitol, and surfactants. Rhinitis medicamentosa caused by topical decongestants, topical and systemic steroids, and saline therapy will be discussed further.

Decongestants

Topical decongestant use for as short as 3 days can cause rebound nasal congestion, whereas prolonged use results in rhinitis medicamentosa. Rhinitis medicamentosa is characterized by rebound vasodilation, nasal obstruction, mucosal edema and erythema, and reduced efficacy of the topical decongestant.[7] Histologic changes include ciliary loss, ulceration, mixed inflammatory cell infiltration, goblet cell hyperplasia, increased submucosal glands, and enlarged gaps between capillary endothelial cells.[7] The mainstay of treatment includes cessation of topical decongestants with symptom control using systemic decongestants, topical antihistamines, and topical and systemic corticosteroids. Only topical steroids prevent rebound congestion during topical decongestant withdrawal.[7] If surgery is considered in prolonged topical decongestant users, the risk of intraoperative bleeding is increased[7] (Table 20.1).

Benzalkonium chloride (BKC) is a quatenary ammonium preservative used in many pharmaceutical nasal sprays since 1935.[6,9] BKC acts by damaging the cell wall of microorganisms. However, there have been multiple reports that BKC may be toxic to nasal epithelium or may exacerbate rhinitis medicamentosa.[6,9] A 2004 meta-analysis revealed eight studies that showed no significant effect and 10 studies that showed a negative effect of BKC on nasal epithelia.[9] BKC will continue to be used, unless further research can definitively show BKC is harmful or a new preservative with a better safety profile is developed.[9]

Table 20.1: Medications used for rhinitis and rhinosinusitis[1-27]

Medication class	*Mechanism of action*	*Clinical indications*	*Medication benefits*	*Side effects*	*Efficacy*	*Other comments*
Oral antihistamines	Histamine-1 receptor antagonist Alters histamine receptor configuration	AR, NAR	Sneezing +++ Itching +++ Congestion +/- Rhinorrhea ++	Sedation (at recommended doses in first-generation antihistamines and cetirizine), anticholinergic effects		
Intranasal antihistamine	Histamine-1 receptor antagonist Alters histamine receptor configuration	AR, NAR	Sneezing ++ Itching ++ Congestion ++ Rhinorrhea +	Systemic absorption may result in sedation	Equal or greater than oral second-generation antihistamines for SAR Less than INCS for AR	
Leukotriene inhibitors	Binds and inhibits cysteinyl leukotriene receptor	AR	Sneezing + Itching + Congestion ++ Rhinorrhea +		Less than INCS for AR Additive effect with antihistamines	Consider in patients with AR and asthma Onset of action occurs within 48 hours
Oral decongestants	Activation of postsynaptic vascular α-adrenergic receptors	Nasal congestion	Sneezing – Itching – Congestion +++ Rhinorrhea –	Hypertension, insomnia, irritability, tremor, palpitations due to effects on CNS and cardiovascular α-1 and α-2 receptors		Cautious use in cerebrocardiovascular disease, hyperthyroidism, closed angle glaucoma, bladder neck obstruction Children <6 years: agitation, psychosis, ataxia, hallucinations, death reported
Topical decongestants	Nonselective α-agonist	Nasal congestion	Sneezing – Itching – Congestion +++ Rhinorrhea –	Reports of cerebrocardiovascular events Rhinitis medicamentosa		Patients with habitual use: increased risk of intraoperative bleeding in nasal/sinus surgery
Oral corticosteroids	Interaction with the cytosolic glucocorticoid receptor with translocation into the nucleus resulting in altered gene transcription in cells involved in immune and inflammatory responses	RS with and without nasal polyps; AFS	Improved nasal polyposis pre-/intra-/post-operatively	See Table 20.2		

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Medication class	*Mechanism of action*	*Clinical indications*	*Medication benefits*	*Side effects*	*Efficacy*	*Other comments*
Topical corticosteroids	Interaction with the cytosolic glucocorticoid receptor with translocation into the nucleus resulting in altered gene transcription in cells involved in immune and inflammatory responses	AR, NAR, rhinitis medicamentosa, vasomotor rhinitis, CRS with and without polyps	Sneezing ++ Itching ++ Congestion ++ Rhinorrhea ++ Reduce/prevent mucosal inflammation, polyp recurrence	Nasal or throat irritation, epistaxis Inhibition of growth in children has been reported with long-term, high-dose use	Equal to or more effective for AR than antihistamines, LTRAs or nasal cromolyn Maximum effect may take several weeks	Clinical response is similar for different formulations ~30% of INCS deposited in the nose Newer agents have systemic bioavailability of <1%
Intranasal cromolyn	Decreases mast cell calcium influx, stabilizes mast cell membranes, prevents mediator release	AR	Sneezing + Itching + Congestion +/- Rhinorrhea +	Excellent safety profile—safe to use in young children and during pregnancy		Must be used prior to allergen exposure Medication duration is 4-8 hours, requiring ≥ QID dosing
Topical anticholinergics	Locally active anticholinergic	AR, NAR, common cold	Sneezing – Itching – Congestion – Rhinorrhea +++		Additive effect with INCS	Caution: elderly, glaucoma, prostatic hypertrophy
Mucolytic (guaifenesin)	Increases volume and decreases viscosity of secretions; likely vagal stimulant		Thins postnasal secretions	Dizziness, nausea, vomiting		Effects are rarely profound
Systemic antibiotics	Various	ARS: No improvement or worsening of symptoms after 7–10 days CRS with acute exacerbation	Bacteriostatic or bacteriocidal effects	Numerous, dependent on specific antibiotic		Potential for antibiotic resistance
Topical antibiotics	Various	CRS: stable and acute exacerbations in postsurgical patients (low-level evidence)	Bacteriostatic or bacteriocidal effects	Risk of systemic absorption is unknown		Optimal nebulized particle size is <5 μm No evidence to support delivery via a nasal spray

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Medication class	*Mechanism of action*	*Clinical indications*	*Medication benefits*	*Side effects*	*Efficacy*	*Other comments*
Oral antifungals	Itraconazole inhibits fungal cytochrome P450 oxidase-mediated synthesis of ergosterol	Considered for AFRS (evidence is lacking)		Hepatotoxicity Cardiotoxicity if administered with several other medications		Avoid in patients with cardiac or hepatic disease May have anti-inflammatory properties
Topical antifungals		Routine use is not currently recommended				
Surfactants	Soluble in water and organic solutions, affect how other molecules behave in solution, decrease mucous viscosity and surface tension, alter the microbe–surface interface Alter microbial cell membrane permeability and cause disruption	Considered for refractory CRS with thick crusting, mucous, or biofilms			Surfactants in Johnson & Johnson baby shampoo (PEG-80 sorbitan laurate, cocamidopropyl betaine, and sodium trideceth sulfate) have shown antibacterial, antibiofilm-forming properties, and clinical efficacy in managing refractory CRS	
Xylitol	Naturally occurring sugar alcohol, antibacterial & antibiofilm properties	CRS			As an additive to saline irrigations has demonstrates improvement in CRS symptoms	

(AFRS: Allergic fungal rhinosinusitis; AR: Allergic rhinitis; ARS: Acute rhinosinusitis; CNS: Central nervous system; CRS: Chronic rhinosinusitis; INCS: Intranasal corticosteroids; NAR: Nonallergic rhinitis; RS: Rhinosinusitis; SAR: Seasonal allergic rhinitis).

Corticosteroids

Corticosteroids are used frequently in rhinology; however, their exact mechanism of action is incompletely understood. They inhibit the proliferation, differentiation, recruitment and activation of inflammatory cells.[10-13] Corticosteroids may limit the availability of interleukin (IL)-1, IL-2, IL-3, IL-5, IL-6, granulocyte-macrophage colony-stimulating factor, fibroblast growth factor, prostaglandins and TNF-α[3-5,17] (Table 20.1).

Oral corticosteroids are commonly used to treat chronic rhinosinusitis (CRS). A recent meta-analysis determined there is a lack of high-quality evidence to support their use in patients without nasal polyps. However, short-term oral corticosteroid[12] use in patients with CRS with polyposis is supported. A benefit has also been shown in subgroups of nasal polyp patients pre- and postoperatively and allergic fungal rhinosinusitis patients postoperatively. Optimal dose and duration still remain to be defined.[13,14] Side effects of oral steroids are numerous and poorly understood (Table 20.2). Prescribing physicians should be knowledgeable of potential side effects, and they should be discussed with patients.[13-18]

Intranasal corticosteroids (INCSs) are used for a variety of sinonasal conditions. Clinical response among the different INCS formulations is fairly consistent.[2] Approximately 30% of INCS is deposited in the nose, with the amount of deposition dependent on the lipophilicity of the drug. The remaining 70% is swallowed and subject to first pass metabolism. Newer agents have systemic bioavailabilities < 1%, making systemic effects unlikely.[1,21] There have been no reports of clinically significant effects of INCS on the hypothalamic–pituitary–adrenal axis in adults or children based on cortisol levels.[21] However, serum cortisol levels are not the most accurate measure of systemic corticosteroid absorption. Hence, long-term studies that explore more accurate measurements of adrenal gland activity are necessary.[22] Inhibition of growth in children has been reported with intranasal beclomethasone dipropionate use for 1 year at twice the recommended dose. No formulations show inhibited growth in children at recommended doses.[2,22] There is no evidence of increased intraocular pressure or cataract formation with use up to 1 year.[22]

Currently, only metered dose nasal sprays are Food and Drug Administration (FDA) approved, but these result in the majority of drug distribution in the anterior nasal cavity.[12] Off-label use of topical nasal steroids has been explored to achieve improved delivery to the sinonasal mucosa in postsurgical patients. Commonly used preparations include budesonide irrigations (0.25 or 0.5 mg/2 mL in 240 mL of saline), or intranasal dexamethasone ophthalmic drops (0.1%), prednisolone ophthalmic drops (1%), and ciprofloxacin/dexamethasone otic drops (0.3%/0.1%).[20] These modalities have shown greater drug deposition in the sinus cavities compared with nasal sprays.[12] Budesonide irrigations result in improved symptom and endoscopy scores without evidence of cortisol suppression after prolonged use. Steroid drops have caused rare cortisol suppression. The dosage and treatment duration with these formulations remains to be defined.[20,24]

Topical Therapies

Theoretically, topical medications result in a higher concentration of medication at the sinonasal mucosal target while simultaneously avoiding systemic side effects. The main challenge of topical therapies is adequate and effective drug delivery. Anatomically, nasal polyps, septal deformities, or mucosal edema may limit the delivery of topical therapies. Topical penetration into nonoperated sinuses is very limited, because ostial size is the main factor determining drug deposition.[12,26-30] The frontal and sphenoid sinuses are essentially inaccessible preoperatively, whereas the maxillary sinus requires an ostium of > 4 mm to obtain penetration.[26] Drug deposition also relies on flow, with higher flow resulting in better deposition.[27,28] Nebulizers and nasal sprays have limited distribution. Less than 50% of most low volume applications reach the middle meatus. However, despite having the best distribution of available delivery devices, large volume, positive pressure irrigations still only result in 1–5% of the irrigation solution remaining in the sinuses.[26,29] Mucociliary clearance (MCC) does not play a role in drug distribution with nebulization or high-volume irrigations.[23] Finally, studies demonstrate that particle sizes can range from less than 5 μm to greater than 12 μm for optimal deposition.[27]

Saline

Nasal saline irrigations are used as an adjunct treatment for rhinitis and rhinosinusitis, with multiple beneficial effects such as improved inflammation, MCC, discharge, and mucosal edema. Saline irrigations facilitate removal of blood, mucous and debris, improve symptom scores, reduce medication use, and improve postoperative healing.[22,28] Rare adverse effects include local irritation, ear

Table 20.2: Potential side effects of oral corticosteroids[14-18]

Organ/system	*Observed effects*	*Mechanism*	*Comments*
Adipose tissue	Cushingoid changes (truncal obesity, moon facies, buffalo hump)	Redistribution of adipose tissue	Incidence > 60% with long-term use at a daily dose ≥ 20 mg but can occur with low doses Higher risk: higher doses, longer treatment duration, women, age < 50, higher initial BMI, high caloric intake
Skin	Cutaneous atrophy, increased fragility, ecchymosis, striae, purpura, acne, hirsutism	Reduced keratinocyte mitotic activity, flattening of ridges, loss of ground substance, decreased fibroblast size	Atrophy and ecchymoses often reversible after discontinuation; striae not reversible
Bone	Bone loss (osteoporosis); avascular necrosis	Bone loss: decreased intestinal calcium absorption, increased urinary calcium excretion, upregulation of PTH, altered androgen production, osteoblast inhibition and apoptosis, osteocyte apoptosis Avascular necrosis: unclear etiology—embolic events, hyperviscosity of blood, hypertrophy of marrow fat cells, bone edema due to damage to venous endothelial cells, cellular cytotoxic factors	Bone loss: starts at the beginning of treatment and maximizes at 6 months; primarily affects trabecular bone; risk of bone loss and fracture increases with increasing dose; calcium and vitamin D supplementation can reduce risk and is recommended. Fracture is one of the most frequently reported adverse effect associated with corticosteroid use Avascular necrosis: primarily in femoral heads; correlated dose and duration of treatment (has been seen with cumulative dose as low as 290 mg of prednisone in 7 days); estimated risk – 0.03%
Muscle	Atrophy; myopathy	Type IIb fiber atrophy; interference with skeletal muscle oxidative phosphorylation, protein synthesis, muscle membrane excitability and carbohydrate metabolism	Usually affects proximal musculature; gradual resolution after cessation
Wound healing	Decreased wound healing	Decreased macrophage influx, delayed re-epithelialization, decreased fibroblast response, slowed angiogenesis, inhibition of collagen synthesis and wound maturation	No accurate data regarding dose or time to occurrence, although longer periods and medium to high dosing are thought to be required
Immune system	Immunosuppression	Decrease in peripheral leukocytes; altered neutrophil and antigen presenting cell function; decreased expression and release of inflammatory mediators	Increased risk of infection, including opportunistic infections, possible increased risk of malignancy

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Organ/system	*Observed effects*	*Mechanism*	*Comments*
Endocrine	Hyperglycemia	Increased hepatic gluconeogenesis, increased proteolysis, decreased glucose utilization in peripheral tissues, decreased insulin binding by hepatocytes and adipocytes	Hyperglycemia: can occur within 12 hours of starting treatment; effects normalize after cessation
	Adrenal suppression	Negative feedback on CRH and ACTH production	Adrenal suppression: generally occurs with high dose or long duration of therapy; suppression can occur low doses and short courses; suppression last for many weeks after treatment
	Growth and sex hormone inhibition	Inhibition of HPA axis	
Cardiovascular	Hypertension, atrial fibrillation/flutter, myocardial infarction, possible cerebrovascular disease	Hypertension—primarily caused by volume overload due to increased renal sodium resorption	Hypertension occurs in at least 20% of patients and is dose dependent; cessation often results in normalization
		Cardiovascular disease—increased cardiac fibrosis; hyperglycemia, increased BMI, may increase serum lipids	Risk of myocardial infarction may be 40–60% higher in those who use corticosteroids; risk seems to decrease after cessation
Gastrointestinal	Gastrointestinal upset, gastrointestinal bleeding, possible acute pancreatitis	Increased gastric acid secretion	Conflicting results regarding the association of peptic ulcer and gastrointestinal bleeding and steroid use
Ophthalmologic	Cataract formation, increased IOP, myopia, exophthalmos, papill-edema, central serous chorioretinopathy, sub-conjunctival hemorrhage	Cataract—proposed mechanisms include steroid molecules binding to the lens, inhibition of Na-K pump in the lens, increased glucose production	Cataract formation dependent on dose and duration. Mostly occurs at doses >10 mg for > 1 year daily; may not be reversible after cessation
		Increased IOP/glaucoma—possible negative effect on trabecular meshwork	IOP—Occurs in approximately 5% of patients within the first few weeks; 18–36% will develop increased IOP with prolonged use; glaucoma more common with treatment > 1 year
Psychiatric	Mild-moderate: memory and sleep disturbance, agitation, anxiety, hypomania, insomnia, irritability, mood lability, restlessness		Psychiatric side effects occur within the first week of treatment; 13–62% experience moderate psychiatric complications; Euphoria and hypomania most common with short-term treatment; 5.7% severe complications; Mania/depression; associated with long-term treatment; past reaction/tolerance not predictive of future reactions; symptoms reversible in 90% with reduction/cessation while 10% may require antipsychotic treatment
	Severe: mania and depression		

(ACTH: Adrenocorticotropic hormone; BMI: Body mass index; CRH: Corticotropin-releasing hormone; HPA: Hypothalamic–pituitary–adrenal; IOP: Intraocular pressure; PTH: Parathyroid hormone).

Table 20.3: Commonly used medications associated with drug-induced rhinitis[38]

Mechanism				
Local inflammatory	Aspirin NSAIDs			
Neurogenic	Centrally acting sympatholytics: Clonidine Methyldopa Reserpine	Peripherally acting sympatholytics: Prazosin Guanethidine Doxazosin Phentolamine	Ganglion blocking sympatholytics: Mecamylamine Trimethaphan	Vasodilators – phosphodiesterase-5 inhibitors: Sildenafil Tadalafil Vardenafil
Idiopathic	Antihypertensives: Amiloride ACE inhibitors Oral beta-blockers Calcium channel blockers Ophthalmic beta blockers Hydrochlorothiazide Hydralazine	Hormones: Exogenous estrogens Oral contraceptives	Psychotropics: Chlordiazepoxide Amitriptyline Chlorpromazine Risperidone Thioridazine	Miscellaneous: Gabapentin

pain epistaxis, headache and rhinorrhea.[20,30] Volume, pressure and frequency vary greatly among irrigation protocols, without consensus on optimal parameters.[20,30] Current experimentation with delivery techniques demonstrates inconsistent sinus penetration regardless of technique.[28]

In vitro studies report deleterious changes to the sinonasal mucosa with hypotonic (mucosal cell damage) and hypertonic (ciliostasis) saline.[22,26] Hypertonic formulations carry a higher risk of nasal discomfort and are poor decongestants. However, hypertonic saline has equivalent or better symptom improvement and may improve radiographic outcomes versus isotonic saline. Thus, it is unclear whether isotonic or hypertonic saline is superior.[20,22]

Irrigation bottles can become easily colonized with bacteria, although clinical relevance is unclear.[31] One study noted a 97% rate of irrigation bottle contamination after 2 weeks of patient use. Cleaning and sterilization of the bottle is advocated, and patients should be educated about the importance of this practice.[31]

ZINC

In the United States, adults have an average of 2–4 colds and children have an average of 6–8 colds yearly.[33] In vitro, ionizable zinc demonstrates antiviral activity, particularly against rhinovirus.[34] The precise mechanism of action remains to be determined, but it inhibits formation of viral capsid proteins, thereby inhibiting viral replication. Zinc ions combine with viral coat proteins, which may inhibit viral interaction with intercellular adhesion molecule-1, preventing cell entry. Zinc also increases interferon-γ, inhibits histamine and leukotriene release, and stabilizes cell membranes.[33,34] Zinc lozenges are sold over the counter as a common cold remedy. The most recent Cochrane Review concluded that oral zinc administered within 24 hours of symptom onset reduces common cold duration and severity, and if taken for at least 5 months may reduce cold incidence.[35]

Reports indicate that many over-the-counter products do not contain efficacious formulations or doses of zinc, and those containing magnesium may actually worsen cold symptoms.[34] Short-term use of zinc appears harmless. Minor side effects include bad taste, nausea, vomiting, dyspepsia and diarrhea. Large quantities ingested over prolonged periods results in copper deficiency.[34] Topical zinc sulfate results in anosmia, with evidence of olfactory epithelial destruction and secondary atrophy of the olfactory bulb.[36] In 2009, the FDA required discontinuation of zinc-containing Zicam intranasal products due to anosmia.[5]

DRUG-INDUCED RHINITIS

Drug-induced rhinitis can be divided into three subtypes: (1) local inflammatory, (2) neurogenic, and (3) idiopathic (Table 20.3). The local inflammatory subtype results from an acute inflammatory response in the nose after medication ingestion. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) likely cause rhinitis by this mechanism, producing rhinorrhea as an isolated symptom or associated with severe rhinosinusitis, nasal polyposis, tissue eosinophilia, and asthma known as aspirin-exacerbated respiratory disease (AERD).[2,3,37-39] The mechanism

of aspirin-induced reactions is related to abnormalities in arachidonic acid metabolism.[37] NSAIDs inhibit cyclooxygenase-1, resulting in increased production of leukotrienes C4, D4 and E4, and increased upper and lower airway reactivity in susceptible patients.[38,39] It is proposed that increased expression of an allele of LTC4 synthase underlies the etiology of AERD.[38]

Neurogenic drug-induced rhinitis occurs when sympathetic and parasympathetic tone to the nasal mucosa, vasculature, and secretory glands is altered. Alpha and β-adrenergic antagonists and phosphodiesterase-5 inhibitors (PDE-5) cause this form of rhinitis.[38] Alpha-blockers are used to treat benign prostatic hypertrophy, whereas PDE-5 inhibitors treat erectile dysfunction.[2] Sympatholytics cause nasal congestion primarily by decreasing sympathetic tone. PDE-5 inhibitors cause turbinate vasodilation.[38]

The third subtype of rhinitis is idiopathic. ACE inhibitors and many other medications cause rhinitis by an unknown mechanism.[2,38]

There are no well-established recommendations for the treatment of drug-induced rhinitis. Cessation of the offending drug and avoidance of similar medications are initial steps. INCSs with or without intranasal antihistamines may help if symptoms persist despite cessation of the offending agent.[38]

DRUG-INDUCED NASAL SEPTAL PERFORATION

With the development of novel systemic chemotherapeutic agents for the treatment of malignancies, rare case reports of septal perforation have occurred. Bevacizumab is a recombinant monoclonal IgG1 antibody that inhibits human vascular endothelial growth factor (VEGF) and prevents angiogenesis.[40,41] It has activity against solid tumors and is often used for metastases.[41,42] Gastrointestinal perforation, poor wound healing, congestive heart failure and thromboembolic events are known side effects. Epistaxis and septal perforation are also potential side effects of bevacizumab.[40] Interestingly, patients with Osler-Weber-Rendu have been noted to have elevated VEGF. Bevacizumab has been used topically in these patients with promising results.[43]

Docetaxel, a semisynthetic taxane, is another agent that has been associated with septal perforations. It is used in the treatment of solid tumors, including breast cancer, non-small-cell lung cancer, ovarian and prostate cancer. Taxanes promote microtubule assembly and inhibit their disassembly, thereby inhibiting mitosis and encouraging apoptosis. Septal perforation may be secondary to lacrimal docetaxel secretion. Docetaxel causes canalicular inflammation and stenosis and nasal mucosal injury.[44] The combination of bevacizumab and taxanes may increase the risk of septal perforation.[43]

Management of the chemotherapy-induced spontaneous nasal septal perforations has yet to be fully described. Autoimmune, infectious, and other causes should be ruled out. Reduction or cessation of the offending agent may be effective, although this must be weighed against the risks of treatment cessation. Nasal irrigations, lubricants and humidification until the perforation stabilizes are advocated. Septal button placement and perforation repair have both been reported.[41-44]

INTRANASAL ILLICIT DRUG USE

Due to the rapid absorption characteristics and accessibility of the nasal mucosa, many recreational drugs are administered nasally. The intranasal route, for some drugs, has higher bioavailability and faster pharmacologic onset versus oral or sublingual administration, and powder formulations result in increased mucosal contact time, thereby increasing absorption.[45,46] Cocaine, heroin, crushed narcotics, antidepressants, and other psychotropics all have abuse potential via the intranasal route.

Cocaine is metabolized by esterases present in nasal mucosa and submucosa into the primary metabolite, benzoylecgonine.[47] Cocaine has high lipid solubility, and nasal uptake likely occurs via passive metabolism.[47] It reaches higher concentrations in brain olfactory tissues after nasal versus intravenous administration, suggesting a direct nose-to-brain pathway via neuronal transport or via another ill-defined pathway.[46,47] Cocaine competes with calcium ions and interacts with voltage-sensitive sodium channels, preventing nerve impulse generation and conduction, thus providing its anesthetic characteristics.[48,49] In the central nervous system (CNS), cocaine inhibits dopamine reuptake from the synapse, resulting in drug-associated euphoria.[47]

Habitual cocaine use may result in septal perforation, destruction of osteocartilaginous nasal structures and palatal erosion, although this occurs in only a small percentage of users.[48] Patients with intranasal tissue destruction may report epistaxis, hyposmia, headache, mucopurulent rhinorrhea and crusting.[48] Vascular ischemia is primarily

Table 20.4: Known carcinogens in unfiltered mainstream cigarette smoke[55]

Classes of agents	*Number of known agents in tobacco smoke*	*Known human carcinogens of this class (IARC class I)*	*IARC classification* (1-4)*
Polynuclear aromatic hydrocarbons	10		2A-2B
Heterocyclic hydrocarbons	5		2B
N-nitrosamines	8		2B
Aromatic amines	4	2-naphthylamine 4-aminobiphenyl	1-2B
N-heterocyclic amines	8		2B
Aldehydes	2		2A-2B
Phenolic compounds	2		2B
Volatile hydrocarbons	7	Benzene	1-2B
Miscellaneous organic compounds	9	Vinyl chloride Ethylene oxide	1-2B
Metals and metal compounds	8	Arsenic Beryllium Chromium Cadmium Polonium-210	1-2B

Virtually all are known carcinogens in experimental animals.
*International Agency for the Research on Cancer (IARC) Classification: 1–carcinogenic to humans; 2A–probably carcinogenic to humans; 2B–possibly carcinogenic to humans; 3–not classifiable; 4–not carcinogenic.

considered responsible for the pathogenesis of cocaine-induced tissue destruction.[49] The exact mechanism, however, is ill defined but may involve drug-induced apoptosis,[44] trauma facilitated by its anesthetic properties, infection, and toxicity secondary to drug additives.[49,50]

Multiple other medications are abused via an intranasal route, including prescription narcotics, antidepressants, antiepileptics, anticholinergics and psychostimulants.[46] This is an increasing form of drug abuse in prison populations.[46] These other drugs cause intranasal complications similar to cocaine due to suppliers adulterating, or "cutting" the parent compound.[49] Intranasal use of hydrocodone–acetaminophen provides more immediate pain relief than oral ingestion. It may result in necrosis of the nasal mucosa.[50] OxyContin also causes septal perforation.[49] Bupropion is a newer generation antidepressant used to treat depression and tobacco dependence. Intranasal abuse of bupropion results in chemical euphoria similar to cocaine.[46]

Treatment of the nasal complications from illicit intranasal drug use includes cessation of the offending agent, conservative therapy and nasal hydration, and possible defect repair. Intranasal complications from drug abuse may increase due to increased prescription drug availability.

Interestingly, with the increasing incidence of deaths related to opioid overdose and new drug formulations for intranasal administration, intranasal naloxone has been used to prevent death from opioid overdose due to respiratory depression. Intranasal naloxone has similar bioavailability and onset of action as intravenous naloxone. Furthermore, intranasal administration is easier and safer than intravenous or intramuscular administration.[51]

TOBACCO SMOKE

The World Health Organization estimates that 35% of men and 22% of women in developed countries smoke cigarettes, whereas 40% of children worldwide are exposed to passive smoking.[52] Cigarette smoke contains over 5,000 different compounds,[53-55] and second-hand smoke (SHS) contains over 4,000 components, 69 of which are known or suspected carcinogens[55,56] (Table 20.4). Irritating and toxic cigarette smoke compounds include acrolein, formaldehyde, carbon monoxide, nicotine, cotinine, acetaldhyde, phenol, potassium cyanide, ammonia, and nitrogen oxides.[53-55,57,60]

Tobacco smoke has been linked to lower respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and cancer, and it is a well-known irritant of the sinonasal cavity, causing nasal dryness, obstruction, rhinorrhea, sneezing, itching and reduced olfaction. Tobacco smoke has also been associated with chronic

inflammatory conditions including allergic and nonallergic rhinitis, nasal polyps, and rhinosinusitis, although the exact mechanisms are not entirely clear.[52,53,57-63] Many of the same genes upregulated in bronchial epithelium are also upregulated in the nasal mucosa after tobacco smoke exposure. Many of these genes encode proteins in the oxidoreductase pathway. Others are potentially involved in cellular differentiation, apoptosis and angiogenesis. These changes may be reversible with cessation of smoke exposure.[64]

Histologically, nasal mucosa from SHS-exposed children reveals ciliary loss, goblet cell hyperplasia, seromucinous acini hyperplasia, and capillary and sinusoid congestion.[62] MMP9, a metalloproteinase associated with tissue remodeling and allergy is elevated in nasal secretions of SHS exposed children, potentially explaining the relationship between smoke exposure and allergic rhinitis.[52] Tobacco smoke exposure also increases the production of proinflammatory cytokines directly, including IL-5, IL-8, GM-CSF (granulocyte-macrophage colony-stimulating factor), beta-defensin and RANTES (regulated upon activation, normal T-cell expressed and secreted).[53,65,66]

MCC removes irritants from the sinonasal cavity and maintains the health and homeostasis of the nose and sinuses.[67] Proper MCC depends on mucous volume and composition, ciliary structure and beat frequency, and the mucus–cilia interaction.[54,67,68] All of these components are adversely affected by tobacco smoke, potentially leading to mucostasis, inflammation and rhinosinusitis.[58,66,68] Tobacco smoke chemicals are ciliostatic and ciliotoxic in vitro.[53,58,67] However, some studies show decreased ciliary beating while others demonstrate increased beating with smoke exposure.[53,67,68] The respiratory epithelial lining may respond to acute challenges from injurious agents by upregulating ciliary beating and secretory processes to remove toxins.[67] This increased ciliary beating may involve nitric oxide-mediated pathways and/or direct neural stimulation.[67,68] Lower smoke doses likely promote the protective acceleration of ciliary beat, whereas prolonged and high dose exposure can result in adverse effects to ciliary formation, structure, number and function.[53,62,65,67] Histologic studies of smokers' airways consistently indicate decreased cilia number.[53]

Mucous composition also changes with tobacco smoke exposure. Goblet cell and seromucinous acini hyperplasia result in increased mucous production. Cigarette smoke inhibits cystic fibrosis transmembrane conductance regulator-mediated chloride transport, the etiology of abnormal MCC in cystic fibrosis, and calcium-mediated chloride channels in vitro.[53,62,65] It also impairs other epithelial transport mechanisms.[68]

With the resultant mucostasis and direct epithelial toxic effects, tobacco smoke may perpetuate an inflamed, hyperplastic, dysfunctional sinonasal epithelium, leading to chronic disease states.[67] Population-based studies suggest a correlation with active tobacco use and self-reported rhinosinusitis, with rhinosinusitis prevalence increasing in a dose-dependent manner.[65] Proposed mechanisms for this relationship include local immunosuppressive effects,[53,63] inhibition of antibody and macrophage responses, increased bacterial adherence encouraging biofilm formation, enhancement of the allergic response, and epithelial disruption.[56,59] Smoke exposure also results in poorer sinus surgery outcomes including worse symptom and endoscopy scores and higher revision rates in smokers in a dose-dependent manner.[53,60,65,66]

OCCUPATIONAL RHINITIS

Occupational rhinitis (OR) is defined as "an inflammatory disease of the nose, which is characterized by intermittent or persistent symptoms (i.e. nasal congestion, sneezing, rhinorrhea and itching), variable nasal airflow limitation, or hypersecretion due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace."[69] Work-exacerbated rhinitis occurs when rhinitis is already present, but workplace exposures result in symptom worsening.[69] Workforce surveys indicate that OR is two to four times more common than occupational asthma (OA), which accounts for almost 18% of all adult-onset asthma.[70]

Agents that cause OA and OR can be divided into high molecular weight (HMW) glycoproteins from vegetal and animal origin and low molecular weight (LMW) chemicals[69] (Table 20.5). Professions with a high prevalence of rhinitis (31–61%) include cleaners, farmers, greenhouse workers, painters, automotive manufacturers, electronic/electrical products assemblers, hairdressers, laboratory workers with animal contact, veterinarians, food workers, and bakers.[69,71] Allergic OR can be IgE-mediated, which occurs with many HMW agents and some LMW agents (platinum salts, reactive dyes and acid anhydrides), or it can be non-IgE-mediated, primarily induced by LMW agents (isocyanates, persulfate salts, aldehydes, wood dusts) acting as haptens. The mechanism seems to involve T-cell activation of both Th1 and Th2 populations.[69-72] Rhinitis symptoms caused by HMW agents are usually more frequent and severe.[70] Non-allergic OR occurs via poorly understood irritant or non-immunologic mechanisms.[69] A dose-response gradient between level of exposure and IgE-mediated sensitization has been identified for various HMW agents.[66,73,74]

Table 20.5: Etiologic agents in occupational rhinitis[73,74]

Agent	*Occupation*
High molecular weight	
Animal-derived allergens	Laboratory workers Veterinarians Textile workers
Insects and mites	Laboratory workers Farm workers Bakers Janitorial workers
Grain and flour dust	Bakers Flour packers Grain elevator workers
Latex	Hospital workers Glove manufacturing workers Textile factory workers
Other plant allergens	Lawn maintenance workers Tobacco manufacturing workers Carpet workers Hot pepper, tea, coffee, cocoa, dried fruit, saffron workers
Biological enzymes	Bakers Pharmaceutical workers Detergent industry workers
Fish and seafood proteins	Seafood packing and processing Aquarists Fish-food factory workers
Low molecular weight	
Diisocyanates	Painters Furniture makers Carpenters Urethane mold workers
Anhydrides	Epoxy resin production workers Chemical workers Electric condenser workers
Wood dust	Carpenters Furniture makers
Metals	Platinum refinery workers
Drugs	Healthcare workers Pharmaceutical workers
Other chemicals	Reactive dye production workers Synthetic fiber production workers Hair dressers Cobblers Paper mill workers

Occupational rhinitis (OR) is considered a harbinger to the development of OA. Symptoms of OR precede the development of OA in 20–78% of cases. Ninety-two percent of patients with OA report OR symptoms.[70,72]

The OR diagnosis requires demonstrating rhinitis and its relationship to work-related exposures. A diagnostic algorithm has been proposed by The Task Force of the European Academy of Allergy and Clinical Immunology.[69] Clinical history, questionnaires, and immunologic tests have a high sensitivity but low specificity for diagnosing OR; the diagnosis may be confirmed using nasal provocation tests.[69,70] In addition to low specificity, immunological testing lacks commercially available, standardized extracts for most occupational agents. Nasal provocation testing is considered the gold standard for confirming OR but suffers from a lack of standard parameters to define positivity. Increased eosinophils recovered from nasal lavage or secretions or a decrease in nasal patency measured by acoustic rhinometry likely provide complementary information for objectively diagnosing OR.[69,70,72]

Early diagnosis and cessation of exposure are the most effective treatment modalities for OR. If complete avoidance is not possible, reduction in exposure should be considered as continued exposure may lead to the development of OA.[70] The possibility of OA should be evaluated in anyone diagnosed with OR.[69,74]

Occupational Sinonasal Toxins

A variety of environmental chemicals and toxins in the work place cause adverse effects on the sinonasal cavities. Although an exhaustive list is beyond the scope of this text, the most common offending agents will be discussed.

Corrosive rhinitis is a subcategory of OR. Corrosive rhinitis causes nasal obstruction, sneezing and itching, but also results in visible destruction or irreversible alterations in tissue (i.e. septal perforation) due to contact with the specific agent.[75] Major classes or corrosive chemicals include strong acids and alkali, oxidizing, and dehydrating agents.[75] Although many chemicals are considered corrosive, most lack evidence as a direct cause of septal perforation other than hexavalent chromium.[49,75,76] Chromium exposure occurs primarily in the electroplating industry.[75,76] Reports of septal ulceration and perforation occurred throughout the 20th century following inhalational exposure to hexavalent chromium and trivalent arsenic, particularly in those employed in chrome production, chrome plating, and arsenic and copper smelters.[36] Nickel, mercury, and copper may also cause septal perforation.[36,75]

On the basis of human and animal studies, over 120 airborne chemicals were noted to adversely affect olfactory function after acute or chronic exposure. Animal

Table 20.6: Nasal toxins

Known or probable human carcinogens of the sinonasal cavity	*Compounds associated with nasal toxicity (ulceration, perforation, anosmia)*
Isopropyl alcohol production	Chromium (VI) compounds
Leather dust	Arsenic
Nickel compounds	Cadmium
Radium-226 & -228	Nickel
Tobacco smoking	Cobalt
Wood dust	Platinum
Chromium (VI) compounds	Fluoride
Formaldehyde	Copper
Textile manufacturing	Zinc

studies demonstrate dose-related olfactory epithelial changes including olfactory neuron degeneration and necrosis. However, few human studies that explore this topic have an adequate study population or an objective measure of olfactory function.[77] The most well-known metal to affect olfactory function in humans is cadmium. Anosmia and hyposmia, affecting odor detection and discrimination, was reported as early as the 1940s and occurs in alkaline battery workers, smelters, welders, and brazing workers.[77,78] Exposure has also been associated with nasal mucosal ulceration.[78] Accumulation of cadmium and other metals may occur in the olfactory bulb.[36] Notably, tobacco is characterized by a high amount of cadmium.[78] Chromium, nickel, manganese, arsenic, zinc, and mercury exposure are associated with olfactory dysfunction as well[36,75,77] (Table 20.6).

Sinonasal Cancer

Occupational and environmental exposures are responsible for many epithelial sinonasal cancers. Malignant sinonasal epithelial tumors are rare, representing ~1% of all neoplasms and 4% of head and neck neoplasms.[79] Occupational risk factors associated with sinonasal cancer include wood and leather dust, nickel, hexavalent chromium, formaldehyde, and polycyclic aromatic hydrocarbons[80] (Table 20.6). In the maxillary sinus, squamous cell carcinoma occurs most commonly, whereas in the ethmoid, poorly differentiated carcinoma and intestinal-type adenocarcinoma (ITAC) may be seen.[81] Occupation-related sinonasal cancers are often characterized by a period of exposure (possibly short) and often a very long latency period.[80]

The most well-known occupational exposures associated with sinonasal cancer include wood and leather and impact forestry, paper, woodworking, construction, footwear, and leather tanning workers.[82,83] Ethmoid ITACs are highly correlated with wood and leather dust exposure.[79,80] Histological sinonasal mucosa precursor changes may include cuboidal and squamous metaplasia, dysplasia, and goblet cell hyperplasia.[79] ITACs are characterized by high mortality, primarily because of local invasion.[79] Prognosis is negatively influenced by a delayed diagnosis.[80] Due to the prolonged latency period preceding carcinoma development and lack of early signs and symptoms, screening programs have been suggested for high-risk workers. Primary prevention is also essential—educating workers, minimizing exposure, and correctly using protective equipment.[80]

Nickel exposure, which can occur in mining, smelting, refining, electroplating, stainless steel, and alloy manufacture, carries an increased risk of sinonasal carcinoma.[82] Nasal mucosal biopsies of nickel exposed workers demonstrate dysplastic lesions and elevated nickel concentrations.[36,84] A dose-response relationship between cumulative exposure to water-soluble nickel and nickel oxide compounds and the risk of cancer exists.[82] Nickel exposure is associated with squamous cell carcinoma and anaplastic/undifferentiated carcinoma of the turbinates and ethmoid sinuses.[36]

Formaldehyde is a known irritant and carcinogen of the upper respiratory tract. Upper airway irritation most frequently occurs at concentrations >1 ppm. Inhalation of concentrations of 100 ppm is immediately dangerous to life. Long-term exposure has been associated with an increased risk of sinonasal and other respiratory cancers.[85]

WORLD TRADE CENTER EXPOSURE

In the aftermath of the World Trade Center (WTC) disaster on September 11, 2001, tens of thousands of first responders, volunteers, and service restoration workers were exposed to a complex mixture of toxins released as dust, metal fumes, acid mists, smoke, and combustion products.[86] WTC dust characterization, although delayed and incomplete, demonstrated the dust had an alkaline pH (9.2–11.5) and consisted of 98% respirable size particles, which included cement, cellulose, glass fibers, asbestos, lead, polychlorinated biphenyls, and polyaromatic hydrocarbons.[87,88] Studies revealed a higher proportion of fine (inhalable) particles closer to the center of the disaster

site, and although diminished over time, remained present almost 9 months later.[87] Thousands have developed chronic respiratory issues related to their exposure, primarily asthma, bronchitis, and aggravated COPD.[86,88] Studies have shown that the majority of these individuals also have concomitant upper airway complaints, with over 75% of workers evaluated complaining of rhinitis, sinusitis, pharyngitis and laryngitis.[88] In addition, substantial impairment in olfactory and trigeminal sensitivity was identified in workers and volunteers compared with a control group.[86]

ENVIRONMENTAL EXPOSURES

Worldwide urbanization has led to a focus on the health impact of vehicle emissions, manufacturing pollutants, and greenhouse gases. Humans inspire between 10,000 and 20,000 L of environmental air each day,[54] and this increasingly contaminated air carries toxins and pollutants into the respiratory tract, including the sinonasal mucosa. Children exposed to high pollutant levels have increased epistaxis, nasal crusting, obstruction, dryness, and sinusitis.[89] Nasal mucosa from similarly exposed children demonstrates basal cell and goblet cell hyperplasia, abnormal or absent cilia, squamous metaplasia, intraepithelial inflammatory infiltrates, and DNA damage.[89-91]

Multiple studies have linked environmental pollutants to rhinitis and rhinosinusitis.[52,92-94] Recent studies show an association between high air pollution levels and increased risk of allergic sensitization and rhinitis.[95] Medical historians note that allergic rhinitis was much less prevalent before the industrial revolution and hypothesize that urban pollution contributes significantly to increased immunologic responses.[6] Interestingly, air pollution has been shown to increase the availability of airborne pollen allergens by triggering the release of allergen granules from grass pollen,[95] whereas pollen morphology is altered due to particle agglomeration on pollen granules.[94] Urban air pollution differs dependent upon the type and number of industrial factories and the amount and composition of traffic in the area.[96] Nitrogen oxides, sulfur dioxide, large and small particulate matter, carbon monoxide, and ozone are associated with upper and lower respiratory illness and are regulated by the Clean Air Act.[52,93,97]

Traffic-related particles coagulate and condensate seconds after emission. Those living near a major road are exposed to higher amounts of traffic-derived particles and gases and to a potentially more toxic freshly emitted aerosol. Multiple studies indicate that persons exposed to transport-related air pollution may be at increased risk for asthma, bronchitis, rhinitis, and sinusitis.[92,94,95,98-100] However, other studies do not demonstrate consistent associations between pollutants and respiratory disease, making the literature inconclusive.[94]

Particulate matter consists of a complex suspension of minute solid material in a gaseous or liquid medium (i.e. nitric and sulfuric acids, organic chemicals, metals, and soil or dust particles).[101] Particles 2.5–10 μm, found near roadways and dusty industries, are "inhalable coarse particles"[101] and have the ability to reach the lower airway.[94] Particles under 2.5 μm are "fine particles" and are emitted from fires and power plant, industry, or automobile gases.[98,101] "Fine" particles can cause cardiopulmonary impairment.[52] There is a positive association with an increase in particulate matter and increased prevalence of respiratory and atopic disease.[94,101,102] Higher levels of particulate matter are significantly associated with sneezing and nasal obstruction during the first 2 years of life.[98]

Diesel exhaust persists for prolonged periods in the atmosphere and consists of hundreds of organic and inorganic gaseous and particle compounds.[100] Diesel exhaust causes eye and nose irritation after short-term exposure and increases upper airway cytokines and chemokines, histamine release, IgE expression, and degranulation of eosinophils, mast cells, basophils, neutrophils, B cells, and macrophages.[52,95,96,100] This is similar to early and late phases of a type I hypersensitivity response. Long-term exposure may increase allergic sensitivity.[52]

Nitrogen oxides are highly reactive gases that form from automobiles, power plants, and off-road equipment emissions, contributing to ground-level ozone formation and fine particle pollution.[103] Short-term exposures (5 minutes to 24 hours) are associated with increased respiratory symptoms, particularly asthma.[103] Epidemiologic studies associate NO_2 with increased dry cough and asthma by age 1, as well as respiratory hypersensitivity and allergic rhinitis, although these findings are not universal among studies.[95,98,99]

Sulfur dioxide is most notable from power plant and industrial fossil fuel combustion.[104] SO_2 and other sulfur oxides may cause or worsen asthma, emphysema, and lower respiratory disease.[104] SO_2 is also correlated with increased patient visits for allergic rhinitis and upper respiratory complaints.[95,102]

Ozone is produced by chemical reactions of volatile hydrocarbons and nitrogen oxides in the presence of sunlight.[90,105] Primary sources include industrial facility, electric utility, motor vehicles exhaust, gasoline vapor, and chemical solvent emissions. Ground level ozone is the main constituent of smog[105] and is a potent nonradical oxidant and known respiratory epithelial irritant.[52,90,96] Approximately 40% of inhaled ozone is taken up in healthy human nasal passages[106] and demonstrates nasal epithelial damage.[90] Ozone may promote the new development of pollen sensitization, as well as increased IgE reactivity, eosinophil infiltration, mucous cell metaplasia, and MUC5AC gene expression.[52,96] Ozone exposure can also increase release and decrease degradation of local tachykinins, which are proinflammatory neuropeptides that promote vasodilation, plasma exudation, and bronchoconstriction.[106] Direct airway epithelial injury by ozone may involve oxygen free radical generation.[106] Nasal mucosa from ozone-exposed children revealed increased DNA damage of nasal epithelial cells.[90]

There is also evidence suggesting that urban pollution may increase risk for sinonasal carcinomas. In Mexico City, a highly industrialized and populated area, DNA damage (strand breakage) is rapidly induced upon arrival and exists in permanent residents. In children, the percentage of nasal-damaged DNA strongly correlates with age and outdoor exposure time. Children's nasal epithelial cells show a threefold increase in 8-hydroxydeoxyguanosine versus matched controls.[90] A significant increase in nasal cell proliferation is seen in exposed permanent residents and in newly arrived subjects after 1 week in the city, which could increase the potential for development of sinonasal malignant neoplasms.[107]

INTRANASAL DRUG DELIVERY

Intranasal administration of systemic and CNS medications has become an area of increasing interest. Currently, there are many medications that are formulated for intranasal use for a wide range of indications, including pain management, hormone replacement therapy, and smoking cessation, with many others under investigation (Table 20.7). The nasal mucosa is readily accessible, facilitating drug administration and potentially improving compliance.[108] Nasal mucosal absorption is efficient and pharmacologic onset is rapid due to the highly vascularized subepithelium and porous endothelial basement membrane.[109-111] It circumvents gastrointestinal degradation and hepatic first-pass metabolism. It is also an avenue by which the blood-brain barrier can be bypassed, resulting in direct CNS drug delivery.[108,111,112]

Intranasal drug delivery also has limitations and challenges. The nasal cavity volume is 15–20 mL, and surface area is approximately 150 cm^2, restricting the volume of administered drug to 100–150 μL.[108] The nasal mucosa permeability to larger, hydrophilic compounds (i.e. peptides, proteins) is low.[111,112] Mucosal proteases can result in drug degradation, and MCC continuously removes substances from nasal mucosa, decreasing drug absorption time.[108,112]

Systemic absorption of intranasally applied drugs occurs by several mechanisms. Paracellular transport occurs between adjacent epithelial cells through hydrophilic porous and tight junctions and is the mode of transport for polar drugs. Rate of transport is inversely related to molecular weight (MW); compounds with an MW >1 kDa have very poor intranasal absorption.[108,110] Transcellular absorption occurs by passive diffusion through the cell's interior, especially for small, lipophilic drugs.[108] Compounds with an MW >1 kDa (peptides and proteins) are transported transcellularly by an endocytic process or via specific transporters.[108] The rate of transcellular transport is dependent on lipophilicity.[110]

The exact mechanism by which intranasal drugs reach the CNS and bypass the blood–brain barrier is not well understood, although several mechanisms have been postulated. The olfactory epithelium may allow transcellular and paracellular transport, and neuronal transport along the olfactory bulb or trigeminal nerve seems to be critical.[108,110,113] Drug transporters have been identified in the olfactory epithelium and bulb[108,114] and vascular, cerebrospinal fluid, and lymphatic pathways have been identified as candidates for transport.[110]

Factors Influencing Intranasal Drug Delivery

There are several factors that affect intranasal drug absorption. Nasal cavity properties considered during drug development include membrane permeability, pH, MCC, disease status, nasal mucosal enzymes, and transporter proteins.[108] Nasal MCC rate is inversely related to drug residence time, and thus, absorption. Conditions affecting MCC include smoking, environmental pollutants, asthma, cystic fibrosis, diabetes, and rhinosinusitis.[108] Conditions causing vasoconstriction also decrease intranasal absorption.[108]

A drug formulation produced for nasal application usually consists of the drug, a vehicle, and the excipients (solubilizer, preservatives, antioxidants, humectants, etc.).[113]

Table 20.7: Various intranasally administered medications[108,112,113,116]

Developed drug	*Drug under investigation*	*Indication*
Butorphanol Fentanyl Ketorolac Morphine	Hydromorphone Ketamine NSAIDs Sulfentanil + ketamine	Pain management
Naloxone		Opioid overdose
Flumazenil		Benzodiazepine overdose
Dihydroergotamine Sumatriptan Zolmitriptan		Migraine and cluster headaches
Lorazepam Midazolam	Diazepam Clonazepam	Antiseizure
Dexmedetomidine Ketamine Midazolam	Diazepam	Preoperative sedation and anxiolysis
	Triazolam	Insomnia
Cyanocobalamin		Vitamin B12 deficiency
Salmon calcitonin		Postmenopausal osteoporosis
	Melatonin	Jet lag
Desmopressin		Diabetes insipidus, nocturnal enuresis
Oxytocin		Labor induction; lactation stimulation; treatment of social, cognitive and mood disorders
	Human growth hormone	Growth hormone deficiency
	Testosterone	Testosterone deficiency
	Progesterone	Infertility, amenorrhea
Estradiol		Hormone replacement
Buserelin		Prostate cancer
Nafarelin		Endometriosis; precocious puberty
Gonadorelin		Undescended testicle
	Sildenafil	Erectile dysfunction
Glucagon		Antihypoglycemic
	Insulin	Mild cognitive impairment, Alzheimer's disease, obesity
	Davunetide	Schizophrenia, Alzheimer's disease
	L-dopa	Parkinson's disease
Nicotine		Smoking cessation
Metoclopramide		Antiemesis
	Interferon beta	Multiple sclerosis
Influenza vaccine, live attenuated		Flu prevention

A variety of drug physiochemical properties must be considered when developing an intranasally administered drug. Absorption for compounds with MW <300 kDa is not significantly influenced by the drug's physiochemical properties; it occurs rapidly, likely via paracellular routes.[108,110] Because the nasal mucosa is lipophilic, small

(MW < 1 kDa) lipophilic drugs are well absorbed, with near 100% bioavailability. However, highly lipophilic drugs do not dissolve easily in the aqueous nasal mucous and may quickly be cleared by MCC, resulting in decreased absorption.[108,113,115] The nasal mucosa is almost completely impermeable to compounds > 1 kDa.[110,113] Polar drugs are also poorly absorbed (1–10%).[116] Hence, proteins and peptides show insufficient nasal bioavailability (< 1%).[110] Membrane absorption is also dependent upon the amount of drug existing as uncharged species, which is dependent on the drug pKa and the pH at the absorption site. Only the molecularly dispersed form of a drug at the absorption site crosses the nasal epithelium. Therefore, sufficient drug solubility is a prerequisite for any drug absorption.[116] To avoid nasal irritation and potential mucosal damage, drug pH should be similar to normal nasal mucosal pH (5.0–6.5).[108] Increased viscosity, which interferes with MCC, may increase nasal mucosa contact time, theoretically resulting in greater drug absorption.[108]

To increase the breadth of compounds for intranasal administration, various strategies have been investigated to overcome issues with poor solubility, insufficient stability, incomplete absorption, and premature metabolism or degradation. Modifying inherent drug properties such as pH, MW, or solubility may improve nasal absorption. Increasing nasal residence time can be enhanced by changing the location of deposition (anterior versus posterior), or by altering MCC (changing the ciliary beat frequency), or drug viscosity or adherence characteristics. Combination with an enzymatic inhibitor may reduce or inhibit metabolism by nasal mucosal enzymes. Drugs may also be combined with an absorption enhancer that induces reversible modifications of the epithelial barrier—changing epithelial permeability by increasing membrane fluidity and/or by weakening or opening tight junctions.[108,110] Because absorption enhancers affect the epithelial membrane, modify cell structures, leach proteins, or strip the outer layer of the mucosa, there is a correlation between enhancing bioavailability and damaging the membrane, some of which is irreversible.[109,116] Well-known absorption enhancers include surfactants, bile salts, cyclodextrans, fatty acids, and chitosan.[108]

Bioadhesion involves improving the attachment of a synthetic or natural macromolecule to a tissue. In the nose, cytoadhesion occurs at the level of the epithelium, cytoadhesion, or at the level of the mucous layer, mucoadhesion. Bioadhesives prolong the contact time between drug and nasal mucosa, potentially increasing absorption.[108] Chitosan is one of the most well-known bioadhesives and absorption enhancers. It is a linear polysaccharide obtained by partial alkaline deacetylation of chitin, a component of the exoskeleton of crustaceans.[117,118] Chitosan has many well-known beneficial properties including being readily bioavailable, biocompatible, and biodegradable. Chitosan is not transported to any significant degree across the nasal epithelium.[109,111,120] Its mechanism of action is believed to involve transiently opening tight junctions, increasing paracellular drug transport. Its overall cationic charge allows it to interact with the anionic mucosal layer and has been shown to have a strong interaction with mucin. Its mucoadhesive properties can enhance absorption by increasing mucosal contact time, reducing enzymatic degradation and promoting the creation of a concentration gradient of antigen.[108,111,116,119,120] It may also enhance the dissolution rate of drugs with poor water solubility.[108,119] Despite its excellent pharmacological characteristics, there are no medications on the market containing chitosan.[119]

Finally, new drug delivery systems are being investigated. Carrier technology couples specific drugs to carrier particles such as liposomes, microspheres, and nanoparticles to improve absorption, change absorption kinetics, and decrease toxicity. A liposome is a microscopic spherical particle formed by a lipid bilayer enclosing an aqueous compartment. A microsphere is a lipid-based polymeric device with a diameter typically between 1 μm to 1 mm.[115] Microspheres used in nasal drug delivery systems are all water insoluble but absorb water into the sphere's matrix, resulting in swelling of the sphere and formation of a gel, thereby increasing viscosity and nasal residence time.[111] A nanoparticle is a well-defined particle, composed of biological or chemical compounds, ≤ 1000 nm with a core shell structure or a continuous matrix structure. It has a high surface to mass ratio enabling it to adsorb and carry other compounds efficiently.[115,121] Nanoparticles must release the drug at the target site and be biodegradable. Nanoparticles are promising for the delivery of chemotherapeutic agents and for penetrating the blood brain barrier.[121] All of these carriers are capable of delivering drugs, protecting drugs from enzymatic degradation and pH imbalances, enhancing absorption and controlling the release of the encapsulated or adsorbed drug.[108-111]

INTRANASAL VACCINES

Mucosal surfaces are a major entry point for infectious pathogens and serve as the first line of defense against

infection. Local mucosal immune responses are important for protection against diseases that occur by these routes. Oral and nasal vaccines are being actively pursued because these routes effectively induce strong mucosal immune responses.[118] There are currently only seven vaccines that are routinely administered via a mucosal route to humans, and only one via the nasal passage.[122]

FluMist, an intranasal influenza vaccine, contains live-attenuated influenza virus.[122] Vaccination is the primary strategy for prevention and control of influenza A, which is highly contagious to humans and results in substantial morbidity and mortality yearly.[123] Locally produced secretory IgA antibodies to viral surface proteins are important for protection of the upper respiratory tract, and corresponding serum IgG antibodies are essential for lower respiratory tract protection and prevention of viremia.[122] Secretory IgA prevents entry across the mucosal barrier, whereas serum IgG antibodies facilitate phagocytosis.[118] The injectable vaccine primarily induces an IgG response while the intranasal vaccine can stimulate IgA and IgG production as well as increase the production of cytotoxic T cells and antibodies that protect the upper respiratory tract. [117,118,122,123] Intranasal vaccination may elicit a long-lasting, broader immune response, closely resembling natural immunity.[122,123] Despite these differences, both live and inactive vaccines have been shown to have comparable efficacy (60–90%).[122,123] Among children, the intranasal vaccine is safe, well tolerated, and up to 93% effective against culture-confirmed influenza.[122]

Intranasal vaccine administration is needle-free, relatively painless, and does not require sterile preparation.[118] Its ease of accessibility theoretically makes vaccination of large population groups easy.[122] Compared with oral administration, there is a lack of acidity and abundant secreted enzymes,[122] and it avoids gastrointestinal enzymatic degradation and first pass hepatic metabolism.[118] Parenteral vaccinations usually require high doses because of a short in vivo half-life and primarily stimulate systemic immunity while poorly inducing mucosal responses.[117,122,123] In contrast, intranasal vaccines can be administered at a lower dose, and they are capable of producing both mucosal and systemic immune responses.[118,122] Nasal-associated lymphoid tissue similar to gut mucosal-associated lymphoid tissue[117] and Waldeyer's ring,[118] contains all subtypes of immunocompetent cells and is the location where mucosal immune responses in the upper respiratory tract are induced, making this an ideal target for vaccinations.[118]

When developing a nasal vaccine, the nasal milieu, the antigen, and the delivery system must be considered. The ideal mucosal vaccine should: (1) not be easily degraded; (2) have limited elimination; and (3) facilitate the couptake of both antigen and adjuvant to antigen presenting cells to stimulate a robust mucosal and systemic immune response.[122] Most prior attempts at antigen delivery through nasal administration have resulted in poor immune response due to limited diffusion of antigens across the epithelium, enzymatic degradation or antigen instability, and most importantly, rapid clearance of antigen due to MCC.[117,118] However, this is an area of active and ongoing research.

CONCLUSION

Rhinitis and rhinosinusitis are well-recognized pathologic conditions of the nasal and sinus cavities that are treated with both systemic and topical therapies. The pathogenesis of these conditions is not clearly understood. However, the immunologic milieu, medications, the environment in which we live and work, and our daily habits can influence our sinonasal health. These factors may contribute to the development of these inflammatory conditions, or may in fact, contribute to the development of sinonasal injury or cancer. Allergens, irritants, and pollutants are constantly being inhaled into the nose and sinuses, whereas the sinonasal epithelium tries to combat these insults with inherent protective mechanisms. Greater awareness and further research is necessary to elucidate the effects of various toxins and pollutants on the nasal and sinus cavities. Researchers are trying to use the nasal epithelium as a portal for systemic or CNS drug delivery because of its many favorable characteristics for drug absorption. Many intranasally administered drugs have been developed, and more are being actively investigated for a wide range of medical indications. Research in this field will likely benefit the treatment of sinonasal conditions in the future.

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CHAPTER

21

Epistaxis

Patricia A Loftus, Alexis H Jackman

INTRODUCTION

The management of epistaxis is one of the most commonly encountered clinical scenarios by the practicing otolaryngologist. The variability of severity can range from outpatient management to admission to the intensive care unit, from conservative treatment with nasal pressure to the necessity of surgical ligation in the operating room, and from a quick and satisfying outcome to a frustrating chronic problem or even life-threatening situation.

This chapter will discuss the current scientific knowledge regarding the etiology, presentation, and range of management options for epistaxis. The magnitude and potential consequences of this condition should not be underestimated, and a methodical approach should be employed. The magnitude and potential consequences of this condition should not be underestimated, and a thorough and systematic approach to any episode of epistaxis should be employed from the outset.

EPIDEMIOLOGY

Epistaxis is the most common otolaryngologic emergency[1] and the second most common cause for otolaryngologic hospital admission.[2] This condition has a lifetime incidence of 60%, yet only 6% of patients with nosebleeds seek medical treatment since most episodes are minor and self-limited.[3,4] Although it is true that most cases of epistaxis are uncomplicated, the severity of this disease process (i.e. more frequent hospital admissions) increases with age.

Epistaxis has a bimodal distribution. The first peak occurs in the pediatric population in children under the age of 10, which are in most cases minor bleeds originating from the anterior nares.[5,6] The second peak is in the adult population over the age of 35–50. These cases tend to be more severe, as posterior bleeds are more frequent in the adult population as compared to the pediatric population.[4,6] Clinical studies have shown that the number of cases of epistaxis is highest during the winter months, e.g. a study by Manfredini et al. illustrated that the highest number of emergency department visits for epistaxis occurred from November to March.[7] The explanation behind this seasonal variance is not entirely understood, but one hypothesis maintains that the increased number of respiratory infections in the colder months causes direct damage to the nasal mucosa that in turn promotes epistaxis.[8] Additional winter-related factors include the lower ambient humidity and dryness associated with indoor heating systems.

ANATOMY

The vascular supply to the nose has contributions from both the external and internal carotid systems. The branches of the external carotid artery (ECA) that provide a significant contribution to this vascular supply are the ascending pharyngeal artery, the facial artery, and the terminal branches of the internal maxillary artery (IMA). The facial artery gives off the superior labial artery, whose septal branch supplies the anterior septum. The facial artery then terminates as the angular artery, which

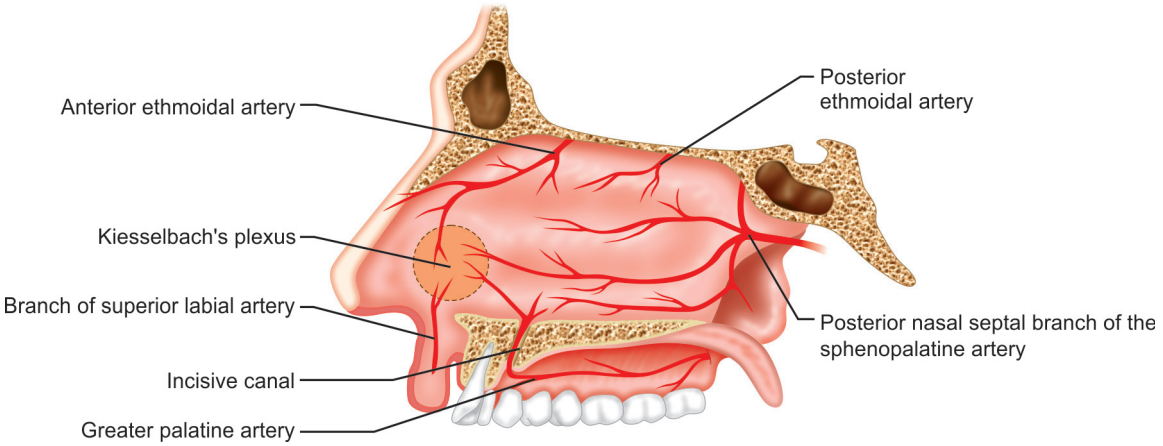


Fig. 21.1: The rich vascular anastomosis on the anteroinferior nasal septum known as Kiesselbach's plexus includes contributions of the four depicted vessels.

supplies the anterior nose laterally. The IMA terminates as the sphenopalatine artery (SPA) that enters the nasal cavity via the sphenopalatine foramen (SPF) at the posterior end of the middle turbinate. This artery gives off posterior lateral nasal branches and ends on the posterior nasal septum as the posterior septal branches, which cross the face of the sphenoid. If a posterior septal branch is cut while surgically enlarging the sphenoid ostium inferiorly, significant arterial bleeding may be encountered.

In terms of the anatomical variations of the SPF and SPA, a study that included 61 cadavers found that an ethmoid crest was present in all specimens, and was located anteriorly to the SPF almost 100% of the time. The most frequent location of the SPF was the transition area between the middle and superior meatus (86.9%), and less commonly in the superior meatus (13.1%). Accessory foramina were identified in 9.8% of the 112 sides evaluated, with the majority occurring in the middle meatus (91.7%). The number of arterial branches exiting the SPF was variable, with one main trunk exiting the foramen in 67.2%, two branches exiting the foramen in 21.3%, and three branches exiting the foramen in 11.5% of the cadavers included in this study.[9]

The other major blood supply to the nose comes from the internal carotid artery system. The ophthalmic artery branches into the anterior and posterior ethmoidal arteries. The anterior ethmoidal artery (AEA) runs with the nasociliary nerve through the anterior ethmoidal canal and into the nasal cavity, where it sends off a branch that supplies the anterosuperior aspect of the lateral nasal wall. The AEA then traverses the roof of the nose and supplies the anterior and middle ethmoidal cells and frontal sinus. As the AEA descends into the nasal cavity, it supplies branches to the lateral wall and anterosuperior septum, and terminates as a branch supplying the dorsum of the nose. The posterior ethmoidal artery (PEA) passes through the posterior ethmoidal canal, after which it gives off a nasal branch that supplies the lateral nasal wall. The PEA traverses the roof of the nose and ethmoid sinuses, crosses into the nasal cavity, and extends into the cribriform plate, and supplies the posterior ethmoidal air sinuses, dura mater of the anterior cranial fossa, and the upper part of the nasal mucosa.

The AEA is usually larger than the PEA and enters the nasal cavity <20 mm (average 14–18 mm) posterior to the nasolacrimal suture line. The PEA enters about 10 mm (average 9–13 mm) posterior to the AEA canal, and the optic canal is located about 4–7 mm posterior to the PEA canal.[10]

The arteries of the external and internal carotid systems make a rich anastomosis in the region of the vestibule and anterior portion of the septum. The German otolaryngologist Wilhelm Kiesselbach and the American surgeon James Little provided independent descriptions of this area in the late 19th century, hence the associated names of Kiesselbach's plexus and Little's area (Fig. 21.1). Anastomosis of four primary vessels occurs in this localized region of mucosa of the anteroinferior nasal septum: the septal branch of the AEA, the lateral nasal branch of the SPA, the septal branch of the superior labial branch of the facial artery, and the greater palatine artery.

The classification system of anterior versus posterior nose bleeds is based on the anatomic source of the

bleeding. A functional distinction also exists, with posterior bleeds representing larger blood vessels, more significant bleeding, and the need for more invasive treatment. More than 90% of nosebleeds, as well as the majority of anterior bleeds, arise from Little's area.[4,6] The other 5–10% of cases of epistaxis are classified as posterior bleeds and most commonly occur along the lateral nasal wall and posterior nasal septum.[11] This area, as stated above, receives its blood supply from the sphenopalatine branch of the IMA.

Woodruff's plexus is described as an arterial plexus formed by the anastomosis between the posterior pharyngeal, posterior nasal, sphenopalatine, and posterior septal arteries at the posterior end of the inferior turbinate in the inferior meatus. These vessels are a source of posterior nosebleeds, although most episodes of bleeding from the area of Woodruff's plexus are now believed to be venous in origin.[12] It should also be noted that some posterior bleeds can be traced back to the internal carotid artery itself or branches thereof.

ETIOLOGY

The most common etiology of epistaxis is spontaneous/idiopathic, followed by traumatic.[13] Digital trauma such as nose picking is common in all age groups, but most common in the pediatric population. The source of these bleeds is usually just proximal to the mucocutaneous junction in the nasal septum where there is little subcutaneous tissue into which the injured vessel can retract. Thinning of the nasal mucosa, increased tendency toward mucosal dryness, and a higher incidence of medical comorbidities have been identified as risk factors in the older age groups. Topical nasal medications such as corticosteroids and antihistamines may cause irritation and intermittent epistaxis in this area. Another cause of intermittent epistaxis is mucosal dryness and irritation from low moisture content in the ambient air. Septal deflections and septal perforations can bleed due to the turbulent nasal airflow caused by these anatomical variations. The raw mucosa around the edges of the perforation can dry out and form a crust that may bleed. Nasal tumors are an important diagnosis to exclude, especially in cases of unilateral bleeding, such as in juvenile nasopharyngeal angiofibroma in male teenagers. A foreign body should be considered when bleeding is accompanied by purulent and foul-smelling discharge, especially in children. Iatrogenic causes of epistaxis include sinus surgery, nasogastric tube placement, and nasal intubation. Other causes of epistaxis include certain medications, rhinosinusitis (which causes mucosal hyperemia), trauma to the septum or nasal bones, vasculitides, congenital syndromes, and systemic conditions associated with coagulopathies. The latter group includes hemophilia, von Willebrand disease, liver and renal disease, and malnutrition. A complete list of etiologies that have been implicated in epistaxis is listed in Table 21.1.

Although increased blood pressure has not been established as an independent risk factor for epistaxis, hypertension does make it more difficult to control active episodes of bleeding. It is believed that high blood pressure thickens vessel walls and that fibrosis of the arteries in elder patients prevents adequate vasoconstriction during a nosebleed.[14] However, in a study by Bhatta, hypertensive medications are usually required in less than half of people presenting with epistaxis and a blood pressure over 140/90 mm Hg.[15] Even so, efforts to normalize the patient's blood pressure during an active episode of epistaxis are recommended.

Hereditary Hemorrhagic Telangiectasia

Special consideration should be given to the disease process known as hereditary hemorrhagic telangiectasia (HHT), or Osler–Rendu–Weber syndrome. This is an autosomal dominant disease with a prevalence of 1 in 5,000–8,000 people.[16] These patients develop telangiectasias on their mucosal surfaces, as well as arteriovenous malformations in the lungs, liver, brain, and gastrointestinal tract. Nasal lesions develop on the septum, inferior turbinates, lateral nasal wall, and the floor of the nose, which can result in spontaneous epistaxis due to the fragility of these vessels. The incidence of other systemic vascular malformations in HHT patients is reported to be 25–50% for pulmonary lesions, 8–16% for hepatic lesions, and 15% for cerebral lesions. Approximately 1/3 of patients experience gastrointestinal bleeding due to telangiectasias, especially later in life.[17]

Epistaxis is the most common presenting sign of this disease process, and approximately half of patients with HHT experience recurrent epistaxis by 20 years of age.[18] The incidence of frequent nosebleeds increases with age, and it is not uncommon to have increasingly severe epistaxis by the time these patients reach their 4th or 5th decade.[18]

The main underlying pathology in HHT that causes vessel fragility is endothelial dysfunction, which is a result of an abnormality of the transforming growth factor β-signaling pathway leading to unregulated vessel

Table 21.1: Etiology

Local factors	
Traumatic	Digital manipulation, nasal bone fracture, facial trauma
Mucosal dryness	Low humidity, chronic nasal cannula use, continuous positive airway pressure
Topical sprays	Local chemical effect
Active infection or inflammation	Nasal polyps, allergic rhinitis, irritant rhinitis, rhinitis of pregnancy
Anatomic deformities	Septal spur, septal deflection
Iatrogenic	Sinonasal surgery, nasal instrumentation
Benign and malignant tumors	Juvenile nasopharyngeal angiofibroma, inverting papilloma, squamous cell carcinoma, esthesioneuroblastoma, SNUC, plasmocytoma, melanoma, lymphoma
Foreign bodies	
Systemic factors	
Medications and herbal supplements	Aspirin, ibuprofen, naproxen, indomethacin, diclofenac, diflunisal, ticlopidine, clopidogrel, dipyridamole, GP IIb/IIIa receptor blockers, warfarin, aminocaproic acid, heparin, diltiazem, propranolol, nitroprusside, nifedipine, nitroglycerin, quinidine, furosemide, SSRIs, amitriptyline, nortriptyline, promazine, chlorpromazine, lidocaine, heroin, cocaine, diphenhydramine, chlorpheniramine, gingko biloba, ginseng, vitamin E, ginger, garlic, cumin, onion, alcohol
Coagulopathies/poor platelet function	Chronic alcoholism, hemophilia, von Willebrand disease, hemolytic anemia, leukemia, idiopathic thrombocytopenic purpura, renal disease, uremia, Vitamin K deficiency, hepatic cirrhosis, malnutrition
Granulomatous conditions	Sarcoidosis, histiocytosis X
Vasculitides	Lupus, syphilis, periarteritis nodosa, granulomatosis with polyangiitis
Congenital/Genetic	Hereditary hemorrhagic telangiectasia, Marfan's syndrome

wall remodeling. The new vessel walls contain very few elastic elements and produce dilated and convoluted postcapillary venules that often directly connect to dilated arterioles.

There are two genotype/phenotypes correlations with this disease. HHT1 is an endoglin mutation located on chromosome 9, and HHT2 is an activin receptor-like kinase mutation located on chromosome 12.[19] Differences in the clinical manifestations of HHT1 and HHT2 have also been found. Patients with HHT1 demonstrate an earlier onset of nasal and oral mucosal telangiectases and a higher incidence of pulmonary AVMs, and patients with HHT2 demonstrate an earlier onset of dermal lesions and a higher incidence of liver AVMs.

Epistaxis from HHT occurs secondary to the presence of multifocal telangiectasia lesions. These lesions cluster in the anterior nasal cavity (nasal septum, inferior turbinates) with a paucity in the posterior nasal cavity, nasopharynx, and paranasal sinuses. In addition to implications for treatment, this pattern supports a two-hit hypothesis for telangiectasia formation: local microtrauma from nasal airflow and mechanical injury in the setting of genetic vascular dysfunction.

The Curacao diagnostic criteria are used to make the diagnosis of HHT. There are four main criteria:

- Recurrent and spontaneous epistaxis
- Mucocutaneous telangiectasia of the lips and oral cavity
- Visceral involvement:
  - Pulmonary arteriovenous malformations
  - Cerebral telangiectasias and/or cavernous angiomas (may cause seizures or hemorrhagic strokes)
  - Gastrointestinal lesions (may result in GI bleeding or intrahepatic shunting)
- Family history of HHT

A definitive diagnosis can be given if 3 or 4 criteria are present. The diagnosis is possible with 2 criteria, and unlikely with 0 or 1 criterion.[20]

The management of a patient with HHT is complex and highly individualized. Initial evaluation includes a full medical and epistaxis history, family history, and possible inclusion of genetic testing for the patient and first-degree

relatives. Consideration of screening for intracranial, pulmnary, and gastrointestinal vascular malformations should be given. Although the incidence of these lesions is less frequent than epistaxis, the potential morbidity is significant.

Management of epistaxis includes treatment of ongoing bleeding and prevention of future bleeding. A long-term approach is indicated given the chronic nature of HHT. Daily use of mucosal hydration with emollients is the mainstay of maintenance for the nasal symptoms of HHT. Active episodes of epistaxis can be controlled using the same measures used for non-HHT epistaxis and include maneuvers such as packing, thermal, and laser coagulation, which will be discussed later in this chapter. The decision to proceed with any of these interventions is based on a concerning degree of epistaxis frequency and severity, especially if associated with anemia and the need for blood transfusions. Several adjuvant therapies have been attempted to reduce the recurrence of telangiectasia lesions, including sclerotherapy using intralesional injections of sodium tetradecyl sulfate. Systemic and topical estrogen therapy may also reduce the severity and incidence of telangiectasia lesions. This hormonal therapy includes estrogen receptor modifiers such as raloxifene, which is a selective estradiol receptor modulator that works by increasing the expression of endoglin and activin receptor-like kinase. Lastly, bevacizumab is a monoclonal antibody inhibitor of vascular endothelial growth factor A (VEGF-A) that can be used as a topical application on the mucosa or as intralesional injections. The theoretical basis of this is the known increased plasma VEGF in patients with HHT.[20]

If bleeding episodes cannot be controlled with more conservative measures, patients can consider a surgical intervention called a septodermoplasty. This procedure is performed by denuding the mucosa of the nasal cavity and placing a split thickness skin graft 270° around the nasal sill. Tacking sutures are then used to hold the graft in place and promote the mucosal healing process. The long-term crusting and recurrence of telangiectasia lesions at the periphery of the graft are known long-term complications. Closure of the nasal cavities by suturing circumferential nasal mucosal flaps, termed Young's procedure, is associated with a significant improvement in epistaxis but is rarely performed given the significant morbidity of obstructing nasal airflow. Overall, HHT is a heterogeneous disease requiring a graduated, long-term treatment plan tailored to the individual patient.[21]

MANAGEMENT

When managing an epistaxis patient, determining the etiology and identifying the location of the bleeding vessel is the priority. In cases where this may be difficult to establish, a step-wise approach is advocated, starting with initial management and followed by appropriate intervention (Flowchart 21.1). The latter step includes general measures, cautery, packing, and surgical intervention.[2]

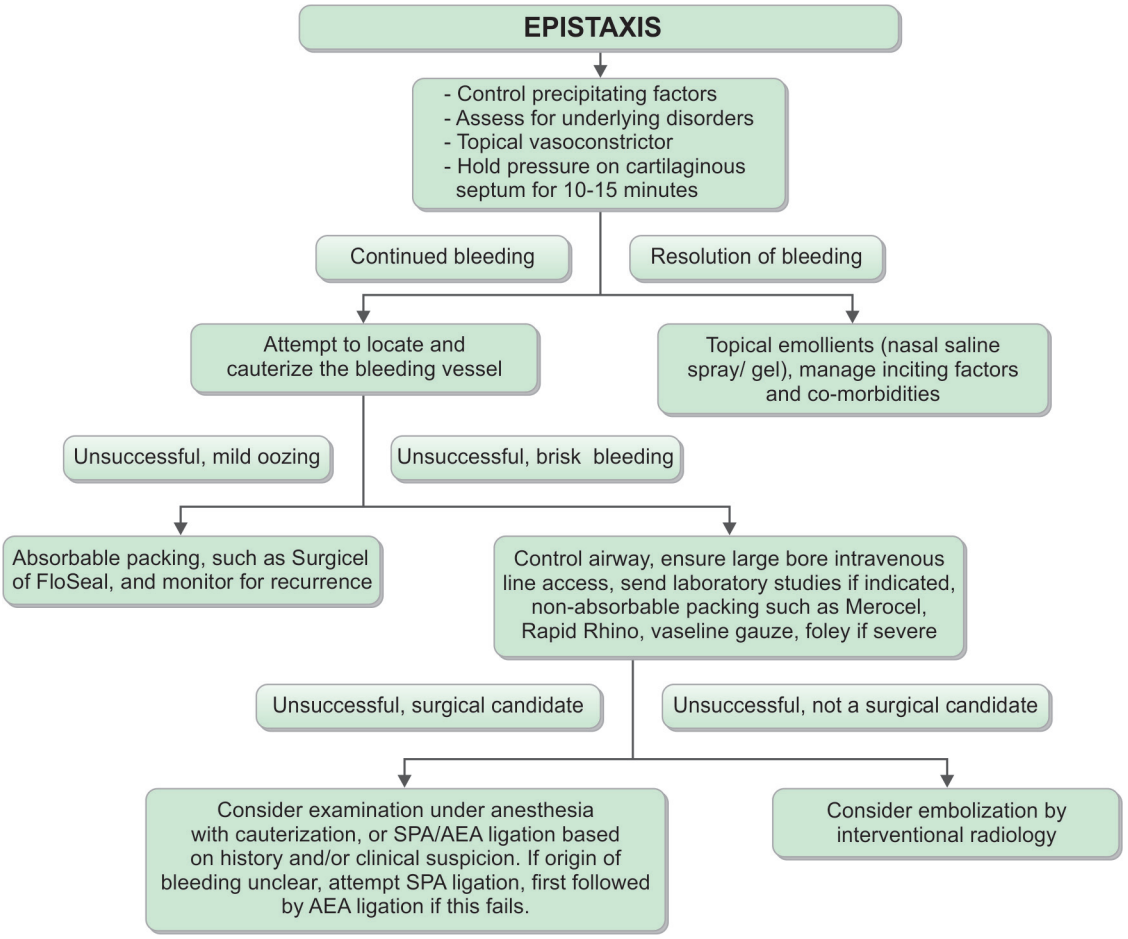
Anterior epistaxis can oftentimes be visualized using anterior rhinoscopy and a headlight; however, visualizing posterior epistaxis can be more difficult, even when using nasal endoscopy. Oftentimes posterior epistaxis is diagnosed solely based on the fact that posterior packing was required to control the hemorrhage.

INITIAL MANAGEMENT

If an episode of epistaxis is severe, such as in cases of anterior skull base and/or facial trauma, ACLS protocol goes into effect as in any case of an unstable patient. If needed, the patient's airway should be secured in instances where aspiration of large amounts of blood results in airway compromise. Rapid sequence orotracheal intubation is preferred to nasotracheal intubation, the latter of which can cause nasal trauma that may exacerbate the hemorrhage. A tracheotomy set should be available in the instance that intubation is not feasible due to blood obscuring anatomical visualization. Two large bore intravenous lines should be obtained for fluid resuscitation and the possibility of blood transfusion if the patient is hemodynamically unstable from massive blood loss. Vitals should be monitored continuously. If it can be determined, a history of how much blood the patient has lost is important in the acute setting.

In active epistaxis, a CBC may be considered based on the patient's clinical picture. A low hemoglobin/hematocrit may mean massive acute blood loss or chronic slow blood loss that has resulted in anemia. The latter group of patients should be started on iron supplementation. A low platelet level may point to an underlying disorder such as idiopathic thrombocytopenic purpura (ITP). Coagulation studies have been found to be helpful in patients on anticoagulation therapy who may have supratherapeutic levels during an epistaxis episode, or in patients with chronic liver disease who made need further medical intervention. However, in healthy patients, routinely checking coagulation studies has not been found to change management.[22]

Flowchart 21.1: Algorithm for epistaxis management.



Once an actively bleeding epistaxis patient is stabilized, a focused history should be taken: duration and frequency of epistaxis, side of the bleeding, predominance of anterior nasal cavity versus posterior nasopharyngeal direction of the bleeding, amount of blood loss, inciting or exacerbating factors, history of previous episodes, medical history, current medications and supplements, history of prior nasal trauma or surgery, illicit drug use, family history of bleeding, as well as excessive bleeding or bruising in other body sites. Nasal endoscopy can be performed to evaluate the septum, turbinates, middle meatus, sphenoethmoidal recess, and the sphenopalatine area for points of bleeding or any suspicious masses or lesions, as well as to look for signs of local or systemic disease that may be the cause of epistaxis.

A bleeding site cannot always be identified, especially in cases of mucosal, posterior, intermittent, or massive bleeds. Intervention to control an active hemorrhage should be undertaken if there is a strong history, even if the source is unclear at that point. One technique that can be used to help control an active episode of epistaxis, while also attempting to determine if the bleeding is coming from the area of the GPA/SPA, is to perform a greater palatine artery block. This technique is performed by injecting a local anesthetic, such as lidocaine, into the greater palatine foramen. This foramen extends in a posterosuperior direction at an angle of 60–80° from the horizontal plane of the hard palate, and this is the area that should be injected.[23] Douglas and Wormald have illustrated that effective infiltration of the pteryopalatine fossa via the greater palatine foramen requires injecting the local anesthetic with the needle bent 25 mm from the tip and at an angle of 45°.[24] Complications of this maneuver, although rare, include Horner's syndrome, infraorbital nerve injury, orbital nerve anesthesia or injury which may result in blindness, and intravascular injection,[25] all due to the proximity of these structures to the injection site.

INTERVENTION

General Measures

Universal precautions, such as wearing gloves, a face mask, and a gown, should be employed throughout the entire process of controlling an epistaxis episode. If an episode of epistaxis is minor and self-limited, conservative management with a topical nasal spray with vasoconstrictive properties (such as 0.05% oxymetazoline) and digital pressure to both nares at the inferior cartilaginous septum (where Kiesselbach's plexus resides) for 15–20 minutes is appropriate. If these maneuvers are successful in controlling the episode of epistaxis, the patient should begin using nasal saline, topical emollients/saline gel, or mupirocin ointment. Barrier ointments work by preventing crusting of the septal mucosa in order to decrease mucosal friability, and antibiotics ointments work by reducing vestibulitis and inflammation as well as by preventing mucosal dryness. Humidifiers may also help, including adding humidification to the oxygen of chronic nasal cannula users.

Cautery

In cases of small anterior mucosal bleeds in which a focal area of bleeding can be identified using a headlight and nasal speculum or a rigid endoscope, cauterization by chemical, thermal, or photocoagulative means is appropriate. Cauterization may also work with some posterior bleeds that can be visualized and accessed endoscopically. Silver nitrate ($AgNO_3$) works by producing a coagulative effect on the tissues via local chemical burn. It should be noted, however, that aggressive cauterization of both sides of the septum could result in a septal perforation. To avoid this complication, a staging process is preferred in cases where a patient may benefit from cauterization of both sides of the septum. Other complications of silver nitrate cauterization include accidental burns, mucosal ulceration, and silver tattooing. If the bleeding does not stop with silver nitrate, alternate measures should be considered rather than further application of silver nitrate to multiple areas of the nasal mucosa.

Packing

Absorbable packs can be considered for minor mucosal bleeding in cases where pressure packing may not be necessary. Examples of these coagulative materials include oxidized cellulose polymer, water-insoluble gelatin, microfibrillar collagen, thrombin gel, and others.[4] Although absorbable packing is generally well-tolerated by patients due to minimal discomfort, disadvantages include limited effectiveness for severe bleeding, and the potential for these materials to incite an inflammatory reaction.[26]

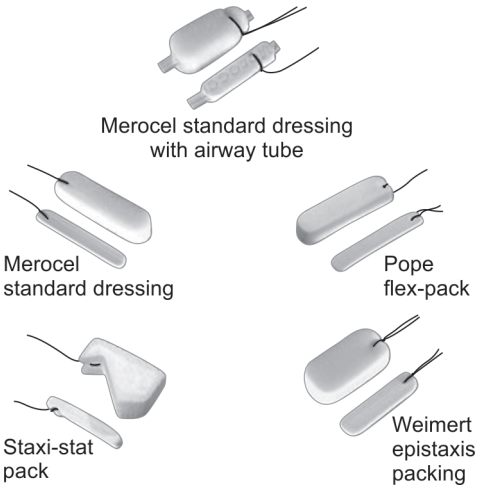


Fig. 21.2: Examples of commonly used packing materials. Image courtesy of Medtronic.

When the more conservative therapies discussed above are not successful, direct tamponade is indicated in the form of nonabsorbable packs. Examples of nonabsorbable packing include Merocel (Medtronic, Jacksonville, FL), Rhino Rocket sponges (Shippert Medical Technology, Centennial, CO), Rapid Rhino inflatable balloon packs (Arthrocare, Sunnyvale, CA), or Vaseline-impregnated gauze used as layered ribbon packing (Fig. 21.2). These packs are made from materials such as hydroxylated polyvinyl acetate (Merocel) and carboxymethyl cellulose with an inflatable cuff (Rapid Rhino).[27] They function by expanding to fill the nasal cavity as they are soaked with blood or are inflated, and thus apply pressure to the area of hemorrhage. In a randomized trial that compared FloSeal (combination bovine-derived gelatin matrix and human-derived thrombin; Baxter, Deerfield, IL) to nonabsorbable nasal packing (Merocel, Vaseline gauze, or Rapid Rhino), FloSeal had a rebleed rate at 1 week of 14% versus 40% for the other therapies, and patients also reported less discomfort with FloSeal.[28] Therefore, absorbable packing is preferred to nonabsorbable packs if it is effective in the situation at hand.

Complications of prolonged nonabsorbable packing include ulceration and necrosis of the skin and soft tissue of the nasal cavity and nasopharynx, synechiae, septal perforation, sinusitis from blockage of the normal nasal sinus

drainage pathways, and toxic shock syndrome (TSS). The incidence of TSS after primary nasal packing is unknown. Although no studies exist that evaluate the effect of systemic antibiotics on rates of TSS due to the rarity of this entity, most otolaryngologists prefer to place patients with nonabsorbable packing on prophylactic antibiotics with gram-positive coverage in order to prevent both TSS and secondary bacterial sinusitis. Packs are generally removed in 48–72 hours if no further bleeding occurs after initial pack placement.

Posterior epistaxis can be difficult to treat as it is oftentimes severe and its location difficult to visualize on initial evaluation. Choices for posterior packing include Vaseline packs, the anterior–posterior version of the Rapid Rhino, and the Epistat (Medtronic). In very severe instances where these packs fail, a Foley catheter can be advanced into the bleeding nasal cavity along the floor and through the nasopharynx until the tip of the catheter is visualized in the oropharynx. The balloon is then inflated with 15 cc saline to occlude the nasopharynx and pulled forward until it plugs the posterior choanae on that side. The nasal cavity should then be packed anterior to the Foley with Vaseline gauze in a layered fashion.[29] The Foley is then secured in place without placing pressure on the nasal ala.

Complications of posterior nasal packing include mucosal damage, septal perforation, alar necrosis, and intracranial penetration in cases of skull base trauma. In cases of bilateral packing, serious complications can include cardiac arrhythmias, apnea, and hypoxia secondary to the nasopulmonary reflex,[30] although the clinical relevance of this reflex has been called into question in certain studies.[31] Nonetheless, these patients should be admitted to the hospital for monitoring if not already in a hospital setting, at least until one posterior pack can be deflated and removed after monitoring for recurrence of bleeding. However, posterior packing is falling out of favor, not only due to the above listed complications, but also because it is uncomfortable for the patient and, if not tolerated, sedation and intubation may be required prior to packing placement. Furthermore, surgical interventions such as ligation and embolization have now been shown to be safe and effective and are beginning to replace the need for posterior packing.

Surgical Intervention

Surgical intervention is required if nonsurgical interventions fail, or if there is a compelling history for earlier surgical intervention, such as severe recurrent epistaxis following recent sinus surgery. Endoscopic bipolar diathermy or Bovie electrocautery to the area can treat many cases of both anterior and posterior epistaxis. Complications of this method are limited and include ineffective control of the bleeding site requiring further intervention, and injury to sinonasal and surrounding neurovascular structures. Laser photocoagulation can be undertaken with argon, potassium-titanyl-phosphate (KTP), or neodymium-doped-yttrium aluminum garnet (Nd:YAG) lasers, and have been found to be a good choice for small telangiectasias in HHT patients. Larger lesions usually contain a central high flow area that continues to persist while lasering, and bleeding then hinders further ablation. The laser technique includes making a rosette shape around the lesion with a focused laser beam. Laser safety precautions must always be used.

Sphenopalatine Artery Ligation

When the above measures fail, are unlikely to be successful due to the nature of the bleeding, or the surgeon has a high suspicion that the bleeding is coming from a branch of the SPA, an SPA ligation is considered, especially for severe or persistent episodes of epistaxis.

The first step to performing an SPA ligation is to create a submucoperiosteal flap anterior to the crista ethmoidalis in order to identify the vessels emerging from the SPF. To do this, an incision is made in the lateral nasal wall, posterior to the maxillary sinus. A submucoperiosteal flap is elevated off the lateral nasal wall just anterior to the posterior attachment of the middle turbinate. This will expose the crista ethmoidalis along the posterior edge of the maxillary sinus, which is a useful landmark to identify the SPF and SPA. In a study that evaluated 22 cadavers, the crista ethmoidalis was located just anterior to the SPF in 21 specimens and 3 mm directly inferior to the foramen in 1 specimen.[32] Studies indicate that the SPF is located higher than the posterior attachment of the middle turbinate.[33,34] If necessary, a middle meatal antrostomy can be performed to help identify where to make the incision and raise the flap posterior to the maxillary sinus.[33]

The SPA can be ligated with bipolar diathermy or may require a combination of diathermy and a clip in order to ensure proper ligation (Fig. 21.3). It is very important to identify, ligate, and cauterize all branches of the SPA to prevent recurrence of bleeding. When satisfactory ligation has been achieved, the submucoperiosteal flap is then placed back into its normal position. SPA ligation has

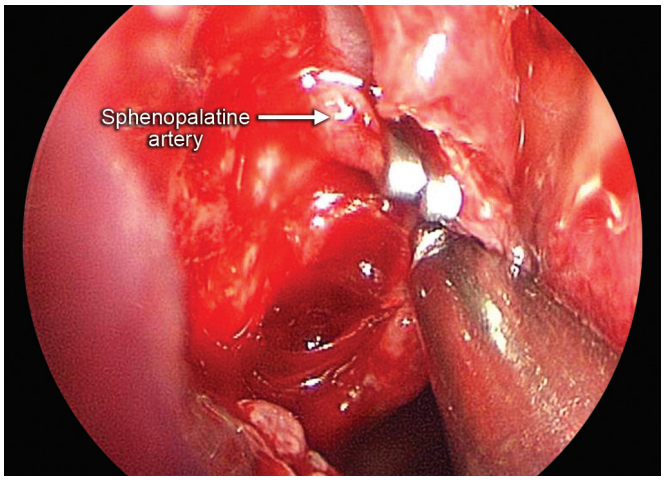


Fig. 21.3: Endoscopic ligation of the sphenopalatine artery demonstrating proper clip placement.

been shown to have a 85–100% success rate, and failure may be due to incomplete ligation of all branches of the SPA, mucosal bleeding, or arterial bleeding from a different site including ethmoidal vessels.[33,34]

Early surgical intervention for epistaxis is favored in certain cases, and studies have shown that this may result in shorter hospital stay and reduced hospital costs as compared to prolonged and recurrent posterior packing.[35] A study by Dedhia et al. demonstrated that endoscopic SPA ligation is cost-saving as first-line therapy for posterior epistaxis, with a savings of $1796 compared to 3 days of posterior nasal packing and $6263 when the duration of nasal packing is increased to 5 days.[36] Complications of SPA ligation include minor rebleeding (15–20% of cases), major rebleeding that requires return to the OR (<1% of cases), crusting (34%), palatal numbness (12%), and sinusitis (3%).[37,38]

Embolization

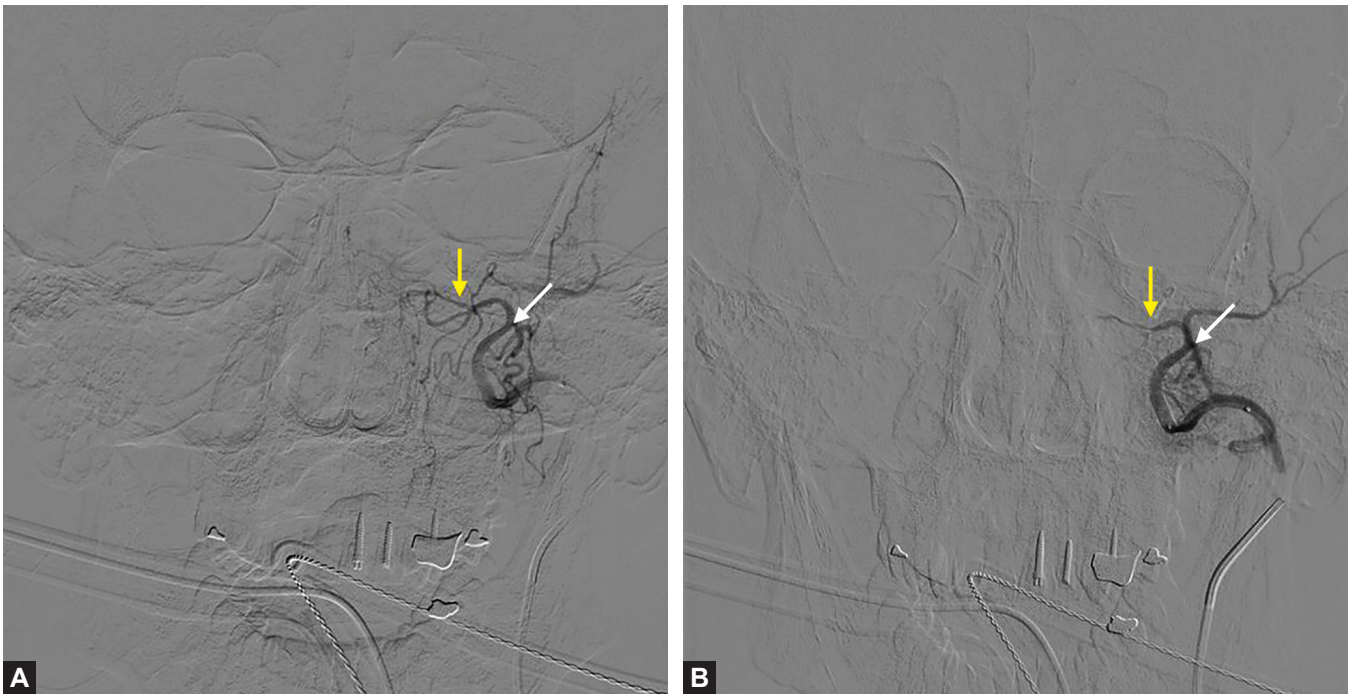
After first described in 1972, angiographic embolization of selected arteries has become an option for the treatment of intractable epistaxis. This process begins with an initial angiogram of the internal and ECA systems via transfemoral catheterization (Fig. 21.4A) since vascular abnormalities must be ruled out prior to embolization. These abnormalities would include post-traumatic or postsurgical pseudoaneurysm, carotid-cavernous fistula, or ECA anastomosis with the ophthalmic artery. After anomalies have been ruled out, the next portion of the angiogram identifies the target vessel, which requires active bleeding to ensure identification of the correct site. The most common vessel identified and embolized is the distal branch of the IMA. Less commonly a branch of the facial or the contralateral IMA is found to be the bleeding vessel. Polyvinyl alcohol microparticles, platinum coils, or gel foam pledgets are used to embolize the vessel. A postembolization angiogram is then performed to ensure success of the procedure (Fig. 21.4B).

The success of this intervention requires a skilled interventional radiologist, and reported success rates range from 71% to 100%, with an average of 88%.[39] There is oftentimes the question of the extent of embolization: IMA versus facial and ipsilateral versus bilateral. Tseng et al. reported the following rates of successful embolization cases: 61% ipsilateral IMA, 13% bilateral IMA, 16% ipsilateral IMA and facial, and 6% bilateral IMA and facial.[40] Failure is most commonly due to involvement of the anterior ethmoid artery, which is not addressed during embolization since it is a branch of the ICA. Other vessels potentially involved but not addressed with embolization include the accessory meningeal artery and the ascending pharyngeal artery, although these are less common sources of bleeding than the AEA. Complications of embolization can be divided into neurological complications and local complications. Neurological complications include stroke, cranial nerve palsies, and visual loss. This is due to anastomotic networks between the ECA system and the orbit, e.g. ethmoidal collaterals and the meningohypophyseal artery. Neurologic complications occur in less than 1% of embolization cases. Local complications include groin hematoma, femoral pseudoaneurysm, alar necrosis, cheek skin sloughing, and peripheral nerve numbness.[39,41]

Anterior Ethmoidal Artery Ligation

In addition to spontaneous epistaxis, other common reasons for a primary AEA bleed include trauma to the skull base or prior sinus surgery. For the most part, AEA ligation is indicated for patients who have failed a prior attempt at ligation of the SPA and/or embolization of the IMA, or if the AEA is known to be the bleeding vessel.

Depending on the patient's anatomy, this procedure can be approached either externally or endoscopically. The feasibility of an endoscopic approach lies in the location of the AEA, so a fine cut CT scan of the sinuses should be obtained preoperatively to identify its location in relation to the skull base (Fig. 21.5). A study by Simmen et al. in 2006 that looked at 34 cadaver heads demonstrated



Figs. 21.4A and B: (A) Pre-embolization angiogram showing opacification of the distal branches (yellow arrow) of the internal maxillary artery (white arrow). (B) Postembolization angiogram again demonstrating the internal maxillary artery (white arrow) but with its distal branches now occluded (yellow arrow).

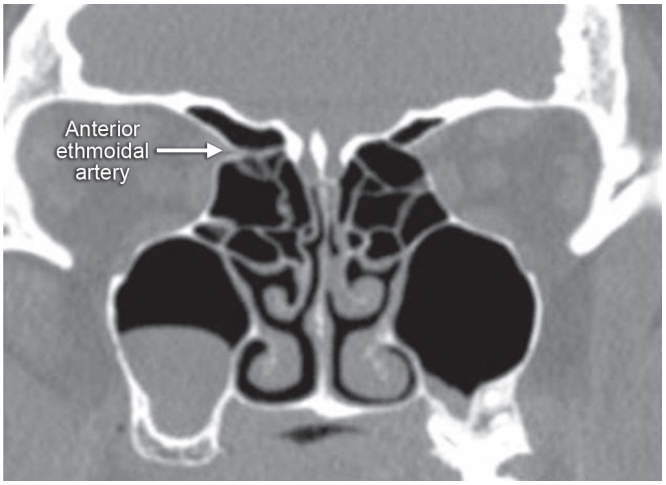


Fig. 21.5: Coronal computed tomography of the sinuses illustrating the location of the anterior ethmoidal artery.

that the AEA was at the skull base in 22(64.7%) cases and separate from the skull base in 12(35.3%). In the latter group, the mean distance from the skull base was 3.5 mm with a range of 1–8 mm.[42]

An endoscopic approach to AEA ligation is a better option and a more straightforward procedure when the AEA is not at the skull base and instead suspended from the ethmoid roof. This way, sufficient mesentery should be available to ensure complete bipolar diathermy or clip placement around the artery.[43] Attempting to clip or cauterize an AEA on the skull base in the presence of a dural tail on the neurovascular bundle could result in CSF leak. Similarly, retraction of the AEA into the orbit resulting in orbital hematoma may occur.

An alternative technique to AEA ligation is an external approach performed via a Lynch incision (external ethmoidectomy incision) measuring about 3 cm in the medial canthal region. This incision is made halfway between the medial canthus and the midline nasal dorsum and brought down onto the bone. The landmarks to locate the AEA are at the nasofrontal ethmoidal suture line and the superior aspect of the lacrimal bone. A subperiosteal plane is established in order to identify the anterior lacrimal crest. An important measurement is that the AEA lies 24.4 mm +/- 3.7 mm from the anterior lacrimal tubercle after gently lifting the lacrimal sac out of its fossa and dissecting posteriorly along the lamina papyracea.[44] The vessel can then be identified as it traverses the space between the lamina papyracea and the orbital periosteum on a horizontal plane at the level of the pupils. The AEA can be cauterized or clipped, and the two-layer wound closure includes the orbital periosteum and skin layers.

Posterior Ethmoidal Artery Ligation

Clinical experience has shown that most cases of epistaxis originate from the anterior ethmoid and IMA and rarely originate from the posterior ethmoid artery. If it becomes necessary to attempt ligation of this artery, risks and benefits must be considered and discussed, including optic nerve injury. It should also be taken into consideration the variable anatomy of the PEA and the fact that this vessel may be absent in up to 5% of people.

CONCLUSION

Epistaxis is a common clinical entity with an array of management and treatment options that are applied individually with a step-wise algorithm. The first steps include controlling precipitating factors, locating the bleeding vessel, and sometimes cauterizing or packing. If the bleeding persists or returns, further management decisions should be based on the severity and location of the bleed as well as the patient's overall medical well-being, and include treatment options such as ligation or embolization. A proper understanding of the underlying mechanism and available treatment options for any episode of epistaxis is paramount to ensuring consistently good outcomes for the large number of patients afflicted by this disease annually.

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CHAPTER

22

Headache and Facial Pain

Charles Parker, Jamie L Gentile, Brian L Hendricks, Ryan A Crane, Allen M Seiden

INTRODUCTION

The American Academy of Otolaryngology—Head and Neck Surgery estimates that 37 million Americans suffer from rhinosinusitis.[1] The Allergy and Asthma Foundation of America estimates 60 million Americans suffer from allergies.[1] These patients will usually have a varying degree of nasal symptoms, including congestion, nasal discharge, and a loss of smell. Many of them will also complain of headache, which in some cases may be the predominant symptom. These patients will often present at some point to an otolaryngologist.

The International Headache Society (IHS) estimates that 28 million Americans suffer from migraine headaches.[1] Migraine headaches are often associated with transient unilateral nasal congestion, part of its vascular complex, often prompting the patient to presume the headache to be related to some sort of nasal or sinus pathology.[2] Even those patients without nasal symptoms but with headaches that are localized anteriorly over the forehead, around the eyes, or in the maxillary region will often presume their pain to be generated by a sinus problem simply because of the location of the pain. These patients will often present at some point to an otolaryngologist as well.

It is therefore important for otolaryngologists to be thoroughly familiar with the various causes of headache and facial pain. This chapter will review the common causes of headache that are likely to present to an otolaryngologist.

PRIMARY HEADACHES

Many patients who present to the otolaryngologist with headache will have a primary headache disorder rather than a rhinologic or sinus headache. It is important for the otolaryngologist to be familiar with these disorders in order to form a correct and broad differential diagnosis and to treat or refer the patient to another provider appropriately.

Migraines

Migraines are a common primary headache disorder affecting approximately 28–30 million Americans: 18% of women, 6% of men, and 4% of children.[3] As a result, migraine carries a large economic burden; in 1 year alone it is estimated to cost 13 billion dollars in lost productivity in the United States.[4]

Though many patients develop headaches, as noted above, migraine sufferers are more commonly female, typically between the ages of 20 and 50. The sex ratio is accepted to be anywhere from 2:1 to 3:1 (female : male).[5] Additionally, migraine prevalence has been shown to increase as socioeconomic status decreases.[6] Migraines have been associated with several conditions: depression, anxiety, bipolar disease, and epilepsy.[3]

Classically, patients will complain of a pulsatile headache usually involving only one side. They may be sensitive to light and/or sound (photophobia, phonophobia) and they may have nausea and/ or vomiting. Patients may have prodromal symptoms prior to developing a headache. These are often noted to be a vague "feeling" or vegetative symptoms, but may also include visual changes or focal neurological signs. This typically precedes the headache by no > 1 hour, and is referred to as the "classic" migraine. The patient will then develop the typical migraine headache following the aura. Following the resolution of the headache, patients may also have a postdrome or hangover period with malaise and fatigue.

Table 22.1: International Headache Society diagnostic criteria for migraine

Migraine without aura	A. At least 5 attacks fulfilling criteria B to D B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated) C. Headache has ≥ 2 of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (i.e. walking, climbing stairs) D. During headache ≥ 1 of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia E. Not attributed to another disorder
Migraine with typical aura	A. At least 2 attacks fulfilling criteria B and C B. Aura consisting of ≥ 1 of the following reversible aura symptoms: 1. Visual 2. Sensory 3. Speech and/or language 4. Motor 5. Brainstem 6. Retinal C. At least two of the following: 1. At least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession 2. Each symptom lasts ≥ 5 and ≤ 60 minutes 3. At least one aura symptom is unilateral 4. The aura is accompanied or followed within 60 minutes, by headache D. Not attributed to another disorder (specifically transient ischemic attack has been ruled out)

Much more common is the migraine without aura. The diagnostic criteria for migraine without aura, according to the International Classification of Headache Disorders III beta (ICHD-III beta), include the following: (1) at least five attacks fulfilling the following criteria; (2) headache lasting 4–72 hours (untreated or unsuccessfully treated); (3) headache has at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity; (4) during the headache the patient has at least one of the following: nausea and/or vomiting, photo, or phonophobia; (5) The headache cannot be attributed to another disorder.[7]

The diagnostic criteria for migraine with aura are the following: (1) the patient must have at least two attacks with these characteristics; (2) the patient must have a migraine aura with one of the following symptoms—visual, sensory, speech and/ or language, motor, brainstem, or retinal auras; (3) the patient must also have at least two of the following four characteristics: at least one aura symptom spreads gradually over > 5 minutes and/or two or more symptoms occur in succession; each aura symptoms last 5–60 minutes; at least one aura symptom is unilateral; the aura is accompanied or followed within 60 minutes by headache. The most common aura consists of one of the following: fully reversible visual symptoms including positive features (flickering lights, spots, or lines) and negative features (such as loss of vision), fully reversible sensory symptoms including positive features (pins and needles) and/ or negative features (numbness), and fully reversible dysphasic speech disturbance. Also, the headache associated with these findings fulfills the criteria for migraine without aura and cannot be attributed to another disorder (especially a transient ischemic attack).[7] The ICHD-III beta criteria are outlined in Table 22.1.

Other types of migraines recognized by ICHD-III beta are migraine with brainstem aura, hemiplegic migraine, retinal migraines, and multiple migraine syndromes with familial predisposition. The first is associated with brainstem features: dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, and/ or decreased level of consciousness. The second is a migraine with aura and also with motor

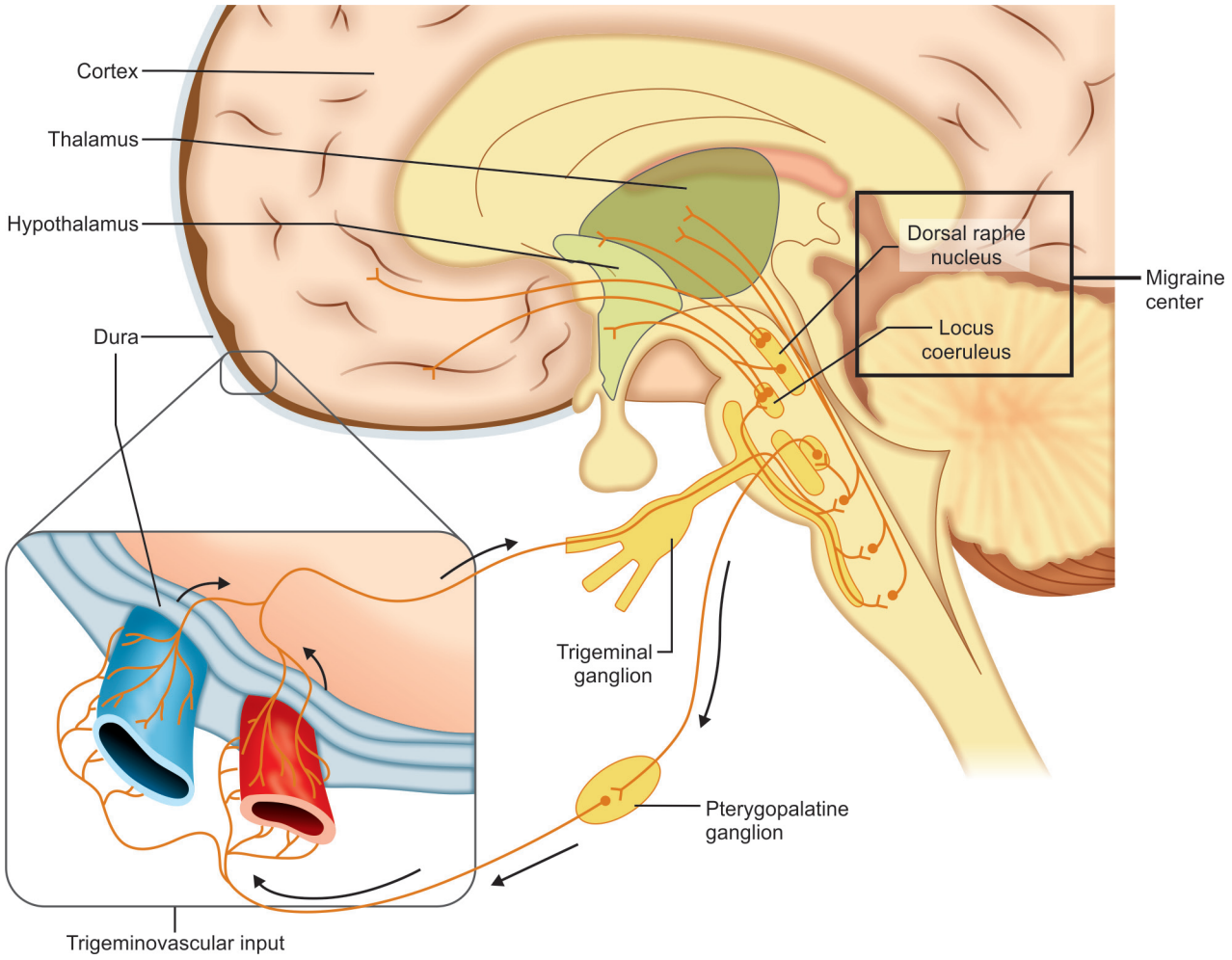

Fig. 22.1: The pathophysiology of migraines via both blood flow and cortical spreading depression. http://pharmacologycorner.com/pharmacologic-treatment-migraine-pathophysiology-clinical-features/

weakness defined as fully reversible motor weakness, and/or fully reversible visual, sensory and/ or speech/language symptoms. One other type of migraine recognized by the ICHD-III beta is retinal migraine. This is a migraine headache that is solely associated with visual symptoms such as scintillations, scotomata, or blindness, with a normal ophthalmologic examination between attacks.[7]

The pathophysiology of migraines is not entirely understood, though information in this regard continues to increase. In general, the pain and aura are thought to be secondary to abnormal activation and modulation of trigeminocervical neurons. More specifically, according to the vasogenic theory originally popularized by Wolff, migraines are a vascular disorder. They are caused by a sudden vasoconstriction followed by a sudden vasodilatation of the blood vessels in the brain. Alternatively, the neurogenic theory (originally described by Leao) suggests that a wave of cortical excitation occurs followed by long-lasting depression. This phenomenon is known as "cortical spreading depression."[8] This phenomenon of cortical spreading depression is illustrated in Figure 22.1. Figure 22.2 also demonstrates the pathophysiology of migraines and illustrates the cause of the pain as well as the other symptoms of migraine (photo/phonophobia and gastrointestinal symptoms). There is also thought to be a genetic component that will make a person more susceptible to developing migraine headaches.

There are some disorders of childhood that have been shown to be precursors to migraines: cyclical vomiting, abdominal migraine, and benign paroxysmal vertigo of childhood. Children who have these disorders may go on to suffer from migraine headaches as adults. Cyclical

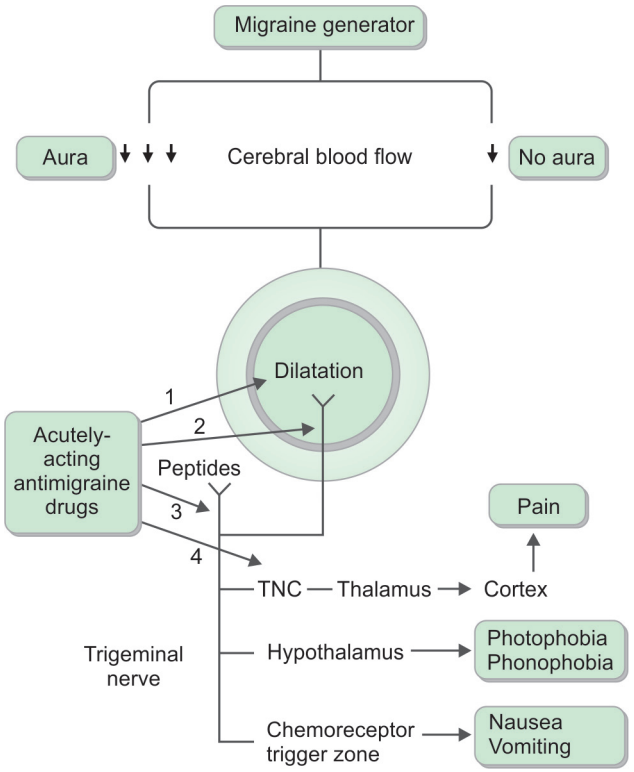

Fig. 22.2: The pathophysiology of migraines and the mechanism of actions of the anti-migraine drugs. From http://pharmacology-corner.com/pharmacologic-treatment-migraine-pathophysiology-clinical-features/

vomiting is recurrent episodic attaches of vomiting and nausea, but the child feels completely normal between attacks. Abdominal migraine is defined as episodic abdominal pain in children that lasts 1–72 hours and again the child is normal between episodes. Benign paroxysmal vertigo of childhood results in children having severe, recurrent, very brief vertiginous symptoms that occur without provocation and resolve spontaneously.[7]

The treatment of migraines is not quite as relevant to the otolaryngology physician. The patient can be referred back to his or her primary care physician or to a headache specialist. However, there are some suggestions that the otolaryngology physician might initiate therapy. The first is to make some lifestyle changes that can help reduce headache. These include improved sleep hygiene, decreased dietary triggers, and better stress management. Other nonpharmacologic treatments that have been shown to be helpful include biofeedback, relaxation techniques, hypnosis, and psychological therapies.

The pharmacologic treatment of migraines is differentiated into two categories: Abortive medications and preventive medications. Abortive medications include nonsteroidal anti-inflammatory drugs (NSAIDs), ergotamine derivatives (i.e. dihydroergotamine), and serotonin 5-HT receptor agonists (triptans). Preventative medications include beta-adrenergic blockers, i.e. propranolol and atenolol, calcium channel blockers such as verapamil and flunarizine, tricyclic antidepressants (TCAs) such as amitryptylines, serotonin antagonists such as methysergide, and antiepileptics such as topiramate and valproate. Other newer approaches for treatment include Botox injection, and nerve stimulation approaches.[9]

There have been few studies indicating a clear link between migraines and complications or comorbid conditions. Some thoughts of "complications" include the lost productivity for patients and society as a whole. There have been studies that have suggested a link between insomnia and migraine headaches. Those who have headache should be evaluated and treated for insomnia.[10] Migraines have also been associated with seizures, and ischemic stroke. Both are most strongly related to migraine with aura.[3] Status migrainosus is another complication of migraine and is a debilitating migraine headache lasting for > 72 hours.[7]

Tension-Type Headache

Tension-type headaches are the most common type of primary headache. In fact most individuals will have experienced at least one tension-type headache in their lifetime. The global lifetime prevalence of tension-type headache ranges from 30% to 78%.[7] It can affect anyone, though in general, sufferers are more commonly female. Patients typically complain of a headache that is like a tight headband/vice compressing his/her head with a dull, aching, and nonpulsatile quality. The headaches are bilateral. They are also associated with neck muscle pain or tightness, and pericranial muscle tenderness.

There are three types of tension headaches according to the ICHD-III beta: infrequent episodic, frequent episodic, and chronic. Infrequent episodic tension-type headache is characterized by the patient having at least 10 episodes of headache occurring on < 1 day per month on average (< 12 days per year). The headache must fulfill the following criteria: (1) headache lasting from 30 minutes to 7 days; (2) headache must have at least 2 of the following characteristics: bilateral location, pressing/tightening (nonpulsing quality), mild-to-moderate intensity, not aggravated by routine activity such as walking or climbing stairs; (3) both of the following: no nausea or

Table 22.2: International Headache Society diagnostic criteria for tension-type headache

Infrequent episodic tension-type headache	A. At least 10 episodes of headache occurring on < 1 day per month on average (< 12 days per year) and fulfilling criteria B to D B. Headache lasting from 30 minutes to 7 days C. Headache has ≥ 2 of the following characteristics: 1. Bilateral location 2. Pressing/tightening (nonpulsating) quality 3. Mild or moderate intensity 4. Not aggravated by routine physical activity D. Both of the following: 1. No nausea or vomiting (anorexia may occur) 2. No more than one of photophobia or phonophobia E. Not attributed to another disorder
Frequent episodic tension-type headache	At least 10 episodes of headache fulfilling B to D above > 1 but < 15 days per month OR > 12 but < 180 days per year
Chronic tension-type headache	Headache > 15 days per month for 3 months OR > 180 days per year

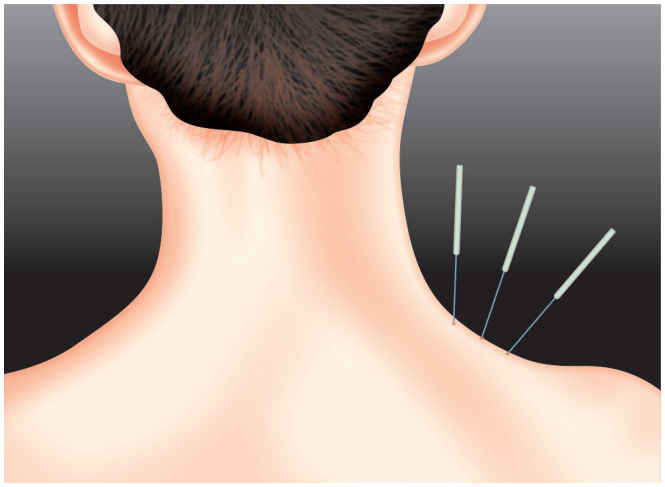

Fig. 22.3: A patient undergoing acupuncture for tension headache.

vomiting, though anorexia may occur; (4) no more than one of photo or phonophobia; (5) the headache cannot be attributed to another disorder. The infrequent episodic tension-type headaches are then subdivided even further into those associated with pericranial tenderness and those not associated with pericranial tenderness.

The next type of tension headache is the frequent episodic tension-type headache. These headaches have the same diagnostic criteria as the infrequent tension headaches but the frequency criteria are different. To be diagnosed with frequent episodes, the patient must have at least 10 episodes occurring on > 1 but not > 15 days per month for at least 3 months (> 12 and < 180 days per year). Similarly, the chronic tension-type headache is also differentiated based on time course. To diagnose this, the patient must have headache occurring on > 15 days per month on average for > 3 months (headaches on ≥ 12 days per year and < 180 days per year) and fulfill the other criteria for tension headaches. An exception is that the headache may be continuous in chronic tension headache (it does not have to be from hours to 7 days).[7] Again, the ICHD-III beta criteria are shown in Table 22.2.

The pathophysiology of tension-type headaches is also not well understood. Both peripheral and central neurological systems are likely involved. There may be a genetic component in that first-degree relatives of patients with chronic tension-type headache are three times more likely to also suffer from headaches.[11] However, episodic tension-type headaches likely have little to no genetic component, and are much more strongly linked to environmental factors.[12]

Treatment is as above with migraines, starting with lifestyle changes and referral if needed. Other considerations include treatment with NSAIDs, TCAs, and Botox injections into trigger points.[9] There is some evidence that acupuncture (or dry needling, seen in Figure 22.3) is very helpful in the treatment of tension-type headaches.[13]

Trigeminal Autonomic Cephalgias

In general, trigeminal autonomic cephalgias are a group of primary headache disorders that are typified by attacks of recurrent unilateral pain usually involving the distribution of the ophthalmic (V1) division of the trigeminal nerve. A sense of restlessness and agitation is an

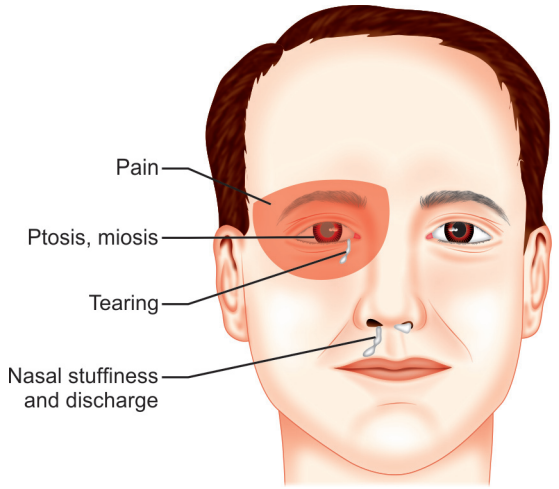

Fig. 22.4: How a patient appears during a trigeminal autonomic cephalalgia with autonomic symptoms.

important characteristic in this type of primary headache.[14] However, only cluster headaches and hemicranias continua continue to have this in their diagnostic criteria in the ICHD-III beta. The autonomic symptoms that the patient experiences during a trigeminal autonomic cephalalgia are illustrated in Figure 22.4.

Cluster

Cluster headaches are categorized as one of the trigeminal autonomic cephalgias. The term cluster comes from how the attacks cluster together in bouts and then have longer periods of remission. Patients with cluster headaches are more likely to be male, in their third to fifth decade of life, often with a ruddy or leathery complexion. There is some genetic predisposition and also an association with smoking.[15]

Patients complain of unilateral pain over the eye, temple, or maxilla. It is burning or pulsing in nature. It is associated with lacrimation, conjunctival injection, nasal congestion, and/ or rhinorrhea. Attacks last between 15 and 180 minutes. The frequency of attacks is between 1 every other day to 8 attacks per day. Periods of remission are at least 1 month long but have been as long as 20 years. The attack clusters last on average 8 weeks. Attacks can be triggered by sleep,[16] smells,[17] and alcohol.[15] In contrast to migraine patients, patients with cluster headaches (as in all the trigeminal autonomic cephalgias) are often very agitated during an attack.[17] Additionally, the pattern of headaches has a distinct circadian and circannual periodicity; meaning that the headaches tend to come at the same time of day and the clusters are during the same time of year.[18]

In order to be diagnosed with cluster headaches, the patient must have headache and the attacks must fulfill the following criteria, according to the ICHD-III beta (seen in Table 22.3): (1) severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 minutes (when untreated); (2) either or both of the following ipsilateral to the side of the pain, conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, forehead and facial flushing, sense of fullness in the ear, miosis and/or ptosis; a sense of restlessness or agitation. This is largely because the pain is so severe (cluster headaches have often been referred to as "suicide headaches"). The attacks have a frequency from 1 every other day to 8 per day. As before, the headache cannot be attributed to another disorder.[7] Cluster headaches can also be classified as chronic with headache attacks occurring for >1 year without remission or with remission periods lasting <1 month.[7] The mainstay of abortive treatment for cluster headaches is oxygen and triptans. The primary preventative medication is verapamil.[19]

Short-Lasting Unilateral Neuralgiform Headache Attacks

This primary headache syndrome is characterized by attacks of unilateral pain with autonomic symptoms similar to cluster headaches and the other trigeminal autonomic cephalgias; however, the attacks are very brief and only last seconds.

The ICD-III beta criteria for this type of headache, in Table 22.4, are that the patient has 20 attacks fulfilling the following criteria: moderate or severe unilateral head pain, with orbital, supraorbital, or temporal stabbing pain lasting 1–600 seconds; pain is accompanied by ipsilateral conjunctival injection and lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, forehead and facial flushing, sensation of fullness in the ear, and miosis and/or ptosis, attacks occur with a frequency from at least one (but can have upwards of 200) per day; and the headache is not attributed to another disorder.[7]

These headaches can be episodic or chronic. Episodic is defined as at least two attack periods lasting 7–365 days and separated by pain-free remission periods

Table 22.3: International Headache Society diagnostic criteria for cluster headache

Cluster headache	A. At least 5 attacks fulfilling criteria B to D B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 min if untreated C. Headache is accompanied either or both of the following: 1. One of the following symptoms: a. Ipsilateral conjunctival injection and/or lacrimation b. Ipsilateral nasal congestion and/or rhinorrhea c. Ipsilateral eyelid edema d. Ipsilateral forehead and facial sweating e. Ipsilateral forehead and facial flushing f. Ipsilateral sensation of fullness in the ear g. Ipsilateral miosis and/or ptosis 2. A sense of restlessness or agitation D. Attacks have a frequency from 1 every 2 days to 8 per day E. Not attributed to another disorder
Episodic cluster headache	At least two cluster periods lasting 1 week to 1 year are separated by a remission period lasting ≥ 1 month
Chronic cluster headache	Cluster periods occur for > 1 year without remission periods or remission periods < 1 month

Table 22.4: International Headache Society diagnostic criteria for short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing	A. At least 20 attacks fulfilling criteria B to D B. Moderate or severe unilateral orbital, supraorbital and/or temporal pain lasting 1–600 seconds C. Headache is accompanied by one of the following symptoms: 1. Ipsilateral conjunctival injection and/or lacrimation 2. Ipsilateral nasal congestion and/or rhinorrhea 3. Ipsilateral eyelid edema 4. Ipsilateral forehead and facial sweating 5. Ipsilateral forehead and facial flushing 6. Ipsilateral sensation of fullness in the ear 7. Ipsilateral miosis and/or ptosis D. Attacks have a frequency of a least one per day to more than half of the time when the disorder is active E. Not attributed to another disorder

of >1 month. Chronic is defined as attacks that recur over >1 year without remission periods or with remission periods lasting <1 month.[7]

Paroxysmal Hemicrania

Paroxysmal hemicrania is a similar type of headache to the above, but shorter lasting, occurring more frequently, and responding in every case to indomethacin. The diagram in Figure 22.5 illustrates how to differentiate the above headaches based on symptom time course. The headaches are always unilateral, though some patients may have side alternating attacks.[20] Paroxysmal hemicrania is very rare. The prevalence of paroxysmal hemicranias is not known but was estimated in one study to be 1 in 50,000.[21] Patients are typically middle aged.[19]

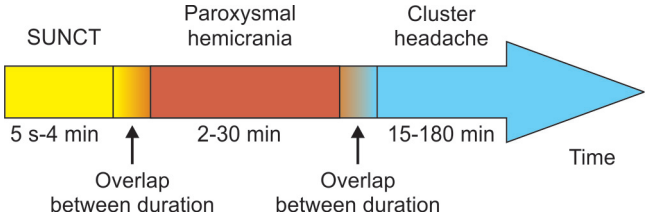

Fig. 22.5: The overlap between the trigeminal autonomic cephalalgias based on duration.
Modified from Leone M, Bussone G. Pathophysiology of trigeminal autonomic cephalalgias. Lancet Neurol. 2009;8:755-64.

Table 22.5: International Headache Society diagnostic criteria for paroxysmal hemicrania

Paroxysmal hemicrania	A. At least 20 attacks fulfilling criteria B to D B. Attacks of severe unilateral orbital, supraorbital, and/or temporal pain lasting 2–30 minutes C. Headache is accompanied by at least one of the following: 1. Ipsilateral conjunctival injection and/or lacrimation 2. Ipsilateral nasal congestion and/or rhinorrhea 3. Ipsilateral eyelid edema 4. Ipsilateral forehead and facial sweating 5. Ipsilateral forehead and facial flushing 6. Ipsilateral sensation of fullness in the ear 7. Ipsilateral miosis and/or ptosis D. Attacks have a frequency of >5 per day for more than half of the time, although there may be periods with lower frequency E. Attacks are prevented completely by therapeutic doses of indomethacin F. Not attributed to another disorder
Episodic paroxysmal hemicrania	Attack periods lasting 7–365 days and separated by pain-free remission periods of ≥ 1 month
Chronic paroxysmal hemicrania	Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month

The ICHD-III beta criteria for paroxysmal hemicrania are headache accompanied by one of the following: Ipsilateral conjunctival injection and/or lacrimation, ipsilateral nasal congestion and/or rhinorrhea, ipsilateral eyelid edema, ipsilateral forehead and facial sweating, ipsilateral forehead and facial flushing, ipsilateral sensation of fullness in the ear, ipsilateral miosis, and/or ptosis. Patients have a frequency of five or more major attacks per day. Attacks are prevented completely by therapeutic doses of indomethacin. Also, the headaches cannot be attributed to another disorder. Paroxysmal hemicrania can be either episodic or chronic. Episodic is defined as at least two attack periods lasting 7–365 days and separated by pain-free remission periods of > 1 month. Chronic is defined as attacks that recur over > 1 year without remission periods or with remission periods lasting < 1 month.[7] The ICHD-III beta criteria are outlined in Table 22.5.

The treatment of paroxysmal hemicranias is indomethacin. Most cases respond within 24 hours but up to a week of therapy may be necessary for some patients to respond.[22] In rare cases where the headache is resistant to indomethacin, the patient may respond to topiramate.[19] There is also some data that neuromodulatory procedures, i.e. greater occipital nerve blockade, blockade of sphenopalatine ganglion, and neurostimulation of the posterior hypothalamus can be helpful. These are reserved for refractory paroxysmal hemicranias.[14]

Hemicrania Continua

Hemicrania continua are sort of a combination of cluster headaches and paroxysmal hemicrania and are another autonomic cephalalgia. In this disorder, the patient has a headache for > 3 months that has all of the following characteristics: unilateral pain without side shift, daily and continuous, without pain free periods, moderate intensity, but with exacerbations of severe pain. The patient will also have either one or both of the following: (1) At least one of the following ipsilateral symptoms or signs: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial swelling, forehead and facial flushing, sensation of fullness in the ear, ptosis and/or miosis; (2) a sense of restlessness or agitation or aggravation of the pain by movement. Also, the patients have complete response to therapeutic doses of indomethacin. Finally, the headache cannot be attributed to another disorder.[7] The requirements to make the diagnosis according to the ICHD-III beta are in Table 22.6.

Hemicrania continua are very rare. The Vaga study of rare unilateral headaches noted that in a study of 1,838 adult parishioners, 18 individuals had symptoms suggestive of hemicrania continua (0.98%).[23] Most hemicrania continua patients are women in their 30s.[24]

There is also a phenomenon of secondary hemicrania continua in which patients have a phenotype that resembles hemicrania continua but is secondary to another

Table 22.6: International Headache Society diagnostic criteria for hemicrania continua

Hemicrania continua	A. Unilateral headache fulfilling criteria B to D B. Present for > 3 months with exacerbations of moderate or greater intensity C. Headache is accompanied either or both of the following: 1. One of the following symptoms: a. Ipsilateral conjunctival injection and/or lacrimation b. Ipsilateral nasal congestion and/or rhinorrhea c. Ipsilateral eyelid edema d. Ipsilateral forehead and facial sweating e. Ipsilateral forehead and facial flushing f. Ipsilateral sensation of fullness in the ear g. Ipsilateral miosis and/or ptosis 2. A sense of restlessness or agitation D. Complete response to therapeutic doses of indomethacin E. Not attributed to another disorder

disorder. Several case reports have noted this in the following conditions: leprosy, metastatic lung cancer, pituitary adenoma, osteoid osteoma, nonmetastatic lung cancer, ipsilateral brainstem infarction, unruptured internal carotid artery saccular aneurysm, internal carotid artery dissection, trauma, pineal cyst, and postpartum.[24]

The treatment of hemicrania continua is primarily with indomethacin; however, many other drugs have been suggested in one- or two-case presentations, including COX-2 inhibitors, topiramate, corticosteroids, Botox, gabapentin, melatonin, verapamil, and neuromodulation with peripheral nerve blockage and occipital nerve stimulation.[24]

SINUS HEADACHE

In 1908, Sluder described a syndrome of unilateral facial and head pain associated with unilateral rhinorrhea and congestion that he attributed to irritation of the sphenopalatine ganglion.[25] Subsequent reports over the years attributed this sphenopalatine neuralgia to impacting nasal septal spurs, although this does not appear to have been Sluder's intent, and the syndrome has become widely known as Sluder's neuralgia. The notion of headache being caused by nasal or sinus pathology has been controversial ever since.

Less well known is that Sluder was one of the first to describe the possibility of a so-called vacuum headache. In a series of experiments, he revealed that closure of the frontal infundibulum could lead to a vacuum or negative pressure within the frontal sinus that resulted in frontal headache.[26] Although vacuum headache is often listed and empirically accepted as a potential cause of pain related to sinus pathology, confirmatory data is quite limited. Stammberger and Wolf cite several studies demonstrating hypoxia in the sinuses giving a sensation of pain.[27] Most other reports appear to be largely anecdotal.

Adding fuel to the fire was a series of experiments performed by Wolff et al. in the 1940s, supporting the concept of referred pain from sinus inflammation.[28] In a small series of human volunteers, noxious stimuli were placed at various sites within the nose and paranasal sinuses. They found that (1) the mucosal lining of the sinus cavities was not very sensitive, (2) Mucosa surrounding the sinus ostia and on the nasal turbinates was much more pain sensitive, and (3) the pain was often not felt locally, but was referred to dermatomes of the first and second division of the trigeminal nerve. This suggested that underlying sinus inflammation could in fact be triggering more distant headache and facial pain.

With the introduction of fiberoptic technology and the adoption of endoscopic surgical approaches for managing sinus disease in the late 1980s and early 1990s, the focus on sinus pathology shifted to small drainage areas at the sinus ostia and within the ethmoid sinus. This emphasized tight areas of inflammation and impaction that were leading to recurrent sinus infections, along with which came the notion of secondarily referred headache pain. Stammberger and Wolf postulated that mechanical stimulation of free trigeminal nerve endings in these areas of impaction lead to the release of Substance P, a neurotransmitter active in pain transmission.[27] This then leads to an orthodromic impulse traveling along nociceptive C fibers interpreted centrally as pain, although

not necessarily well-localized peripherally. At the same time, an antidromic impulse causes greater localized neurogenic edema and hypersecretion, resulting in more swelling and theoretically more pain. This further inspired the concept of contact point headaches.

Studies looking at contact points within the nose or paranasal sinuses as a cause of facial or head pain have focused primarily on three areas: nasal septal spurs that impact the lateral nasal wall,[29-31] enlarged middle turbinates (usually pneumatized) that impact either the nasal septum or lateral wall,[32-34] and superior turbinates (also usually pneumatized) that impact either the septum or lateral wall.[35,36] Outcomes are usually based on subjective headache improvement or resolution following surgical correction. In general, results have been mixed with some patients reporting improvement, albeit incomplete and in some cases temporary. A recent review of this literature found most of these studies to be small nonrandomized case series subject to selection bias, providing no control group with limited follow-up, and subject to observer bias as well.[37] The notion of contact point headaches therefore remains controversial. There is general agreement that patients need to be selected very carefully before surgery is recommended, preferably after more traditional medical treatment of primary headache syndromes has failed.[38]

Patients presenting with acute onset of nasal congestion and purulent nasal discharge in the setting of acute sinusitis will often complain of a pressure headache or facial pain, usually localized to the sinus involved. This is well accepted, even by the latest IHS criteria for the classification of headaches.[39] For reasons that are less clear, chronic sinusitis seems less often associated with pain. Nevertheless, when symptoms of nasal congestion, drainage, and loss of smell are present, treatment of chronic sinusitis is more clearly indicated. When headache is the only complaint, an accurate diagnosis and best course of therapy are less straightforward.

The American Academy of Otolaryngology—Head and Neck Surgery, to develop criteria useful in the diagnosis of acute and chronic sinusitis, formed the Rhinosinusitis Task Force in the late 1990s.[40] A list of major and minor factors, based on symptoms and physical findings, was published in 1997 with a revision published in 2003.[41] Facial pain/pressure was considered a major factor or symptom, but by itself not considered to be diagnostic of sinusitis.

A number of studies have noted that the majority of patients presenting with a diagnosis of "sinus" headache (either their own diagnosis or given by a physician) fit the IHS criteria for migraine headache.[1,2,42] The confusion over migraines versus inflammatory sinusitis as a source of pain stems from a variety of factors. In a series of 100 patients presenting with self-diagnosed sinus headache, Eross et al. found that only 3% were found to have actual sinus pathology, while the remainder fit the classification of migraine or one of the other primary headache disorders.[1] Ninety-eight percent of these patients localized their pain as being over the sinuses. In 83%, the pain was triggered by weather change, convincing the patients their pain was sinus related, even though this is a common migraine trigger. Seventy-three percent of these patients had associated rhinorrhea, which along with turbinate congestion has been reported as a potential manifestation of the vascular changes associated with migraine headache.[43]

It is worth noting that a majority of the studies looking at patients with "sinus headache" exclude all those who have mucosal changes on CT.[38] While this is done to avoid confounding factors, it also potentially eliminates those patients who may indeed have a nasal or sinus inflammatory source for their pain. Currently there are no well-controlled, randomized trials evaluating this population for headache. Patel et al. reviewed the literature pertaining to "sinus headache" and concluded that such patients should be thoroughly evaluated for a possible rhinologic diagnosis with nasal endoscopy and CT scan, as well as a neurologic diagnosis using the patient's history and IHS criteria, acknowledging that most such patients will be found to have migraine.[38] Considering the frequency of both migraine and chronic rhinosinusitis in the general population, it is of course possible for both to coexist in the same patient.[44]

This possibility of coexistence is emphasized by the relatively poor response of headache to surgical intervention for chronic rhinosinusitis. Soler et al. reviewed 207 patients undergoing endoscopic sinus surgery (ESS) for chronic rhinosinusitis.[45] Symptoms included nasal congestion, fatigue, hyposmia, nasal drainage, facial pain/pressure, and headache, the latter described as the most disabling condition. At 18 months follow-up, all symptoms statistically were improved except headache. In a meta-analysis, Chester et al. found that after ESS, nasal obstruction was most improved, facial pain and post nasal drip moderately improved, and hyposmia and headache least improved.[46]

GIANT CELL ARTERITIS

Giant cell arteritis (GCA), also known as temporal arteritis, is a vasculitis that primarily involves branches of the external carotid arterial system. It predominately affects Caucasian women over the age of 50, and the incidence of disease appears to rise with population age.[47]

Due to its variable and systemic involvement, GCA can present in a variety of fashions. The most common presenting symptom is a temporal or occipital headache that is made worse with palpation.[48] The arteries involved may be nodular and firm. Patients may experience jaw pain while chewing for several minutes, which subsequently resolves with rest. When present, a history of jaw claudication has shown a positive correlation with the likelihood of obtaining a positive temporal artery biopsy.[49] In one study, audiovestibular dysfunction was present in approximately 90% of patients with a diagnosis of GCA. Vestibular symptoms generally improved after several days of steroid therapy, while hearing loss generally did not.[50] Visual loss is a debilitating manifestation of the disease, and once developed is often profound and irreversible.[51] Early recognition is important to reducing morbidity, as unilateral visual deficits can quickly progress into bilateral vision loss if treatment is delayed or stopped prematurely.[52]

The diagnostic guidelines set forth by the American College of Rheumatology include the presence of any three of the following five criteria: (1) age at onset ≥50 years, (2) new headache (3) temporal artery abnormalities (such as tenderness, nodularity, or reduced pulsation), (4) elevated ESR ≥50 mm/h, and (5) positive temporal artery biopsy. These criteria were designed to serve as guidelines rather than strict diagnostic requirements, and a negative temporal artery biopsy does not preclude the diagnosis.[53-55] Due to the presence of skip lesions, a minimum biopsy length of 1 cm is recommended, though >2 cm is preferable when readily obtainable.[52,56] Bilateral temporal artery biopsy has shown varying value in separate studies.[57,58] The use of steroid therapy prior to biopsy may reduce histopathologic evidence of inflammation, so surgical specimens should be obtained soon after the initiation of medical therapy. Specimen procurement within 2 weeks of steroid initiation has shown the greatest yield, though positive specimens have been identified >4 weeks into therapy.[59] The use of steroids should not be delayed for the sake of obtaining a temporal artery biopsy.

Treatment of GCA is directed towards tempering the inflammatory process to prevent ischemic complications. An oral regimen of prednisone 40–60 mg/day is a common starting dose with a slow tapering regimen over the course of greater than a year.[60,61] In patients with significant disease-related complications such as visual loss, intravenous methylprednisolone is given to induce remission.[61] In the absence of contraindications, low-dose aspirin is recommended to reduce the rate of ischemic complications.[61,62] Patients should be adequately counseled regarding the adverse effects of long-term steroid therapy including weight gain, bone loss, hyperglycemia, hypertension, peptic ulcers, and cataracts. To minimize these complications, prophylactic initiation of proton pump inhibitors and calcium supplementation is advocated.[52,61] Surveillance of blood glucose levels, blood pressure, and bone density are also appropriate, and should be coordinated with the patient's primary care physician. Failure to respond to steroid therapy should raise questions regarding the diagnosis. Patients who have shown response to therapy are still susceptible to relapse of disease. In recurrent or refractory cases of GCA, methotrexate and other immunotherapies have shown some benefit as adjuvant treatments, though further investigation is still warranted.[63,64]

MEDICATION OVERUSE HEADACHE

The development or progression of headaches in a patient who frequently uses analgesic or headache medications can be secondary to their overuse. It is estimated to affect 1–2% of the population.[65] Its pathophysiology remains unclear, though patterns have been noted in the literature. Medication overuse headaches (MOH) occur more frequently in patients with pre-existing headache conditions than patients using these medications for other purposes.[66-69] It seems to have a predilection for patients who suffer from migraine and tension headaches rather than other headache conditions.[69] Its development can be related to the use of ergotamine derivatives, triptans, opioids, or other analgesics. Headache-prone patients who use analgesics for separate conditions are also susceptible to developing MOH.[70,71] The diagnosis is suggested by the presence of headaches for at least 15 days per month in a patient who has been overusing any of the above medications for over 3 months. To classify overuse, the ICHDs criteria suggests >15 days per month usage of simple analgesics such as acetaminophen, aspirin, NSAIDs, or >10 days per month usage of ergotamine derivatives, triptans, or opioids. Alternatively, use of a combination of these drugs without individual overuse also fits the criteria.[39,72] Caffeine should not be overlooked as a potential contributing factor.[73]

The treatment of choice for MOH involves withdrawal of the offending drugs. Abrupt cessation is generally preferable for most headache medications, while a tapering plan might be advisable for opioids, benzodiazepines, or barbiturates.[74] The mean duration of withdrawal headaches is approximately 4 days for those experiencing MOH secondary to triptans, 7 days for ergotamines, and 10 days for NSAIDs.[75] Prednisone, amitriptyline, and topiramate have shown some potential benefit in the treatment of withdrawal headaches.[74,76-80] Neurology consultation is recommended for assistance with the management of this disorder.

If after 2 months of withdrawal of medication an improvement in headaches has not been identified, then an alternative diagnosis should be considered. It is important to counsel patients about this potential problem when evaluating or treating them for chronic headache pain.

FACIAL PAIN

The head and neck region is one of the most common areas to be involved in chronic pain.[81] Studies show that about 25% of adults suffer from orofacial pain and of these 7–11% may be chronic in nature.[82,83] Acute facial pain is most often secondary to odontogenic processes, while chronic pain is more often secondary to a musculoskeletal or neuropathic etiology. The patient presenting with facial pain can be a diagnostic challenge for many clinicians. The complex anatomy of the head and neck may lead patients with facial pain to be referred to a number of specialists, i.e. dentists, oral surgeons, otolaryngologists, neurologists and pain specialists, resulting in a potential myriad of diagnoses and treatment regimens. Failed diagnosis often leads to delays in treatments, continued pain and poor quality of life.[84]

One reason for the difficulty in accurately diagnosing the etiology of facial pain is the lack of objective testing for many of these disorders. In most cases the diagnosis must rely solely on history and physical examination. The IHS[85] and the International Association for the Study of Pain (IASP)[39] have each established a classification and diagnostic criteria for facial pain disorders. The IHS and IASP classification schemes are useful in providing a list of etiologic possibilities for facial pain (Table 22.7).

The most important tool in the evaluation of the patient with facial pain is the history. The components of a thorough pain history are listed in Table 22.8.[86] The patient should be allowed to express in their own words their pain, as their choice of words may often be pathognomonic for certain disorders.[87] Due to the comorbidity of other psychiatric illnesses and the role stressors play on facial pain, a thorough social history, including recent or ongoing stressors should be extracted.[83]

Imaging and laboratory testing should be guided by the history and physical examination. Routine laboratory testing is rarely useful. Laboratory testing is warranted when autoimmune or infectious processes are suspected. Imaging may be indicated if a patient presents with altered mental status, intractable pain, neurologic deficits, post-neurosurgical procedure, and/or a history of neoplasm.

While multiple disease processes can cause facial pain, the recognition and management of most acute disorders are straight forward, such as facial cellulitis or a dental infection. Chronic pain is typically pain that persists past the normal time of healing; most often this is >3–6 months.[85] It is chronic pain that may pose a diagnostic challenge to the practitioner. The diseases that follow are listed because they may present a diagnostic or therapeutic challenge to the otolaryngologist.

Trigeminal Neuralgia (Tic Douloureux)

The IASP defines trigeminal neuralgia (TN) as a "sudden, usually unilateral, severe brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve." TN is a rare disease. Recent studies show the overall incidence to be 12.7 cases per 100,000 per year. Higher incidence rates of up to 27 cases per 100,000 per year have been shown when TN was diagnosed by general practitioners. This higher rate is likely due to the misdiagnosis of other causes of facial pain; misdiagnosis may be as high as 48% in patients with facial pain. Females (66% of patients) are more commonly affected than males. The mean age at diagnosis is 51.5, with a peak incidence between the fifth and sixth decade.[88]

TN can be classified as either classical (idiopathic or primary) or symptomatic (secondary). Classical TN is the most common form (85% of cases) and is frequently thought to be due to vascular compression at the root entry zone by a vessel, most often the superior cerebellar artery.[89] Symptomatic TN pain develops secondary to another pathologic process such as CNS space-occupying lesions, multiple sclerosis plaque, trauma or infection.[90-92]

Devor's ignition hypothesis is the most widely accepted hypothesis for the development of TN. This hypothesis states that compression of the trigeminal nerve, commonly at the root entry zone, leads to demyelination of

Table 22.7: IASP and IHS classification of disorders associated with facial pain; headache excluded from the IASP classification

IASP classification – relatively localized syndromes of the head and neck (excluding headaches)	IHS classification—painful cranial neuropathies and other facial pains
Neuralgias of the head and face 1. Trigeminal neuralgia 2. Acute herpes zoster 3. Postherpetic neuralgia 4. Geniculate neuralgia 5. Neuralgia of the nervus intermedius 6. Glossopharyngeal neuralgia 7. Superior laryngeal nerve neuralgia 8. Hypoglossal neuralgia 9. Occipital neuralgia 10. Tolosa-Hunt syndrome 11. SUNCT syndrome 12. Raeder syndrome (paratrigeminal syndrome)	Trigeminal neuralgia Glossopharyngeal neuralgia Nervus intermediaus Occipital neuralgia Optic neuritis Headache attributed to ischemic ocular motor nerve palsy Tolosa-Hunt syndrome Paratrigeminal oculosympathetic Recurrent painful ophthalmoplegic neuropathy Burning mouth syndrome Persistent idiopathic facial pain Central neuropathic pain
Craniofacial pain of musculoskeletal origin 1. Temporomandibular joint disorder 2. Facial dyskinesia; dystonic disorder 3. Crushing injury of head and face	
Lesions of the ear, nose, and oral cavity 1. Maxillary sinusitis 2. Odontalgia 3. Glossodynia (burning tongue) 4. Cracked tooth syndrome 5. Dry socket 6. Inflammatory diseases of the jaw	
Vascular or cerebrospinal fluid syndromes 1. Carotidynia 2. The syndrome of "jabs and jolts" 3. Temporal arteritis	
Pain of psychological origin in the head, face, and neck 1. Delusional or hallucinatory pain 2. Hysterical, conversion or hypochondriacal pain 3. Associated with depression	

Table 22.8: Key components of a pain history

Onset	Date of initial presentation, inciting event, sudden or gradual, time of day, duration, frequency, constant or intermittent
Quality	Sharp, throbbing, burning, aching, stabbing, cramping,
Intensity	Severity, numerical analogue scale 1–10 "I can usually ignore the pain" or "The pain is so bad I can't function"
Location	Can the patient point with a finger to site of pain? Does it radiate or travel?
Associated symptoms	Nausea, fatigue, behavioral changes, physical changes
Aggravating factors	What makes it worse? Any triggers?
Alleviating factors	What makes it better?
Therapies thus far and success	Over-the-counter and prescription medications, acupuncture, ice, heat, massage

neurons, rendering them hyperexcitable. This neuronal demyelination has been shown on electron microscopy of trigeminal nerve specimens obtained during surgical decompression. These injured hyperexcitable neurons may come into contact and stimulate neighboring neurons resulting in explosions of electrical activity or pain with innocuous stimulation. After this burst of electrical activity, the neurons undergo a period of hyperpolarization that leaves them refractory to further excitation despite stimulation.[93,94]

Patients with TN present with pain that is often described as electric-like, shooting, shocking or cutting. The pain is severe in nature and at times may cause the patient to contract their face in a "tic"-like appearance. Paroxysms of acute pain typically last a few seconds but several bursts of activity may occur in succession giving the impression of an attack lasting for minutes. These events are then followed by a refractory period, which may last for minutes, where further attacks cannot be triggered. Patients may experience recurring daily attacks or multiple attacks per hour. Episodes of attacks may last from 1 day to 4 years, median 49 days. Katusic et al. found that after the first episode, 65% of patients had a second within 5 years and 77% within 10 years.[95] Rasmussen followed 106 patients with TN and found pain free intervals between episodes to last years (6%), months (36%), weeks (16%), or days (16%).[96] Episodes present along a wide spectrum between patients, lasting from days to years, with attacks within episodes occurring once daily to hundreds per day. Over time the period of remissions between episodes becomes shorter and duration of episodes become longer and more severe but significant changes in the location or quality of pain should alert the physician to the possibility of an alternative diagnosis.[97]

In 95% of patients, the pain is unilateral and located superficially along the skin or buccal mucosa where the trigeminal nerve innervates. The pain does not cross to the contralateral face but may present bilaterally in up to 5% of patients. The pain is typically an all or none phenomenon with no gradual build-up or decline in severity. Pain distribution is most commonly along V2 and V3 (32%); however, it may present in any number of combinations: V1 only (4%), V2 (17%), V3 (15%), V1 + V2 (14%), V1 + V2 + V3 (17%).[98] Attacks are often triggered by benign events such as chewing and talking (76% of patients), touching (65% of patients) and cold (48% of patients). In 50% of patients a trigger zone can be identified usually along the nose or mouth.[99] Identifying extraoral trigger points from intraoral only trigger points can help the physician to differentiate TN from a purely odontogenic process. Patients often avoid any activity that may precipitate an attack, which may lead to weight loss and social withdrawal. The pain usually diminishes at night and infrequently occurs during sleep causing the patient to wake. Patients may experience autonomic symptoms such as lacrimation or erythema of the eye, rhinorrhea or nasal congestion. One study found that 67% who underwent microvascular decompression, preoperatively, experienced one autonomic symptom and 14% had four or more; those patients with autonomic symptoms were likely to have a poorer response to surgery.[100] Neurologic examination rarely detects any abnormalities but is necessary due to the possibility of other neuropathies that could be seen in symptomatic TN. It is also important to repeat the neurologic examination periodically as a small percentage of patients (6.3%) have been diagnosed with symptomatic TN after an initial diagnosis of classical TN.[92] Symptomatic TN should be suspected in the patient with bilateral involvement or sensory deficits and possibly the younger patient. Patient characteristics not suspicious for symptomatic TN are involvement of the first division of the trigeminal nerve and unresponsiveness to medical treatment.[101]

The IHS has established diagnostic criteria. Care should be taken to differentiate classical from symptomatic TN as the management differs (Table 22.9). Classical TN is purely a clinical diagnosis. Patients with no suspicious signs for symptomatic involvement may forgo any further testing and begin medical therapy. Imaging should be obtained in those where symptomatic TN is suspected or if the diagnosis is not clear. MRI with and without contrast should be obtained to rule out structural

Table 22.9: IHS diagnostic criteria for classical trigeminal neuralgia

IHS classical trigeminal neuralgia
A. At least three attacks of unilateral facial pain fulfilling criteria B and C
B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
C. Pain has at least three of the following four characteristics: 1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes 2. Severe intensity 3. Electric shock-like, shooting, stabbing, or sharp in quality 4. Precipitated by innocuous stimuli to the affected side of the face
D. No clinically evident neurological deficit
E. Not better accounted for by another ICHD-3 diagnosis

lesions or multiple sclerosis plaques. Imaging may identify structural causes of TN in up to 15% of cases. Current guidelines do not recommend routine MRI if "normal" vascular compression is suspected as in classical TN, as current neuroimaging techniques are too insensitive to determine vascular compression. Abnormal trigeminal reflex testing, blink reflex, has been shown to have a high specificity (94%) and sensitivity (87%) in distinguishing symptomatic TN from classical TN.[101]

A recent report from the American Academy of Neurology and the European Federation of Neurological Societies (AAN/EFNS) describes the medical and surgical management of TN.[101] Carbamazepine remains the initial drug for the management of classical TN. It has been shown to provide nearly complete pain relief in 70% of patients in placebo-controlled trials. Doses range from 200 to 1,200 mg/day and are started low initially and escalated as needed every three to seven days. Most patients will experience pain relief in just a few days after starting the medication. Oxcarbazepine is often the second-line drug if carbamazepine is not tolerated due to side effects or drug interactions. Other drugs that have been shown to be effective in randomized controlled trials include lamotrigine, baclofen, and tocainide. Many of the drugs used should be monitored closely for side effects, most of which are neurologic such as drowsiness, ataxia and diplopia. There are no guidelines on the management of patients who fail first-line therapy. Several studies support add-on therapy with lamotrigine or switching to baclofen. Currently there is insufficient evidence to support the use of IV administered medications in the management of acute pain. Several studies have shown pain relief with IV fosphenytoin.[102] Topical lidocaine has been shown to provide short-lasting pain relief when injected or applied topically onto trigger zones.[103]

Determining when a patient with classical TN should undergo surgery is not straightforward and the AAN/EFNS guidelines found insufficient evidence to suggest at what point surgical intervention should occur. Most agree the discussion about surgery should begin early and not wait for when medical management is no longer effective or tolerable. Surgical treatments are performed at three levels of the trigeminal nerve: peripherally (distal to the Gasserian ganglion), the Gasserian ganglion, and the root entry zone at the posterior fossa. Surgical options are of two categories, those that preserve the trigeminal nerve (nonablative) and those that destroy the trigeminal nerve (ablative). Of these options microvascular decompression is the only nonablative procedure whereas the others involve palliative destruction of the trigeminal nerve. Ablation can be performed thermally (radiofrequency, cryotherapy), chemically (glycerol, alcohol, phenol) and mechanically (ballooning). Peripheral ablation has a low morbidity but studies show 50% of patients with recurrence of pain after 1 year. Destruction at the Gasserian ganglion can be performed percutaneously with the use of a cannula through the foramen ovale to directly attack the trigeminal nerve. Ninety percent of patients will experience immediate pain relief but by 5 years 50% of patients will have recurrence of pain. Microvascular decompression is the most invasive surgical option with a mortality risk of 0.2–0.5% but provides the highest long-term pain relief, with 73% of patients' pain free at 5 years. The AAN/EFNS guidelines state that while microvascular decompression provides the longest duration of pain relief there is inadequate direct comparative studies between different surgical techniques to definitively state the relative efficacy of each technique.[101]

Glossopharyngeal Neuralgia

Defined by the IASP as "sudden severe brief stabbing recurrent pains in the distribution of the glossopharyngeal nerve;" this disorder is similar but rarer than TN.[85] It has a reported incidence of 0.2 to 0.8 per 100,000 per year, 1/100th the incidence of TN. The mean age is 54 years but in one study 43% of patients were diagnosed before 40 years of age. There is an equal presence in both males and females.[104,105]

Glossopharyngeal neuralgia (GPN) is very similar to TN; in fact, about 10% of patients have both.[104,105] Similar to TN is the thought that the pain in GPN arises due to vascular compression of the ninth or tenth cranial nerve at the root entry zone, most commonly by the vertebral or posterior inferior cerebellar artery. Rare cases of GPN develop secondarily from tumor compression, trauma, multiple sclerosis, tonsillitis or an elongated styloid process (Eagle syndrome).[105-107]

Patients present complaining of paroxysms of pain often triggered by swallowing, particularly cold or acidic fluids, coughing, and/ or touching the neck or external ear canal. Trigger zones may be found along the tonsillar fossa or posterior pharynx. An attack typically lasts seconds to minutes but there may be a constant dull background ache before and after attacks. Similar to TN, there are

Table 22.10: IHS diagnostic criteria for glossopharyngeal neuralgia

Glossopharyngeal neuralgia
A. At least three attacks of unilateral pain fulfilling criteria B and C
B. Pain is located in the posterior part of the tongue, tonsillar fossa, pharynx, beneath angle of the lower jaw, and/or in the ear
C. Pain has at least three of the following four characteristics: 1. Recurring in paroxysmal attacks lasting from a few seconds to 2 minutes 2. Severe intensity 3. Shooting, stabbing, or sharp in quality 4. Precipitated by swallowing, coughing, talking or yawning
D. No clinically evident neurological deficit
E. Not better accounted for by another ICHD-3 diagnosis

clusters of attacks characterized by shooting, stabbing or cutting pain along the throat radiating to the ear that may last from weeks to months with periods of remission in between. Paroxysms typically manifest during the day but may occur at night awaking the patient. Pain is usually unilateral and more frequent on the left.[104] Some report attacks associated with vagal symptoms such as coughing, hoarseness or arrhythmias leading to syncope.[108]

Diagnosis relies on clinical criteria, listed by the IHS, and ruling out secondary causes as determined by a thorough head and neck examination and imaging with MRI (Table 22.10).[39] In office application of local anesthetic along the tonsillar fossa or posterior pharynx that results in pain relief is also considered diagnostic.

Medical management is the same as in TN, with carbamazepine as the drug of choice. Surgical therapy is reserved for those who fail medical management. Procedures include intracranial sectioning of the ninth cranial nerve or vascular decompression, with similar results as noted for TN.[105,109-113]

Postherpetic Neuralgia

The IASP defines postherpetic trigeminal neuralgia (PHN) as chronic pain with skin changes in the distribution of one or more roots of the fifth cranial nerve subsequent to acute herpes zoster.[85] Acute herpes zoster infection is common. Approximately one in three people will develop acute herpes zoster during their lifetime.[114] Of these approximately 10–18% will be at risk of persistent postherpetic neuralgia at all body sites after 1 year of onset; however, this risk increases to up to 48% in those >70 years.[115,116]

Reactivation from a latent phase of the varicella-zoster virus is the inciting cause of herpes zoster or shingles. Infectious spread of the virus along sensory nerves results in the corresponding acute dermatomal pain and rash. Pain that develops during the acute herpes zoster infection is likely produced by inflammation and damage to sensory nerves to the skin and dorsal root ganglia of affected cranial nerves. This damage may leave neurons susceptible to spontaneous activity manifested as pain after resolution of the acute phase.[117] Risk factors for the development of PHN include elderly (>50 years), severe pain or rash during acute herpes zoster infection, ophthalmic location, and female.[118,119]

Postherpetic trigeminal neuralgia most commonly manifests along the ophthalmic division of the trigeminal nerve but can occur along the second and third as well. The pain is typically characterized as itching, burning or crawling. There may be associated eye tearing, eye pain or blindness in 10–25% of patients.[119] The pain is continuous but may be associated with flares when the corresponding area is touched. Examination will often reveal skin changes such as scarring, pigmentation changes and dysesthesia or allodynia. IHS diagnostic criteria for PHN are listed in Table 22.11.[39] Imaging or laboratory evaluation is not necessary.

Management of PHN begins with prevention. The FDA approved the zoster vaccine for those >50 years. Studies have shown it to be effective in reducing both the incidence of herpes zoster and PHN. No serologic testing is required to demonstrate past varicella exposure prior to administration.[119] Effective management of acute herpes zoster with antivirals within 72 hours of onset or administration of amyitriptyline during the acute infection may prevent PHN development according to some studies;[120-122] however, a recent Cochran review showed no significant reduction in the incidence of PHN with acyclovir therapy but insufficient evidence for newer antivirals.[123] Prevention of PHN is most important

Table 22.11: IHS diagnostic criteria for postherpetic trigeminal neuropathy

Postherpetic trigeminal neuropathy
A. Unilateral head and/or facial pain persisting or recurring for > 3 months and fulfilling criterion C
B. History of acute herpes zoster affecting a trigeminal nerve branch or branches
C. Evidence of causation demonstrated by both of the following: 1. Pain developed in temporal relation to the acute herpes zoster 2. Pain is located in the distribution of the same trigeminal nerve branch or branches
D. No better accounted for by another diagnosis

Table 22.12: Wilkes classification of temporomandibular joint dysfunction

Stage 1	Early reducing disk displacement
Stage 2	Late reducing disk displacement
Stage 3	Nonreducing disk displacement: acute or subacute
Stage 4	Nonreducing disk displacement: chronic
Stage 5	Nonreducing disk displacement: chronic with osteoarthritis

Source: Adapted from Wilkes.[129]

because up to 50% of those with PHN do not respond to pain management.[124] Guidelines in the treatment of PHN have been established by the American Academy of Neurology.[125] FDA approved and first-line therapies for PHN include gabapentinoids, topical lidocaine, opioids, and TCAs. Combination therapies are often needed due to the complex pain mechanisms involved in PHN. Common combinations include gabapentin in addition to topical lidocaine patch, nortriptyline or morphine. Often a limiting factor in patients obtaining complete pain relief is the development of adverse drug effects or drug interactions, especially in the elderly population,[126] and thus management of PHN should be individualized in each patient.

TEMPOROMANDIBULAR JOINT DISORDERS

Temporomandibular joint disorders (TMDs) are characterized by pain associated with the temporomandibular joint (TMJ) or muscles of mastication. Associated symptoms include pain both at rest and with joint movement, tenderness to palpation of the joint, headache, ear pain, or facial pain. Physical examination may reveal crepitus, clicking, popping, jaw deviation, and trismus. Disorders of the TMJ are a relatively common cause of facial pain, with significant symptoms reported in approximately 5–10% of the adult population. Females are more commonly affected than males, and the peak incidence is in the second to fourth decades of life.[127,128] This section will review the anatomy of the TMJ and discuss the various TMDs, a term that denotes both true dysfunction of the TMJ itself and pain associated with the muscles of mastication. Available treatment options and indications for intervention will also be addressed.

Disorders of the Temporomandibular Joint

The TMJ may be affected by the multiple conditions that affect other joints of the body, including congenital or developmental anomalies, trauma, degenerative or inflammatory joint disease, and neoplasms, both primary and metastatic. Primary disorders of the TMJ are those that affect the joint capsule or its components. The TMJ is also associated with chronic orofacial pain, but this relationship is more complex.

Intracapsular Disorders

The most widely cited classification system for intracapsular disorders of the TMJ was described by Wilkes (Table 22.12).[129] Displacement of the articular disk is a primary feature of intracapsular disorders. This displacement is usually the result of trauma, and in many cases may be secondary to repeated episodes of microtrauma from tooth grinding or jaw clenching, which are also referred to as parafunctional habits.

The pathology is further classified with respect to the presence or absence of disk reduction. Patients who experience disk dislocation with reduction will often complain of a clicking or popping sensation on opening of the jaw that may be painful. Mandibular motion is usually unrestricted. Asymptomatic disk displacement is common and requires no treatment. Treatment should therefore be guided by the degree of functional impairment, and first line therapy includes soft diet, NSAIDs, splinting, and

physical therapy. More invasive surgical procedures should be reserved for those patients who fail more conservative treatment methods.[130-132]

Patients who exhibit disk displacement without reduction will present with impairment of mouth opening, referred to as a "closed lock." The anteriorly dislocated disk restricts the ability of the jaw to open, and pain is common with forced opening. Chronic dislocation may result in changes in the shape of the articular disk, which can impair efforts at manual reduction. Management is typically aimed at reducing pressure on the soft tissues located behind the articular disk by use of a bite splint, along with the aforementioned conservative measures.

The TMJ is also susceptible to osteoarthritis and degenerative joint disease. This typically occurs as the result of age-related wear on the articular surfaces, and displacement of the articular disk can contribute to the development of degenerative disease, as this alters joint motion and results in repetitive microtrauma. Conservative treatment strategies are again the first-line therapy and are aimed at improving symptoms through anti-inflammatory medications and reducing stress on the joint with splints and soft diet. Surgical management, if indicated, should focus on removal of diseased bone and restoration of a smooth articular surface.[133]

Inflammatory arthritis of the TMJ can also occur. Inflammatory arthritis should be managed through use of anti-inflammatory and immunosuppressive agents, and physical therapy exercises should be encouraged to prevent the loss of range of motion when acute symptoms are present. Bony ankylosis of the joint is commonly a result of rheumatoid arthritis or traumatic injury and requires surgical intervention for joint reconstruction. Physical therapy in the postoperative period is important in maintaining function of the reconstructed joint.

Temporomandibular Disorders and Chronic Orofacial Pain

The most common TMD presentation includes multiple complaints of facial, musculoskeletal, and jaw pain without an identifiable structural source. There is overlap between these types of TMD with other chronic pain syndromes such as fibromyalgia. Coincident psychological conditions such as anxiety and depression are frequently present. Therefore, therapeutic strategies aimed at addressing the pain itself along with the associated psychosocial factors are necessary.[134-136]

Certain habits appear to have an association with chronic TMD, including jaw clenching and bruxism, but no causal relationship has been established. Malocclusion does not appear to be a consistent factor. Reliable evidence to indicate which patients will develop TMD is lacking, and common complaints such as jaw popping or clicking with movement are present to a large degree in the nonaffected population.[136-139] This understanding of the disorder suggests that certain parafunctional habits work in concert with underlying psychosocial or psychologic conditions to cause alterations in pain sensation, and disorders of central pain regulation systems have been identified in patients affected by TMD.[140,141]

The observation that most cases of TMD seem to be related to altered pain sensation as opposed to true joint dysfunction has led to the use of cognitive behavioral therapy and muscle relaxation techniques in the management of TMD.[142] Treatment should aim to provide symptom relief and methods of coping with pain. Anti-inflammatory, antidepressant, and anxiolytic medications may be helpful, especially for those with chronic pain.[143] Most patients with TMD will improve with noninvasive, symptomatic management.[133,136]

The literature regarding different treatment strategies for chronic TMD is controversial; and recent Cochrane reviews of various invasive and noninvasive therapies including arthoscopy,[144] joint lavage,[145] orthodontic appliances,[146] splints,[147] and pharmacologic intervention[148] demonstrated a variable level of evidence and no clearly beneficial strategies. Interventions aimed at addressing psychosocial factors appeared to have a weak effect, and the authors advocated that priority be given to these reversible, noninvasive treatment modalities in the absence of strong evidence supporting more aggressive strategies.[149] Indications for surgical treatment are relative. Surgery should be considered for cases in which more conservative therapies have failed and for those patients in whom the dysfunction is more clearly limited to the joint itself (Table 22.13).[150-155]

HISTORY, PHYSICAL, AND IMAGING IN HEADACHE AND FACIAL PAIN

History

As the differential diagnosis for causes of headache and facial pain is broad, a comprehensive history and physical examination is required to ensure that an accurate diagnosis is made. Fundamental questions regarding

Table 22.13: Selection of surgical candidates in TMD

1. The temporomandibular joint causes pain or dysfunction that results in significant impairment
2. Appropriate nonsurgical management did not relieve symptoms
3. The pain is clearly localized to temporomandibular joint
4. Interferences with proper joint function are mechanical
5. The patient desires surgical intervention
6. There are no contraindications to surgery

Source: Adapted from Goldstein.[130]

characteristics or quality of the pain, location, duration of onset, severity, exacerbating or relieving factors, associated symptoms, and similar prior episodes should be asked of all patients. In those patients presenting with headache, the location or distribution of the pain may help the physician to narrow the diagnosis. For example, a pulsating hemispheric or unilateral headache would suggest migraine, while a headache with a "band-like" distribution around the head would be most consistent with tension headache. Patients should be asked about associated symptoms, especially neurological issues such as numbness, weakness of the face or in the extremities, visual changes, and olfactory sensations. While these neurological complaints may be the manifestation of a migraine aura, patients should be carefully examined for focal neurologic deficits and the physician should entertain the possibility of cerebrovascular accident. Similarly, photophobia and nausea with or without vomiting may be suggestive of migraine, but the presence of fever or nuchal rigidity should alert the physician to the possibility of meningitis and appropriate work up initiated. A unilateral temporal headache or jaw pain with jaw claudication in patients over 50 years of age, especially if associated with visual changes should suggest temporal, or giant cell, arteritis. Those patients with facial pain should be asked about fever, purulent nasal discharge, postnasal drip, epistaxis, otalgia, nasal airway obstruction or congestion, hyposmia or anosmia, and visual complaints. While the complaint of facial pain may generally be considered more benign, the possibility of occult malignancy or rapidly progressive infection remains, especially in patients at higher risk due to significant alcohol or tobacco use, or those with immunodeficiency. A careful review of systems will assist the physician in identifying those patients that may experience catastrophic consequences if inaccurately diagnosed.

The patient's past medical history should be reviewed, especially for uncontrolled hypertension or diabetes, allergic or atopic conditions, recurrent episodes of sinusitis, prior facial trauma, malignancy, and systemic inflammatory or rheumatologic conditions. Reasons for immunocompromise or immunodeficiency should be considered. In a patient reporting prior episodes of sinusitis, the number, duration, and prior medical or surgical treatment of these episodes should be determined. A list of the patient's medications should be reviewed and a family history obtained. The patient's social history should be explored, including prior and current use of alcohol, tobacco, and illicit drugs.

Physical Examination

The examination of the patient presenting with headache or facial pain should focus on the head and neck and the nervous system. The patient should be inspected for signs of new or recent trauma. The external auditory canals and tympanic membranes should be examined. The frontal and maxillary sinuses should be assessed for tenderness, and anterior rhinoscopy should evaluate for inflamed or hypertrophied turbinates and purulent drainage. Septal deviation or bony spurs should be identified and documented. Patients in whom sinus disease is suspected should be considered for complete endoscopic nasal examination. The oropharyngeal examination should pay special attention to the maximum degree of mouth opening, dental occlusion, jaw deviation, and evidence of teeth grinding (bruxism). The TMJs should be palpated to assess for any popping or clicking with mandibular movement. The cranial nerves should be evaluated and fundoscopic examination performed. A neurologic examination should assess for any gross motor or sensory deficits. The new onset of a focal neurologic deficit significantly increases the chances of discovering an intracranial abnormality on subsequent imaging, and, conversely, if the neurological examination is nonfocal, the likelihood is increased that no intracranial pathology will be identified. A detailed physical examination is critical in the evaluation of these patients, and will greatly assist the

physician in determining the necessity of radiologic imaging, as well as the imaging modality most appropriate for each clinical situation.

Imaging

The physician tasked with evaluating the patient with headache or facial pain will often face the decision whether or not to obtain imaging studies to rule out serious pathology. The advances in CT and MRI have made these imaging modalities readily available to most practitioners, with a corresponding increase in utilization. The benefits of obtaining imaging include the identification of particular pathologic processes, along with the reassurance provided to the patient when a study returns without any significant abnormality. These benefits need to be balanced against the risks of radiation exposure from CT scanning and the economic cost of obtaining imaging. To assist the clinician in making the decision to obtain imaging, the American College of Radiology has published Appropriateness Criteria regarding the imaging of patients with headache and suspected sinus disease.[156,157]

Headaches are a relatively common complaint in the outpatient setting and emergency department. The incidence of serious intracranial pathology associated with headache is rather low, with the majority of headache complaints being the result of relatively benign tension or migraine-type headaches. Therefore, the indiscriminate use of imaging technology in the patient presenting with isolated headache, i.e. without accompanying neurologic findings – results in a low yield for identifying pathology and a high rate of false-positive studies. For reference, the rate of brain tumors (primary and metastatic) in the American population is reported to be 46 per 100,000 and the rate of subarachnoid hemorrhage is 9 per 100,000. Given this low prevalence of intracranial abnormality in the general population, the yield for imaging in isolated, nontraumatic headache is 0.4%. If one assumes a cost of $400 per CT scan or $900 per MRI, the cost to detect a lesion by CT scan is $100,000 and $225,000 by MRI. Imaging yield is higher, however, in particular high-risk patient populations, which will increase the utility of imaging studies. The clinician should therefore aim to identify those patients who are at higher risk of serious pathology based on the history and physical examination. For example, patients presenting with the sudden onset of the "worst headache of their life," often called a "thunderclap headache," have a significantly higher incidence of intracranial hemorrhage, and imaging yield is as high as 47%. Other high-risk groups include patients older than 55 years of age who present with new headache in the temporal region (as in temporal arteritis), pregnant women, and those patients with chronic headache that suddenly changes in character or location. Patients with HIV, known malignancy, or those living in certain geographic regions with a high burden of parasitic disease (e.g. cysticercosis in South America) are also at higher risk, and the threshold for obtaining imaging should be correspondingly lowered.[156]

Patients with suspected sinonasal disease are most likely to benefit from imaging when there is concern for intracranial or orbital extension of disease, or when the patient meets criteria for surgical intervention, in which case imaging is an important part of preoperative planning. Those patients with uncomplicated, acute rhinosinusitis are unlikely to benefit from imaging, as most cases are managed successfully with medical treatment alone. However, patients who have HIV or are otherwise immunocompromised may benefit from imaging in the acute phase, especially if the history or physical examination suggests a rapidly invasive process.

The imaging modality of choice for most cases of recurrent acute or chronic rhinosinusitis is the CT scan without contrast, as this provides the clearest bony detail while still allowing adequate mucosal visualization. MRI studies are most useful in cases in which there is concern for intracranial or orbital extension of disease, whether infectious or malignant, as this imaging modality will provide the highest level of soft tissue detail. CT and MRI should likely be considered complimentary in cases of invasive disease: the CT scan will assist in delineating the complicated and variable bony anatomy of the sinus cavities, while the soft tissue detail of MRI allows the clinician to evaluate the extent of soft tissue invasion and the amount of resection required for adequate extirpation of disease.[156]

While the preceding discussion provides a broad overview of the use of imaging in headache and sinonasal disease, a more thorough discussion is available through the American College of Radiology, and the interested reader is encouraged to utilize those resources for more information on this topic.[156,157]

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SECTION 6

Rhinosinusitis: Etiology, Pathophysiology and Medical Therapy

CHAPTER

23

Classification and Diagnosis of Rhinosinusitis

Troy Woodard, Michael S Benninger

INTRODUCTION

Rhinosinusitis (RS) is a complex group of disorders characterized by infection and inflammation of the mucosa of the nose and paranasal sinuses.[1-4] It is very common and affects approximately one in seven Americans.[5,6] RS occurs in all ages, both genders and all ethnic groups. Loss of productivity and missed work/school are a major economic factor with patients suffering a significant decrease in quality of life.[5,6]

The RS is multifactorial and is associated with several disorders. Not only is there no one single etiology, but the spectrum of disease can vary dramatically from individual to individual. This complex nature makes it difficult to treat patients. As a result, an RS task force was developed in 1996 to standardize the definitions of sinusitis and to help confront difficulties in staging and performing research. Subsequently, RS has been characterized by duration of symptoms and objective findings into acute, recurrent acute, subacute, and chronic RS (CRS).

ACUTE RHINOSINUSITIS

Acute RS (ARS) occurs when the mucosal inflammation of the nose and sinuses lasts less than 4 weeks. ARS can be further classified into acute viral RS (AVRS) and acute bacterial RS (ABRS). It appears that the incidence of ABRS is increasing.[3,7] ABRS is estimated to affect 3 in every 1,000 people in the United States each year, with some individuals having multiple episodes.[3]

Typically, during the first 7–10 days of a respiratory tract infection, the predominant organisms are viruses that are responsible for the common cold. These include rhinovirus and adenovirus. There is strong evidence that viruses alone can cause inflammation in the sinuses, and this has been confirmed by computed tomographic (CT) scans performed during a viral upper respiratory tract infection.[8] Viruses may play a role in the alteration of the host immune system to allow for increased bacterial colonization and aggregation in the lymphoid tissue of the nasopharynx. Adenovirus types 1, 2, 3 and 5 have been shown to upgrade receptors for *Streptococcus pneumoniae*, which may increase adherence of the bacteria and subsequently increase the risk of infections.[9]

It is important for the healthcare practitioner to be able to distinguish between AVRS and ABRS. Although the symptoms are similar for both entities, AVRS is usually only lasts 10 days and is self-limited. Generally, symptoms peak within 2–3 days of onset and then decline over the next week. In contrast, ABRS is associated with a longer duration of symptoms that often initially slightly improve and then is followed by a worsening of symptoms.[10-12] After the initial 10 days of inflammation, there is a pathogen shift to bacterial organisms.[13]

Streptococcus pneumoniae (20–45%) and *Haemophilus influenzae* (22–35%) are the predominant bacterial organisms in ABRS in adults, whereas *Streptococcus pneumoniae* (30–43%), *Haemophilus influenzae* (20–28%), and *Moraxella catarrhalis* (20–28%) are the predominant organisms as traditionally reported in ABRS in children.[7] Although *Staphylococcus aureus* has been identified as being cultured in many prospective clinical trials, it was often considered a contaminant. A recent meta-analysis suggests that *Staphylococcus aureus* is a real pathogen in

approximately 10% of cases of ABRS.[14] There has also been recent discussion that although *Moraxella catarrhalis* is a pathogenic organism and that it is frequently cultured in ABRS as well as other upper respiratory tract infections, it is typically a self-limited infection that does not require antibiotic treatment under most circumstances.[14,15] In addition, it appears that disease severity based both on symptoms and on radiographic findings is worse for *Streptococcus pneumoniae* than for *Haemophilus influenzae* and *Moraxella catarrhalis*.[16]

RECURRENT ACUTE RHINOSINUSITIS

Recurrent ARS is diagnosed when an individual has four or more episodes of ABRS per year. Signs and symptoms of these episodes should be present for at least 10 days and include the same diagnostic criteria that are present for ABRS (≥10 days duration, purulent nasal drainage, nasal obstruction, and facial pain/pressure).[10] These patients must also not have any signs or symptoms between the episodes. Because of the nature of the infections, it may be difficult to confirm a true bacterial episode. Therefore, examination of the patient during an active infection is beneficial to corroborate the diagnosis. Middle meatus examination for the presence of purulence and bacterial culture aids in the diagnosis. In contrast to acute sinusitis, imaging is beneficial in patients with recurrent acute sinusitis. Anatomical obstructions that predispose the patients to infections can be identified and then surgically addressed.

SUBACUTE RHINOSINUSITIS

Subacute RS occurs when the inflammation and infection of the nose and sinuses lasts longer then 4 weeks but less than 12 weeks. Evaluating the subacute RS is difficult since it is often only when the symptoms persist long enough to become chronic that a diagnosis is made. In addition, the patients tend not to have as significant symptoms as are seen in ABRS and they often are confused for having other diagnoses, such as allergic rhinitis or chronic rhinitis. In addition, there may have been a short period of improved symptoms following the acute infection, which may also make it difficult to determine whether this is another primary acute infection or a subacute inflammatory process. Lastly, the patient may have been initially treated with an antibiotic, which raises questions as to whether they were inadequately treated with the initial episode or whether the persistent inflammation is noninfectious.

In most cases subacute RS has a typical pathogen pattern similar to ABRS with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, and *Staphylococcus aureus* predominating. There may be some pathogens more typical of CRS, particularly in the third month. If the patient has been treated with an antibiotic at the early portion of the infection, there may be either a shift in pathogens or some selection for more resistant strains.

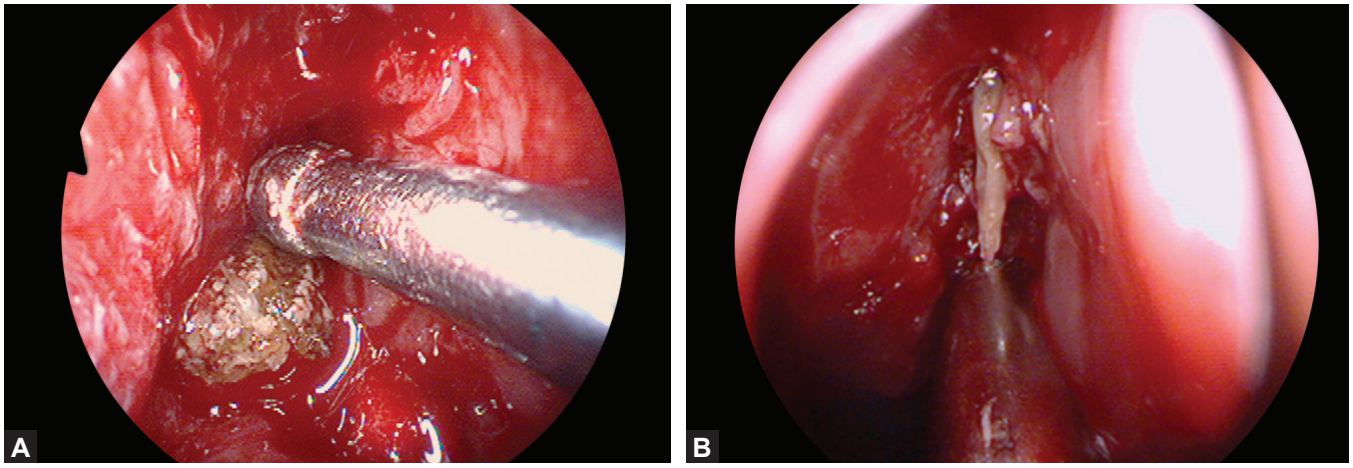
CHRONIC RHINOSINUSITIS

Chronic rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration.[1] It is a very common illness and reportedly more widespread than arthritis and hypertension, affecting over 31 million Americans.[2,4] CRS has significant symptoms that results in the loss of productivity and negatively impacts quality of life.[17] This complex disorder has many potential etiologies, and the spectrum of disease can vary dramatically from individual to individual. Common causes of chronic sinusitis include viral, bacterial, fungal, allergic, and idiopathic. Because of the heterogeneity of CRS, there are several classification schemes. While one grouping divides CRS based on pathophysiologic mechanisms (extrinsic and intrinsic factors to the host), another popular schema subdivides CRS into three categories CRS with polyps (CRScNP), CRS without polyps (CRSsNP), and allergic fungal RS.[2,18]

CRSsNP is the most common form of CRS.[11] Nasal mucosa within these patients lack nasal polyps and eosinophilic mucin. Structural abnormalities and mechanical obstruction have been associated with its etiology.[12]

CRScNP is distinguished from CRSsNP by the presence of nasal polyps within the nasal cavity and sinuses. In contrast to the nasal mucosa in CRSsNP, the polypoid tissue contains eosinophils, increased levels of histamine, and interleukin 5 and 13.[11] This subset of CRS is often associated with aspirin sensitivity and asthma.

Allergic fungal RS affects 8–12% of patients with CRS.[19] It is diagnosed by the presence of five criteria, which include Type I hypersensitivity, nasal polyps, characteristic CT findings, eosinophilic mucin without signs of fungal invasion, and positive fungal stain or culture.[20] Patients have characteristic allergic fungal mucin, which is a thick, tenacious, eosinophilic secretion with characteristic histologic findings (Figs. 23.1A and B). CT scans may demonstrate



Figs. 23.1A and B: Endoscopic views of allergic fungal mucin within the paranasal sinuses. It has a very thick, sticky, and tenacious quality. It has been classically described as having a "peanut butter or rubber cement" texture.

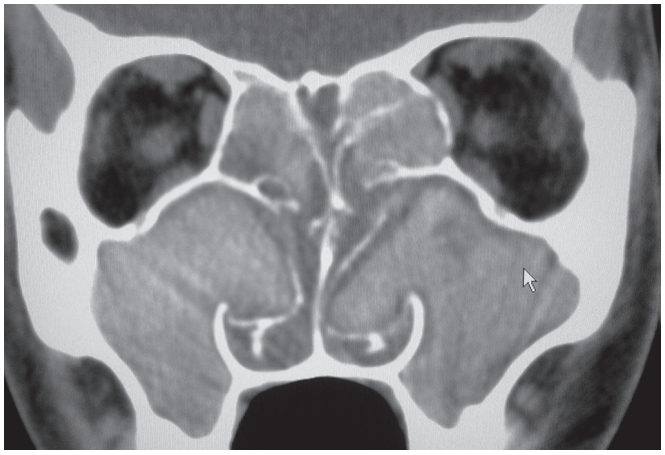


Fig. 23.2: Computed tomographic scan of patient with allergic fungal rhinosinusitis. There is pansinusitis with significant bony expansion, and heterogeneous signal intensity thought to be from hemosiderin and deposition of heavy metals, such as iron and manganese (*see* white arrow).

bony erosion and expansion and reveal heterogeneous signal intensity thought to be from hemosiderin and deposition of heavy metals such as iron and manganese (Fig. 23.2).[21]

DIAGNOSIS

The Rhinosinusitis Task Force Committee of the American Academy of Otolaryngology—Head and Neck Surgery has identified major and minor clinical factors believed to be significant for the diagnosis of sinusitis. Major factors are facial pain/pressure, nasal obstruction, nasal discharge/discolored postnasal drip, hyposmia/anosmia, purulence on examination, and fever (only in acute sinusitis). Minor factors include headache, nonacute fever, halitosis, dental pain, fatigue, cough, and ear pain/pressure/fullness (Table 23.1).[2] According to their guidelines, there must be the presence of at least two major factors or one major and two minor factors to diagnose RS.

Table 23.1: Factors associated with the diagnosis of rhinosinusitis.

Major factors	*Minor factors*
Facial pain/pressure	Headache
Nasal obstruction/blockage	Fever (all nonacute)
Nasal discharge/purulence/discolored postnasal drainage	Fatigue Halitosis
Hyposmia/anosmia	Dental pain
Purulence in nasal cavity on examination	Cough
Fever (acute rhinosinusitis only)	Ear pain/pressure/fullness

Previous studies and consensus statements utilized a combination of major and minor symptoms to diagnose and define ARS.[1] However, recent studies have shifted more in favor of using three cardinal signs or symptoms.[10,11] They include nasal congestion, anterior and/or posterior purulent rhinorrhea, and facial pain or pressure.

The ARS can be diagnosed by history and clinical findings alone. Either anterior rhinoscopy or nasal endoscopy can be used to assess for purulent rhinorrhea. Although nasal endoscopy provides a better examination of the middle meatus and sphenoethmoidal recess, it is not available in most primary care offices and is not necessary to diagnose ARS.

In contrast to ARS, CRS diagnosis must be based on subjective findings and confirmed with objective findings on physical examination and/or imaging.[3,11] Although the physical examination is of marginal value in ABRS, it is very important in CRS. Purulent nasal drainage and edematous nasal mucosa, along with characteristic symptoms can help make the diagnosis. When combined with duration of the disorder, it can help distinguish between a bacterial and viral infection. Although improvement in these findings may be a reasonable outcome assessment in an individual patient, the findings on physical examination are not well standardized and are difficult to use as a measure of outcome in population-based investigation. The role of physical examination other than nasal endoscopy has not been well studied in CRS.

Nasal Endoscopy

Nasal endoscopy has limited value over symptoms and physical examination in ABRS, although the selectivity of the examination would likely be greater. A prospective study comparing history and anterior nasal examination and history and nasal endoscopy did not demonstrate a difference in ultimate diagnosis. In only two patients of the 100 studied was the diagnosis changed after nasal endoscopy.[22] Its use in establishing the severity of disease and assessing the response to treatment may be of a greater value. Endoscopic-guided culture of middle meatus mucopurulence is an important adjunct in select patients with ABRS, including those with severe disease, possible resistant organisms, or failure to improve following first-line medical therapy.

In CRS, nasal endoscopy has been found to be a valuable tool in diagnosis, response to treatment, and postoperative care. Nasal endoscopy has also been used in a number of studies to assess the effectiveness of treatment and has been recommended to be one of the outcomes measurement tools in research in CRS.[2] This includes the use of nasal endoscopy as one of the key measurements in validating the effectiveness of nasal steroids in the treatment of CRScNP and ultimately attaining approval for such drugs for the treatment of polyps with international drug agencies.[23]

Imaging

The role of imaging has increased in both the evaluation and measurement of treatment response in RS, predominantly CRS. Plain sinus radiographs are still used in some circumstances, but their role has diminished with advent of the development of CT scan and magnetic resonance imaging (MRI). CT scan of the sinuses without intravenous contrast is considered the gold standard for radiographic evaluation of the paranasal sinuses. CT imaging offers an objective method to evaluate and monitor paranasal sinus inflammation. Although air–fluid levels can be visualized during an acute exacerbation, the hallmark of chronic sinus disease on CT scan is mucosal thickening.[24]

The CT scans are used to confirm diagnosis, stage disease extent, and evaluate anatomy for surgical intervention. One of the roles of a CT scan is to exclude aggressive infections or neoplastic processes. Osseus destruction, extrasinus extension of disease, and local invasion suggest malignancy.[10] CT scans provide excellent bony detail; however, they are unable to distinguish between soft tissue and nasal secretions.[10]

The MRI is usually an adjunct to CT scan and is generally reserved for patients with concern for neoplastic process, but it can be useful in fungal diseases as well. The advantage of MRI is that it provides excellent soft tissue detail and can be used to differentiate between brain, tumor, and inspissated secretions.[10] The disadvantages are that it does not provide bony detail and is time consuming and costly.

The utility of using imaging to either diagnose or evaluate outcomes in ABRS is limited due to the lack of both sensitivity and specificity. While plain radiographs tend to underassess sinus disease, CT scans have been shown to be nonspecific. Patients with a viral upper respiratory infection have been shown to have abnormal CT scans as well.[8] The Cochrane review of maxillary sinusitis suggested that although most assessment tools were of low methodologic quality, when compared with the gold standard of sinus taps, radiography was the most effective in supporting the diagnosis and ultrasound had little value.[25] Despite this, radiography has been found to be not cost-effective in the diagnosis of ABRS,[3] and there is little data to suggest that it is a good tool to measure outcomes, particularly since the radiographs may remain abnormal for some time after the symptoms have cleared and treatment stopped.[8] However, obtaining CT scans in patients with ABRS may have a role in special circumstances in which there is severe disease, an immunocompromised state, or a suspected complication.

Nasal and Paranasal Sinus Cultures

Nasal and paranasal sinus cultures have played an important role in treating RS. Pretherapy and post-therapy

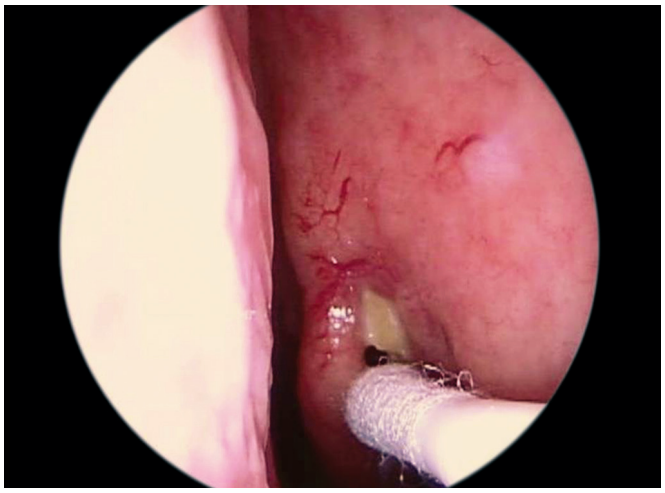


Fig. 23.3: Endoscopic view of culturing the middle meatus with a culture swab. This allows for direct visualization and aids in selecting the appropriate antimicrobial treatment.

cultures are an excellent measurement of outcome of treatment. The increased incidence of drug resistant bacteria has prompted many otolaryngologists to initiate culture-directed antibiotic therapy in their practice. Traditionally, the gold standard for obtaining sinus cultures was by maxillary sinus taps through the canine fossa or inferior meatus. However, this method is not ideal because it is more invasive, associated with increased discomfort, requires local anesthesia, and has a potential small risk of injury to the teeth, infraorbital nerve, and lacrimal apparatus. Advances in endoscopic techniques have allowed for the development of endoscopic-guided aspiration or swab of a variety of sinuses under direct visualization (Fig. 23.3).

Endoscopic-guided cultures have been shown to be well tolerated and as effective as maxillary sinus taps.[26-28] A meta-analysis by Benninger et al. compared the results of endoscopic-directed middle meatal (EDMM) cultures and maxillary sinus taps in patients with acute bacterial maxillary RS. The meta-analysis demonstrated that EDMM is both highly sensitive and specific (80.9% and 90.5%, respectively) and is a viable and preferred method of culturing patient with RS.[29]

The role of cultures in CRS is more complex. Since CRS is a group of disorders with various etiologies including but not limited to allergic, idiopathic, autoimmune, and infectious causes. The role of cultures may be limited. However, when evaluating and treating patients with an acute exacerbation of CRS, sinus cultures are not only important in determining treatment but may be effective in measuring responsiveness.

OUTCOMES MEASUREMENT TOOLS

The high prevalence and significant costs related not only to diagnosis and treatment but also to the economic impact of RS have driven an interest in more objectively assessing the disease impact on a given patient's quality of life. This area of evaluation has largely been defined as outcomes measurement.

There are a number of disease-specific quality-of-life instruments that have been developed to assess RS. The more commonly used instruments are the RS Disability Index (RSDI),[30] the 31-Item RS Outcome Measure[31] and the subsequently shortened versions, 20-Item Sino-Nasal Outcome Test (SNOT-20),[32] 22-Item SNOT (SNOT-22),[33] and the Chronic Sinusitis Severity Survey (CSS).[34] Each questionnaire measures specific symptoms, overall quality of life, and has been used in both patient care and research. The most widely utilized surveys are the SNOT-20 and the SNOT-22, which have been commonly used to measure treatment response in the literature. The difference between the two instruments is the inclusion of the symptoms of nasal obstruction and anosmia n the SNOT-22.

The CSS has a notable disadvantage in that it also includes prior antibiotic prescriptions in the evaluation of severity, which may be physician dependent and may not be an appropriate treatment for many patients with CRS, and therefore it may introduce unintended bias. The RSDI has unique advantages in that it has also been validated in other nasal and sinus disease, such as allergic and nonallergic rhinitis, so that it may be used initially even if it is unclear if the patient's symptoms are caused by RS. In addition, this survey assesses the impact of the disease on sexual function,[35] which is often an important quality-of-life issue for patients.

The choice of the quality-of-life instrument is probably less important than the routine use of them. If administered before and after therapy, they can be strong predictors of responsiveness to treatment and good measures of outcomes.

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CHAPTER

24

The Pathogenesis of Rhinosinusitis

Michael S Benninger, Janalee K Stokken

DEFINITIONS OF ACUTE AND CHRONIC RHINOSINUSITIS

In order to understand the pathogenesis and pathophysiology of rhinosinusitis, it is important to realize that there are different varieties of rhinosinusitis and the inciting mechanism may vary dramatically between the different subtypes. Although "sinusitis" is a term that is commonly used for any inflammation or infection of paranasal sinuses, this term has largely been replaced by "rhinosinusitis" since the nose is almost always involved at the same time as the sinuses.[1] Since there are many potential factors that contribute to rhinosinusitis, there has been some debate concerning the exact definition. In general terms, rhinosinusitis is defined as "a group of disorders characterized by inflammation of the mucosa of the paranasal sinuses".[2] In 1997 the "Rhinosinusitis Task Force" of the American Academy of Otolaryngology-Head and Neck Surgery[3] developed a now well-accepted classification of rhinosinusitis and this was reported by Lanza and Kennedy.[1] This classification relies on the identification of symptoms to make a diagnosis. The symptoms are broken into major and minor categories, with purulent nasal drainage, nasal congestion, facial pressure or pain, decreased smell, and posterior purulent drainage serving as the major symptoms.[1] When a patient describes two major criteria or one major and two minor criteria, rhinosinusitis can be diagnosed (Table 24.1). The classification of rhinosinusitis types is based primarily on temporal time frames from the onset of symptoms. More recently, a stricter division for chronic rhinosinusitis (CRS) has been described based on endoscopic findings. These include CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). The European position paper on rhinosinusitis and nasal polyps 2012 (EPOS 2012)[4] further defines the disease process accordingly for both the adult and pediatric populations (Table 24.2).

Table 24.1: Rhinosinusitis symptoms/signs (requires two major factors or one major and two minor)

Major symptoms	*Minor symptoms*
Facial pain/pressure	Headache
Facial congestion/fullness	Fever (nonacute)
Nasal obstruction/blockage	Halitosis
Nasal discharge/purulence/ discolored posterior drainage	Fatigue
Hyposmia/anosmia	Dental pain
Purulence on nasal exam	Cough
Fever (acute rhinosinusitis only)	Ear pain/pressure/fullness

An inflammatory response is an expected sequela of an infectious process. Sinonasal inflammation can result from a variety of elements that result in sinus ostial obstruction and predispose patients to an infection. Many factors have been described as playing a role in the development of acute bacterial rhinosinusitis (ABRS).[1,5,6] These include factors related to the host: genetic factors such as immotile cilia syndrome or cystic fibrosis; anatomic abnormalities such as a concha bullosa, septal spur, or paradoxical turbinate; certain systemic diseases or medical treatments that predispose individuals to infections; neoplasms; and allergic or immune disorders. Rhinosinusitis may also

Table 24.2: Clinical definition of rhinosinusitis in adults

Inflammation of the nose and the paranasal sinuses characterized by two or more symptoms:
• One of which should be either nasal blockage/obstruction/congestion or anterior/posterior nasal discharge: – ± Facial pain/pressure – ± Reduction or loss of smell (± cough in children)
and either:
• Endoscopic signs of: – Nasal polyps, and/or – Mucopurulent discharge primarily from middle meatus and/or – Edema/mucosal obstruction primarily in middle meatus
and/or:
• Computed tomography changes: – Mucosal changes within the ostiomeatal complex and/or sinuses
Chronic rhinosinusitis with nasal polyps: chronic rhinosinusitis as defined above and bilateral, endoscopically visualized polyps in middle meatus
Chronic rhinosinusitis without nasal polyps: chronic rhinosinusitis as defined above and no visible polyps in middle meatus, if necessary following decongestant

develop in relationship to environmental factors including bacterial, viral, or fungal infections, or inflammation that occurs secondary to fungal or bacterial colonization;[2,7] trauma; primary or secondary tobacco smoke exposure;[8] chronic or acute irritants or noxious chemicals; or iatrogenic factors including surgery, medications, nasal packing, or nasogastric tube placement.[9] There is evidence that individuals with allergic rhinitis have a higher incidence of developing both acute and CRS. An association of ABRS with asthma has also been suggested, although this may also relate to the presence of allergic rhinitis.[10-12]

The distinctions between acute rhinosinusitis (ARS), recurrent acute rhinosinusitis, subacute rhinosinusitis, CRS, and acute exacerbation of chronic rhinosinusitis (AECRS) are based on the temporal differences in the presentation and in some cases on the clinical presentation. Each of these subcategories may be associated with different pathophysiologic processes and the predisposition to their development may vary from patient to patient. Given these differing etiologies, the pathogenesis will be described based on this classification.

ACUTE RHINOSINUSITIS

Acute bacterial rhinosinusitis is a very common disorder that at one time or another impacts most people. From a temporal standpoint, ARS lasts for up to 4 weeks.[1] Acute rhinosinusitis results from interactions between a predisposing condition such as allergic rhinitis, nasal septal deviation, immune deficiency, a viral infection, and a resultant inflammatory response. The inflammation then leads to edema and obstruction of the sinus ostia. The normal ventilation and physiology of the sinuses are then impaired and a secondary bacterial infection ensues.

Viruses account for the majority of the cases of ARS and include rhinovirus, coronavirus, influenza, respiratory syncytial virus, and parainfluenza. There have been attempts at estimating the prevalence of ARS. It is estimated that children have between 6 and 8 upper respiratory tract infections (URIs) per year and adults average 2–3.[13] If an assumption is made that 90% of patients with colds have sinusitis (bacterial or viral), then it can be estimated that in the United States there are over a billion cases of viral and bacterial rhinosinusitis annually (260 million people × four episodes per person = approximately one billion cases).[14]

Acute bacterial rhinosinusitis has been defined as sudden in onset and with duration of less than 4 weeks.[1] Since most cases of rhinosinusitis are from a self-limited viral infection and bacterial infections usually occur following aviral URI, ABRS may be diagnosed after at least 7–10 days of symptoms, or in patients whose symptoms are worsening after 5–7 days.[1,4,15] Acute rhinosinusitis becomes a bacterial infection in only about 0.5–2% of cases. This distinction has been endorsed in most of the guideline development for the treatment of ABRS5 (Fig. 24.1). The diagnosis may be more difficult in children, because they often have difficulty describing their symptoms.

In ABRS, *Streptococcus pneumoniae* (20–45%), *Haemophilus influenzae* (20–43%), *Moraxella catarrhalis* (14–28%) are the predominant organisms.[5,15-17] Although previously thought to be a contaminant, *Staphylococcus aureus* is now being considered a real pathogen in ABRS accounting for 8–11% of cases.[16,18] Methicillin-resistant *Staphylococcus aureus* (MRSA) generally accounts for about half of all isolated *S. aureus*.[16,19] Since *M. catarrhalis* is largely a self-limited pathogen, and since MRSA is becoming a bigger healthcare issue, ABRS secondary to *S. aureus* may be more important to treat. *Staphylococcus aureus* is also a well-recognized pathogen in both CRS and in AECRS.[15,18-20]

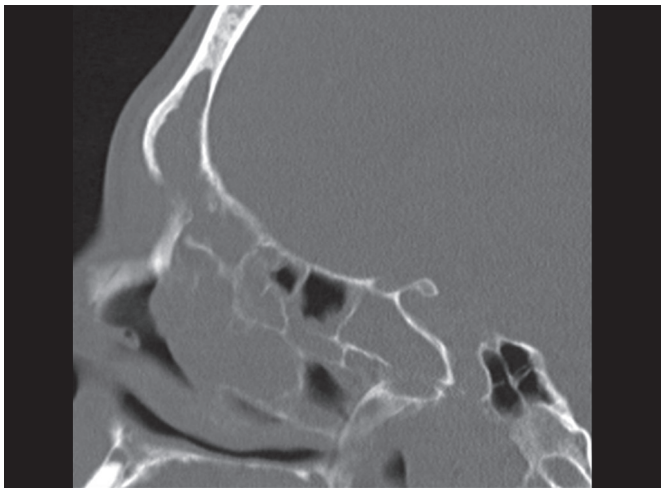

Fig. 24.1: Sagittal computed tomography scan from a patient with acute rhinosinusitis and forehead swelling revealing dehiscence of the anterior table of the frontal sinus and opacification of the frontal, ethmoid, and sphenoid sinuses.

Acute bacterial rhinosinusitis is a self-limited disease in many cases. Evaluation of placebo-controlled antibiotic trials has shown that there is a high self-resolution rate.[5,14,15] *Morexella catarrhalis* and, to a lesser extent, *H. influenzae* are most likely to resolve without antibiotic treatment. *Streptococcus pneumoniae* is least likely to resolve without treatment. It may become important therefore to identify which patients have which organism through a culture. The maxillary sinus tap represents the traditional method of obtaining sinusitis cultures but is difficult and impractical in the outpatient office setting. The advancement of endoscopically guided middle meatal cultures have resulted in a shift to this method in clinical practice.[20,21] An evidence-based review has revealed that endoscopic middle meatal cultures are as sensitive and specific to those obtained by maxillary sinus taps.[21] In clinical practice, however, cultures are often only obtained when there has been a treatment failure. The severity of the symptoms and radiographic findings may help to identify different pathogens in that patients infected with *S. pneumoniae* have been found to have more significant symptoms and worse radiographic findings than those infected with *H. influenzae*.[22]

With the widespread utilization of 7-valent conjugated pneumococcal vaccination, there has appeared to be a shift in the overall distribution of pathogens in ABRS. In a recent study assessing the pathogenesis of ABRS, the proportions of the recovery of pathogens obtained by endoscopic directed cultures in adults with acute maxillary sinusitis were compared between the 4 years prior to and the 5 years after the introduction of the conjugate pneumococcal vaccine. *H. influenzae* increased from 36% to become the most common pathogen at 43%. At the same time, *S. pneumoniae* was found to decrease from the most common pathogen at 46% of isolates to 35% after the use of the vaccine, while there also was an increase in the cases caused by *M. catarrhalis* and *S. aureus*.[23] In a similar study, nasopharyngeal cultures were obtained in children with acute maxillary sinusitis before and after widespread use of conjugate pneumococcal vaccination. *Streptococcus pneumoniae* decreased from 43% of isolates to 25%, while H. influenzae increased from 35% to 41%, *M. catarrhalis* remained stable 13–14%. *Streptococcus pyogenes* increased from 7% to 12% and *S. aureus* increased from 4% to 8%.[24]

Following widespread pneumococcal vaccination there appears to also have been changed in the serotypes of *S. pneumoniae* responsible for not only ABRS but also for acute otitis media (AOM), with an increase in serotypes not found in the vaccine.[25-27] There has, however, been some speculation that this serotype replacement may reduce the long-term efficacy of the 7-valent conjugate pneumococcal vaccine.[27] Multiple studies have shown that there has been a reduction in both the nonsusceptible and high-level resistant strains of *S. pneumoniae* cultured in AOM and to a lesser extent in ABRS.[28-32] Whitney et al. showed that there was a 35% reduction in strains nonsusceptible to penicillin.[29] High-level resistance of *S. pneumoniae* to penicillin also appears to have dropped, having been reported to have decreased from 15% to 5%.[31] There has been an associated increase in the β-lactamase producing strains of *H. influenzae*.[32] Although the data related to the shift in pathogens is less well supported in ABRS than in AOM, there has been a clear shift in the pathogens associated with both ABRS and AOM and this shift is parallel between the two groups. This is not unexpected since the pathogenic organisms are similar for ABRS and AOM and the shift in the microbiology of ABRS has been suggested to have occurred because of the involvement of the same pathogens in AOM and ABRS.[33]

The mechanism by which the viral inflammation of a viral URI can lead to ABRS has been suggested in a number of reports.[6,34] As mentioned above, ARS typically develops in conjunction with an acute viral URI. The propensity to develop a viral URI may occur more commonly in predisposed individuals. The viral infection can result in swelling of the mucosa of the nose or sinuses and the resultant swelling and engorgement can result in occlusion or

obstruction of the sinus ostia. A reduction in oxygen tension occurs that can reduce mucociliary transport and transudation of fluid into the sinuses.[6] The inflammation also results in changes in the mucous that become more viscous and alterations in cilia beat frequency often occurs. These changes in the nasal–sinus environment lead to reduced clearance and stasis of the mucous and bacterial colonization. If the sinuses remain obstructed or the mucociliary transport system does not return to normal, a bacterial infection can ensue. The ability of the body to respond to the viral challenge and reduce the inflammation may, in part, determine whether a secondary bacterial infection occurs.

The role of allergies in the development of rhinosinusitis has been strongly suggested but not proven.[10-12] Antigen–antibody reactions result in an IgE-mediated hypersensitivity resulting in mast cell degranulation and the release of histamine and other mediators of inflammation. These mediators cause changes in vascular permeability, destabilization of lysosomal membranes, and other reactions that produce inflammation, mucosal swelling, and ostial obstruction.[6] Although infectious agents can be primary causes of sinus inflammation, they may also represent a secondary infection. The type and magnitude of the reaction may be related to the host response and how it relates to the disease process and progression. There are limited studies on the effect of topical nasal steroids, allergen avoidance, or immunotherapy in preventing recurrent ABRS.

Recurrent ARS is defined by four or more episodes per year, with each lasting greater than 7–10 days and an absence of intervening signs or symptoms that would suggest an ongoingor CRS.[1] Although recurrent viral respiratory tract infections are common, in general it is rare for people to develop true recurrent episodes of ABRS to meet the above criteria of recurrent ABRS. When they do, it is expected that the bacteriology and pathophysiology would be similar to individual episodes of ABRS.

INVASIVE FUNGAL RHINOSINUSITIS

There is a very small subset of patients with ARS where the inciting pathogen is neither viral nor bacterial. This is acute invasive fungal sinusitis (IFS). IFS is almost always confined to patients with altered host defenses. A recent review of 807 patients with IFS revealed that most patients are in an immunocompromised state with 47.8% having poorly controlled diabetes, half of which presented with diabetic ketoacidosis, 39% with a hematologic malignancy, 6.3% with solid organ transplant, and 2.3% with HIV or AIDS. Twenty-seven percent were on chronic steroids.[35] Any disorder that results in immune suppression or an immunodeficiency can predispose to an invasive fungal infection. The survival of this population is low despite improvements in medical therapies and aggressive surgical resection with an overall survival rate of 49.7%. [35]

Although historically the most common organism that has been reported to result in IFS has been *Mucormycosis* in the past decade, *Aspergillus* is now more common, especially in diabetics.[36] Alternaria species, and *Pseudallescheria boydii* have also been identified in IFS. On clinical presentation and examination early in the disease course, however, it may be difficult to identify IFS. Invasive fungal sinusitis is suspected when the immunocompromised patient develops a fever and symptoms suggesting a complication of sinusitis, such as facial swelling, ophthalmoplegia, proptosis, vision loss or significant facial pain, as well as nasal congestion and nasal discharge.[35] Patients may present with anesthesia of the face, mucosa, or palate and they can have palate ulcerations or necrosis. Nasal endoscopy may show crusting, ischemia, or necrosis of the nasal mucosa or there may even be a blackish color, which might be suggestive of *Mucormycosis*. If there is significant necrosis, the tissue may not bleed when manipulated or biopsied.

If the diagnosis of IFS is suspected, a sinus computed tomography (CT) and often a magnetic resonance imaging (MRI) scan should be obtained. Since abnormal sinus radiography is common in immunocompromised patients with up to 42% of patients with leukemia in one series having abnormal sinus radiographs,[37] suspicion for IFS should rely on clinical symptoms and findings on CT or MRI. Changes seen on sinus CT or plain radiographs usually make it indistinguishable from bacterial sinusitis, although they may show bony erosion or soft tissue invasion. Histopathologic evaluation of biopsies or surgical specimens will show fungal elements within and invading the tissue. Positive prognostic factors have been found to include surgical resection, diabetes mellitus, and the use of liposomal amphotericin. The lowest survival rates were seen in patients with mental status changes, aplastic anemia, renal or liver failure, intracranial or cavernous sinus involvement, and neutropenia.[35]

CHRONIC RHINOSINUSITIS

Chronic rhinosinusitis is diagnosed when the signs and symptoms last for longer than 12 weeks.[1] Since it has

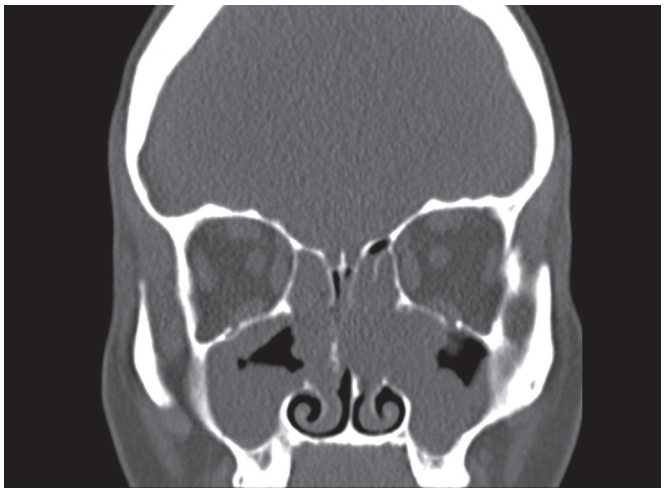

Fig. 24.2: Coronal computed tomography of a patient with bilateral chronic rhinosinusitis with polyposis involving the maxillary and ethmoid sinuses.

become clear that inflammation is the major universal finding in all patients with rhinosinusitis, newer definitions have been developed to describe rhinosinusitis: "Chronic Rhinosinusitis" is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks duration.[2,7] The overall prevalence of CRS is 10.9% with marked geographical variation (range 6.9–27.1).[38] The pathogenesis of CRS is unclear and there are many hypotheses being studied and debated. CRS is frequently subdivided into two separate entities based on the presence or absence of polyposis (Fig. 24.2). This distinction is appropriate for clinical and research purposes, however, histologically their profiles can be similar. Clinically, the two have similar presentations but can be easily distinguished on nasal endoscopy. CRS without polyps accounts for about 60% of cases.[39] There is evidence to suggest that the two entities follow distinct inflammatory pathways and have different cytokine profiles.[39-42] The Th2 inflammatory profile might be more characteristic of CRSwNP and the Th1 profile may be more characteristic of CRSsNP; however, there is evidence of overlap in both groups.[43] Aside from these two broad classifications there may be other subtypes of CRS such as allergic fungal rhinosinusitis and aspirin-exacerbated respiratory disease (AERD). Patients with CRSmay have intermittent acute flare-ups. In such cases, this is called AECRS.[1]

While ABRS is a common disorder with well-established diagnostic criteria and treatment algorithms, the definitions and treatment for CRS have been particularly difficult to establish due to the wide variety of potential contributing factors. Although the role of bacteria and antibiotic therapy is well established in ABRS, the role of bacteria in CRS is not well supported. Therefore, the use of symptoms to try to define CRS is not as effective as they are in ABRS.[2,7]

Inflammation in the nose and sinuses, from a variety of causes, can result in paranasal sinus ostial obstruction and predispose to the development of further inflammation or an infection. There are many potential causes of inflammation, and current medical treatment options have been designed to both treat the inciting factors and to reduce the subsequent inflammatory reaction. Although bacteria, fungi and viruses can be primary causes of sinus inflammation, they may also occur as a secondary infection, or even colonizers of the mucous. Much of the recent interest has been in the host response to the inflammatory precipitant and how it relates to the disease process and progression. The Th1 cytokine profile is typically present in CRSsNP with upregulation interferon-Y, transforming growth factor beta, and interleukin 1 (IL-1). The inflammatory infiltrate is mostly neutrophils, lymphocytes, and plasma cells.[7] Histologically, CRSsNP is characterized by basement membrane thickening, goblet cell hyperplasia, glandular hyperplasia, limited subepithelial edema, and prominent subepithelial fibrosis. In comparison CRSwNP typically has a Th2 profile with upregulation of IL-4, IL-5, and IL-13. There is local production of polyclonal IgE. Histologically, CRSwNP is characterized by epithelial damage, epithelial shedding, pseudocyst formation containing albumin thickened basement membrane, and a reduced amount of blood vessels and glands. In addition, there are other factors that have also been identified that may play a role in the development or perpetuation of CRS. These include bacterial biofilms, superantigens, and osteitis.[2,7,44-47]

One of the major problems with identifying the pathogenesis of CRS is that neither clinical evaluation nor radiographic studies are independently sufficient to make the diagnosis. One study showed that current symptom-based criteria had only a 47% correlation with a positive CT scan.[48] Furthermore, in patients who have sinus disease objective patient-based descriptions and measures do not correlate with the severity of CT findings.[49] When comparing people with a diagnosis of CRS undergoing surgery, and comparing these to control patients who clinically do not have disease using an established grading scale for disease severity, the CT scan exhibited good sensitivity and specificity but only at 85% and 59% levels respectively.[50]

There are also a number of conditions that have been found to clinically masquerade as CRS. These include rhinitis, laryngitis associated with reflux, and headaches.[51,52]

The potential pathophysiologic mechanisms that may play a role in the development or perpetuation of CRS are discussed in chapters throughout this book. The multiple theories related to pathophysiology have also been well discussed in other reports.[2,7] Given the definition suggesting that the key criteria is an inflammatory reaction, any mechanism that can cause inflammation in the nose and sinuses could theoretically lead to CRS. Trying to identify the pathophysiologic mechanisms in CRS has been very difficult for a number of reasons. The first is that until recently there was not a well-accepted definition or criteria to make the diagnosis until the recent Sinus and Allergy Health Partnership report.[2] The second issue is that knowledge of this disease is still dramatically evolving and trying to identify the mechanisms that result in the disease is complicated since the science is so dynamic. Another significant issue is that there has been a tendency to try to identify a single, unified etiology for all cases of CRS. Based on the new definitions of "a group of disorders", such a unified concept may not be easily identified, or perhaps even possible. There are some pathophysiologic mechanisms that are becoming more established.

Bacterial infection is associated with CRS in some patients. Bacteria can both infect or colonize the sinuses. Whether the bacteria play a role in the disease via a classic infectious mechanism or one related to inflammation, or both is not yet know, but in some patients eradication of the bacteria improves symptoms or can even resolve the CRS. Although the bacteria involved in ABRS are well established, studies looking at the bacteriology of CRS have revealed significant differences in the microbial pathogens present. *Streptococcus pneumoniae* and *H. influenzae* are often identified, but they are present in much lower concentrations and a number of other bacteria are commonly found. *Staphylococcus aureus*, coagulase-negative *Staphylococcus* spp., *Corynebacterium* spp, *Pseudomonas aeruginosa*, Enterobacteriaceae, and even enteric Gram-negative bacteria are reported as being identified.[2,16,53-55] Anaerobic organisms are often present. Resistant bacteria, including MRSA, are encountered more frequently. Whether or not these bacteria have their relationship with the chronic inflammation via a classic infectious process or through an allergic or inflammatory mechanism is debated. For whatever reason, many patients respond to antibiotic therapy, which has prompted an interest in the role of anti-inflammatory properties of certain classes of antibiotics such as the macrolides.

Another mechanism where bacteria may play a role in the pathogenesis in CRS relates to the ability of certain bacteria to release exotoxins. This mechanism has been discussed in the pathogenesis of CRS with polyps, but does not appear to plan a role in CRS without polyps. Certain bacteria, such as *S. aureus* possess the ability to release exotoxins, which can be pathogenic and cause significant, sometimes, life-threatening reactions in humans.[56] Superantigens are a group of proteins or particles produced from bacteria that can elicit an aggressive inflammatory response.[2,7,46,53,56,57] It has been proposed that exotoxins can also be released locally into the tissues, eliciting a local inflammatory response without resulting in the overwhelming systemic effects as seen in toxic shock syndrome. Enterotoxins from noninvasive *S. aureus* act locally as superantigens on T lymphocytes and induce a multiclonal B-cell activation. The resulting release of IL-5 from Th2 cells results in eosinophilic activation and the production of multiclonal IgE.[44] Patients with polyposis appear to have a higher incidence of colonization by *S. aureus* compared to patients with CRS without polyps and control patients. However S. aureus colonization rate appears to be about 65% in CRS patients with polyps.[58] Thus, this mechanism cannot account for the pathogenesis for all polyps.

An understanding of the role of bacterial biofilms in the pathogenesis of CRS has evolved over the past decade.[2,47,59] Bacterial biofilms are defined as an assemblage of microbial cells enclosed in a self-produced polymeric matrix that is irreversibly associated with an inert or living surface.[47] These organized communities of bacteria can then release planktonic bacteria that travel to new anatomic areas and case acute exacerbations. Bacteria in biofilms are more resistant to host defenses and antimicrobial agents. Bacterial susceptibility to antibiotics can be decreased by 1,000-fold.[60] Biofilms do appear to be present in a large number of patients with CRS. Studies have shown that 25–100% of patients with CRS have biofilms.[59] There are multiple methods for identifying biofilms all with unique advantages and disadvantages; this may account for the wide incidence range. The exact mechanism that biofilms play in the pathogenesis of CRS has not been established; however, there is increased data to support a contributory role.

Another proposed pathophysiologic mechanism is the impact of bone osteitis in the perpetuation of the chronic

inflammatory response.[61,62] Concurrent osteitis can be found in 36–53% of patients with CRS using radiographic and pathology criteria respectively.[63,64] Although it is thought that the osteitic changes noted are a secondary reaction to the inciting inflammatory precipitant, it may play some role in prevention of response to treatment or increase the likelihood of recurrence.

Just like in ABRS, one of the factors that appear to be associated with CRS is allergy. There appears to be an increased relationship between allergies, particularly allergic rhinitis and CRS.[2,10,65] Although a direct cause and effect relationship has not been established, in theory allergies can result in inflammation and if that inflammation persists long enough, it can be manifested as CRS. The association of allergy and CRS has been reported from 25% to 50%, which is greater than would be expected in the general community.[2] Allergy could potentially lead to CRS through a number of different mechanisms, including allergic induced inflammation alone or the inflammation resulting in obstruction of the sinus ostia from nasal inflammation and swelling resulting in infection. It is also possible that allergies induce neurogenic stimulation, or predispose to secondary bacterial or fungal infection independent of an obstructive mechanism.[2,66] There is also a strong relationship between asthma, CRS, allergy, and in some cases aspirin hypersensitivity. These would support the suggestion that some people suffer from a more diffuse hyperactive airway disease, or common unified airway, which involves both the upper and lower airways. These patients also seem to be more prone to other mucosal inflammatory conditions such as acute or chronic otitis media. A strong association between asthma and CRS at all ages was reported recently in a large multicountry epidemiologic study. The association with asthma was stronger in those reporting both CRS and allergic rhinitis (adjusted OR: 11.85). CRS in the absence of nasal allergies was positively associated with late-onset asthma.[67]

There are a number of other inflammatory participants that play a role in the development of CRS. In addition, it has been suggested that anatomic abnormalities may predispose to earlier obstruction of the sinuses allowing for the development of CRS. One area of growing interest is the effect of inflammation caused by environmental irritants such as industrial pollution on secondary environmental tobacco exposure (ETS). The ETS is becoming more strongly associated with a number of airway conditions such as asthma, acute and CRS and rhinitis.[8,68] Although epidemiologically it may be difficult to control for such exposures, stronger associations are being identified.[68] The Sinus and Allergy Health Partnership's Task Force on Chronic Rhinosinusitis identified a large number of systemic host, local, and environmental factors that have been suggested to play a role in CRS, and these are listed in Table 24.3.

Table 24.3: Factors associated with chronic rhinosinusitis

Systemic host factors
• Allergic
• Immunodeficiency
• Genetic/congenital
• Mucociliary dysfunction
• Endocrine
• Neuromechanism
Local host
• Anatomic
• Neoplastic
• Acquired mucociliary dysfunction
Environmental
• Micro-organisms
– Viral
– Bacterial
– Fungal
• Trauma
• Noxious chemicals/pollutants/smoke
• Medications
• Trauma
• Surgery

Source: From the Sinus and Allergy Health Partnership.[2]

One of the more widely explored theories regarding the pathogenesis of CRS is the role of fungi.[2,7,45,53,69-72] There are likely a number of different ways that fungi can play a role in CRS. For a number of patients with chronic sinus disease, obstruction of the sinuses can lead to an accumulation of mucous and debris along with noninvasive fungal colonization in the sinuses. This fungal colonization is readily amendable to surgical removal and these patients usually have good outcomes with no long-term inflammatory sequelae.

Another group of patients have fungal associated disease secondary to a more classic Type I, IgE-mediated hypersensitivity reaction or more classic allergic (atopic) disease.[70,71] These patients have "allergic fungal sinusitis" (AFS) (Fig. 24.3). The AFS is identified in patients that

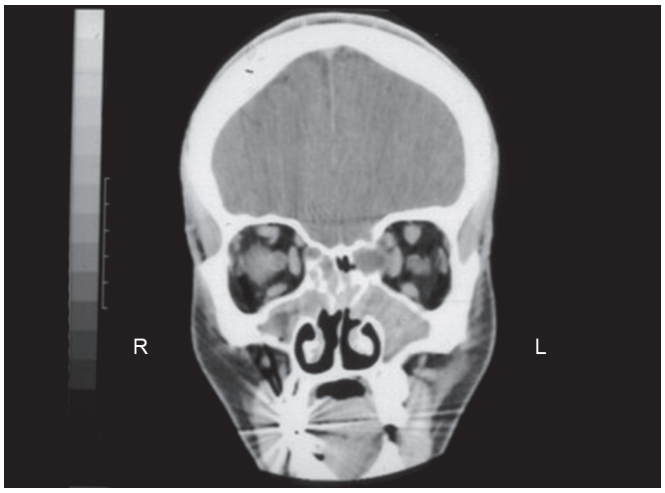

Fig. 24.3: Computed tomography scan of paranasal sinuses in a patient with allergic fungal sinusitis who has developed a mucocele with extension into the left orbit.

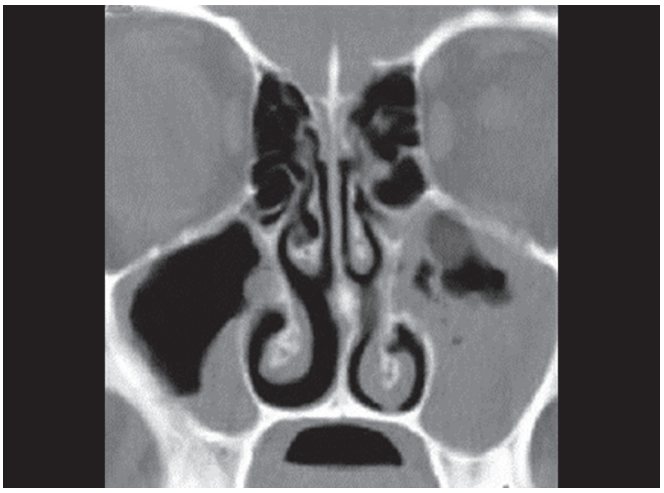

Fig. 24.4: Computed tomography scan from a patient with acute exacerbation of chronic rhinosinusitis. The scan not only shows evidence of mucosal hypertrophy in both maxillary sinuses and left ethmoid but also air fluid levels in the left maxillary sinus.

demonstrate five characteristics features with nasal polyps, eosinophilic mucin containing noninvasive fungal hyphae, characteristic radiographic findings particularly on CT scans, allergy and immunocompetence.[7,69,70-72] There are therefore patients that are hyper-responsive to fungi through this IgE-mediated reaction.

There are other mechanisms by which fungi can participate in or are related to the development of CRS. There are patients who develop an inflammatory response to fungi through non-IgE mechanism. In some cases, this may be due to a Type III (immune-complex) hypersensitivity reaction.[2,7,45,69,73] it has been found that fungus can be cultured from the noses of almost all people.[45,73] People, therefore, are chronically exposed to fungi and those fungi often colonize people's noses. Despite this, most people colonized by fungi do not display any noticeable reaction or inflammation. There is a small subset of individuals who develop a more intense inflammatory reaction that is felt to be in response to the presence of the fungus.[7,45,73-75] In such cases, eosinophils appear to play a very important role in this reaction, prompting recommendation of a new term, "Eosinophilic Fungal Sinusitis".[45,73,75] It has been proposed that this eosinophilic reaction to fungi may play an important role in nearly all episodes of CRS. With the multiple potential etiologic or associated conditions recognized with CRS, this assumption of a common fungal etiology would seem a significant simplification and may be important in only a selective group of CRS patients.

The role of the eosinophil, however, may be much more important than previously recognized.[2,45,70,71,73,75] Whether through classic Type I hypersensitivity, eosinophilic reaction to bacteria, viruses or fungi, or as a common inflammatory step, eosinophilic inflammation is being recognized as being involved in a majority of patients with CRS.[2] Some speculate that "eosinophilic inflammation may occur as a common pathway in response to a number of different inflammatory starting points".[71] The studies in fungal rhinosinusitis may have helped not only to create a great interest in the role of fungi but also have substantially moved the understanding of the various inflammatory mediators that are involved with CRS.

ACUTE EXACERBATION OF CHRONIC RHINOSINUSITIS

Acute exacerbation of chronic rhinosinusitis is a term that is used to describe patients with CRS who have an acute flare-up. This may manifest in the acute worsening of chronic but overall stable symptoms, usually with an increase in nasal mucous production that may become more purulent, increased nasal congestion, further loss of smell, and associated systemic symptoms such as fatigue, malaise or even fever[76,77] (Fig. 24.4). In such cases, there may be a change in the bacteriology of the disease, so that there is a blend of bacteria seen in both CRS and ABRS. Where ABRS is primarily aerobic and CRS has a high proportion of Gram-negative organisms and anaerobes, AECRS has both of these. There is an increase in the numbers of the common ABRS organisms such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* but with a large

percentage of anaerobic organisms such as *Peptostreptococcus* species and *Fusobacterium*. Where in CRS, the effectiveness of antibiotics is debatable, antibiotics that cover both the common ABRS and CRS organisms are effective in reducing the exacerbation. Aggressive anti-inflammatory agents such as systemic steroids may also be necessary. With acute treatment, patients tend to return to their steady CRS state following the exacerbation.

SUMMARY

The pathogenesis of rhinosinusitis is dependent on the classification of the rhinosinusitis. There are environmental factors that appear to predispose to any episode such as allergy, smoke, or chronic irritants. Viruses and aerobic bacteria are the major causes of ABRS. Invasive fungal sinusitis occurs in immunocompromised hosts and is largely secondary to *Mucormycosis* and *Aspergillus*. Chronic rhinosinusitis is a disease with a heterogeneous group of potential causes or associated etiologic factors. In any individual host, there may also be more than one factor. Bacteria, fungi, allergies, biofilms, osteitis, and superantigens, along with a number of other factors, have been implicated. There are also a group of patients who have diffuse inflammatory upper and lower inflammatory disease associated with CRS. Currently, there is no single common pathway or etiology that can adequately describe all CRS phenotypes. Acute exacerbation of CRS is an acute change in symptoms from the baseline. This is generally associated with an increase in pathogenic bacteria, both aerobic and anaerobic. The investigation of the pathogenesis of rhinosinusitis is dynamic and ongoing.

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CHAPTER

25

Genetic Basis of Rhinosinusitis

Andrew P Lane, Josef Shargorodsky

INTRODUCTION

Chronic rhinosinusitis (CRS) consists of a set of symptoms associated with persistent nasal and paranasal sinus mucosal inflammation. Sinus disease represents one of the most common healthcare problems in the United States, affecting approximately 16% of the population,[1,2] with a cost exceeding $8 billion per year and causing a significant adverse effect on the quality of life of affected patients.[3] According to the American Academy of Otolaryngology Head and Neck Surgery guidelines, the diagnosis of CRS requires 12 weeks of associated symptoms, with objective confirmation via nasal endoscopy or computed tomography (CT) imaging.[4] The physiologic causes of CRS have long been debated, and the few available therapies generally concentrate on decreasing mucosal inflammation and eliminating sources of infection.

As the understanding of CRS has progressed, the characterization of the disease process has become increasingly refined. Phenotypic distinctions have been developed, separating cases by factors such as the presence or absence of polyposis or hypersensitivity to aspirin or fungus. Accordingly, the physiologic underpinnings of the different phenotypes are under study. As the volume of available basic science research mechanisms has grown,[5] an increasing number of genotypic associations have been discovered in individuals with various phenotypes of CRS. The distinct associations between genotypic variations and phenotypic outcomes in sinusitis demonstrate a significant genetic role in the development of sinus disease. This chapter will describe the current understanding of the genetic basis of rhinosinusitis, including active areas of research, the associated genes, and the current and potential clinical impact on patient care.

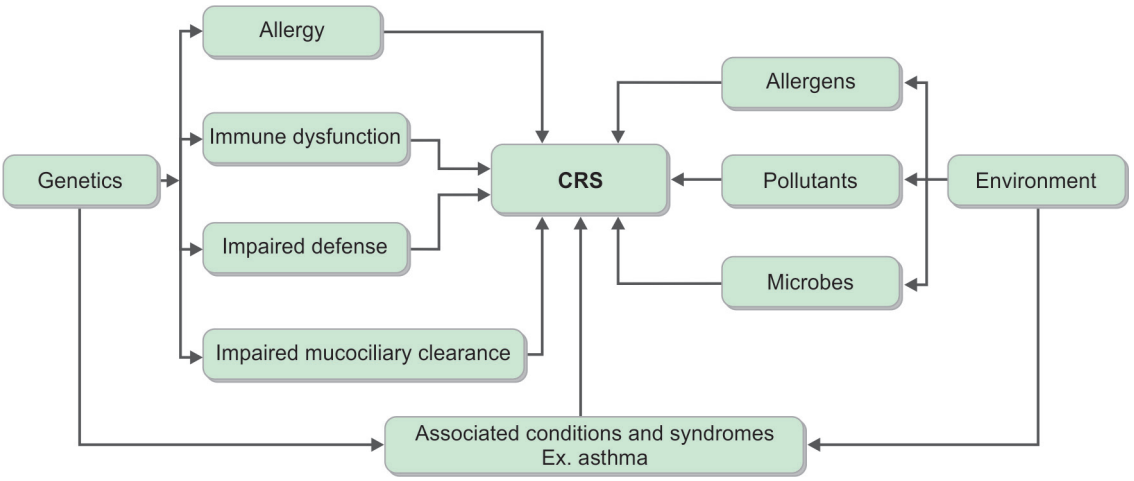
EVIDENCE FOR A GENETIC BASIS OF RHINOSINUSITIS

The genetic basis of rhinosinusitis has long been suspected. Initial evidence was derived from reports of familial inheritance patterns.[6] From early reports of families with a high prevalence of rhinosinusitis, to cases of concordant disease in monozygotic twins,[7] inheritance patterns have suggested a genetic predilection for the condition. Epidemiologic studies have demonstrated that CRS patients are more likely to report a family history of CRS than those without CRS.[8,9] As the definition and characterization of symptoms evolved, it became apparent that CRS is also a part of multiple syndromes with strong genetic associations, such as cystic fibrosis (CF),[10] and Kartagener syndrome.[11] In addition, multiple phenotypes of CRS share biochemical and physiologic processes with other upper airway conditions with well-established genetic components.[12] The symptoms and processes of CRS frequently coincide with those of asthma and allergic rhinitis, suggesting a shared genetic underpinning.[13] The multiple potential genetic contributions to the mechanisms and pathogenesis of CRS are demonstrated in Flowchart 25.1.

BASIC MECHANISMS TO STUDY GENETICS OF RHINOSINUSITIS

Progress in understanding the genetic basis of rhinosinusitis has coincided with advances in research techniques

Flowchart 25.1: A summary of the genetic and environmental contributions to the development of chronic rhinosinusitis (CRS).



enabling investigators to study the basic mechanisms of sinus disease. Current laboratory methods for studying sinus disease include real-time polymerase chain reaction (PCR), epithelial cell culture, flow cytometry, genomics/single-nucleotide polymorphism (SNP) detection, microarrays, and genetic animal models.[5] Each of these techniques offers a distinct contribution toward understanding the genetic mechanisms of CRS.

Developed in 1983, PCR has been utilized for the amplification of DNA sequences, enabling the amplification of a single copy or multiple copies of DNA across several orders of magnitude.[14] Real-time PCR is a technique based on the PCR and enables the simultaneous amplification and quantification of a targeted RNA molecule. The amplified complementary DNA is detected as the reaction progresses in real time, allowing for a quantitative measurement of gene transcription. Clinical applications of these techniques have allowed for determination of differential gene expression between individuals with and without CRS, or within individuals in response to the administration of an agent or to changes in environmental conditions. Multiple markers have been identified in the nasal tissue of CRS patients,[15] demonstrating the utility of these methods.

A common application of real-time PCR in the study of rhinosinusitis has been to compare levels of expression of target genes in whole sinonasal tissue among patient groups, as a function of disease phenotype or treatment. Such investigations cannot determine the specific cellular sources of RNA species but have helped identify cytokines and subcellular pathways playing potential roles in disease pathogenesis. To explore gene expression in particular cell populations, special techniques must be employed to either obtain RNA individual cells or to isolate groups of cells for subsequent RNA extraction. One example is the study of gene expression by sinonasal epithelial cells (SNECs). These cells may be readily obtained using endoscopic brushings of sinus epithelium or by enzymatic digestion of mucosal samples. Once isolated in suspension, SNECs may be grown in culture, either submerged or differentiated at the air–liquid interface to mimic the natural microenvironment of the nose. The cells can be artificially stimulated or suppressed and subsequently analyzed by PCR for gene expression. Such studies have demonstrated innate immune activities of SNEC that relate to Th2-associated inflammation in CRS,[16,17] elucidating the association between innate and adaptive immune mechanisms underlying mucosal inflammation in patients with CRSwNP (CRS with nasal polyps).

The recent developments in genome sequencing have allowed for evaluation of associations between genetic polymorphisms and chronic disease. An SNP is a DNA sequence variation that occurs when a single nucleotide differs among the population. Other polymorphisms exist as well, including restriction fragment length polymorphisms and copy number polymorphisms.[18] SNPs occur in noncoding regions more frequently than in coding regions, but when they occur in the coding regions they create variability in the amino acid sequence.[19] These variations in the DNA sequence can affect how individuals develop disease and respond to pathogens, chemicals, drugs, and other environmental factors.[20] An example of such a disease is CF, where disease phenotype has been shown to associate with variation in the CFTR gene.[21]

Table 25.1: A summary of the single nucleotide polymorphisms associated with chronic rhinosinusitis

Study	*Cases*	*Controls*	*Single nucleotide polymorphisms*
Zhang et al.[80]	638	325	Thymic stromal lymphopoietin
Zhang 2012[99]	638	315	Ring1A and YY1 binding protein, acyloxyacyl hydroxylase
Fruth et al.[83]	74	30	Serine proteinase inhibitor Kazal type 5 gene (SPINK5)
Sitarek 2012[100]	195	200	Cyclooxygenase-2 (COX-2), proto-oncogen MET (MET)
Zhang 2011[101]	206	196	Nitric oxide synthase1 (NOS1)
Park 2010[102]	106	108	2 single-nucleotide polymorphisms (SNPs) for toll-like receptor 2 (TLR2)
Wang 2010[103]	203	730	Matrix metaloprotein-9 (MMP-9)
Castano 2010[104]	206	196	Met proto-oncogene (MET)
Bernstein et al.[22]	179	153	Tumor necrosis factor (TNF)- α 308
Castano 2009[105]	206	196	5 SNPs of interleukin (IL)-1R gene
Endam 2009[106]	206	196	3 SNPs of IL22RA-1
de Alarcon 2006[107]	89	66	Leukotriene C4 synthase (LTC4S)
Cheng 2006[108]	88	103	IL-1R antagonist
Takeuchi 2000[109]	38	38	TNF B*2 allele

Numerous SNPs associated with inflammatory mediators have been demonstrated in CRS patients (Table 25.1). Positive associations have also been found between SNPs and CRS progression. As an example, a polymorphism in tumor necrosis factor alpha (TNF)-α was associated with a twofold increase in developing CRSwNP.[22] An SNP in leukotriene C4 synthase (LTC4S) has been found to be associated with chronic hyperplastic eosinophilic sinusitis (CHES). Studies of SNPs provide strong evidence for the genetic basis for CRS phenotypes. A summary of the known SNPs for chronic sinusitis is provided in Table 25.1.

While the SNP studies evaluate the associations between single nucleotide variation and disease processes, RNA microarray technology allows the measurement of expression levels of large numbers of genes simultaneously. First reported in 1982,[23] the technique can be used for large scale genotyping, gene expression profiling, comparative genomic hybridization and sequencing, among other applications. The microarray is a set of gene probes to which cDNA copies of RNA expressed within a cell are hybridized.[24] The technique utilizes complementary nucleic acid sequences specifically pairing with each other by forming hydrogen bonds between complementary base pairs. A high number of bonded pairs in a sequence create tighter bonding between two strands. Fluorescent labeling of the target sequences that bind to a probe sequence generate a detectable signal, the strength of which depends on the amount of target sample binding to the probes. Computer-enhanced laser detection then assists with quantification of the hybridization. Two primary methods are currently used for microarrays: the GeneChip (Affymetrix Corp, Santa Clara, CA, USA) and cDNA microarrays. The GeneChip contains DNA probes directly synthesized onto glass slides. In the cDNA microarray method, cDNA clones are fixed on a glass slide by mechanical microspotting or with noncapillary pens. These arrays are manufactured in the laboratory and tend to be more expensive and time consuming.[24] Regardless of the method, microarrays are a powerful tool for gene function analysis.

The DNA microarray studies have identified multiple potentially causative genes within the spectrum of CRS. A 2006 study by Anand et al. used the GeneChip to compare gene expression in chronic hyperplastic sinusitis and control patients and found four overexpressed genes in the CRS patients [interleukin (IL)-6, IL-12A, IL-13, TNF-α].[25] Other microarray studies have also identified increased expression of genes for IL-8, monocyte chemoattractive protein,[26] c-met proto-oncogene, and protein phosphatase 1 regulatory subunit[27] in patients with the CRSwNP phenotype. A summary of the significant genetic associations identified with microarray technology is presented in Table 25.2. Although there has been significant interinvestigator variability in identifying significantly dysregulated genes in CRS, the gene microarray studies have identified numerous gene targets for further investigation.

Table 25.2: Summary of the microarray studies identifying genes associated with rhinosinusitis

Author	*CRS type*	*Cases (N)*	*Controls (N)*	*Tissue*	*Highlighted findings*
Fritz 2003[110]	AR/NP	3	4	Polyp vs MT or uncinate	Upregulated mammaglobin
Liu 2004[111]	CRSwNP	10	4	Polyp vs sphenoid	Upregulated statherin, PIP, DMBT1, lactoferin; downregulated CC10
Wang 2006[112]	CRSwNP	4	4	Polyp vs IT	Upregulated IL-17, IL-17R
Orlandi et al.[87]	EMCRS	7	*	Polyp	Upregulated cathepsin B, sialyltransferase 1, GM2 ganglioside activator protein, S100 calcium binding protein
Stankovic et al.[27]	CRSwNP	20	10	Polyp vs IT or ethmoid	Upregulated MET, PP1R9B; downregulated PIP, AZGP1
Payne et al.[26]	CRSwNP	8	8	Polyp vs ethmoid	Upregulated IL-6, IL-8, monocyte chemoattractant protein, CXCL1, autocrine motility factor
Wu 2009[113]	Any CRS	11	10	nasal mucosa (both)	Upregulated CXCL13, CXCL5, serum amyloid A, serpin B4, defensin B1
Rostkowska 2011[114]	CRSwNP	53	28	Polyp vs IT	Upregulated MMP10, NOS2A, ALOX15, IL-8; downregulated DMBT1, ALOX12, LTF

* Standardized from the general population.
(AR: Allergic rhinitis; NP: Nasal polyposis; EMRS: Eosinophilic mucin rhinosinusitis; MT: Middle turbinate; IT: Inferior turbinate; MET: Met proto-oncogene; PIP: Prolactin-induced protein; GILZ: Glucocorticoid-induced leucine zipper; CRS: Chronic rhinosinusitis; CRSsNP: CRS without nasal polyps; CRSwNP: CRS with nasal polyps).

CHALLENGES IN GENETIC RESEARCH OF RHINOSINUSITIS

Evaluating the genetic contributions to sinus disease has its obstacles. Rigorous study design is critical to the validity of genetic studies of complex multifactorial diseases. One important element of study design is the careful classification of disease phenotype. This is a considerable challenge in CRS, where multiple phenotypes have been proposed and reports in the literature often lack detailed information for classification of study participants.[28] Variation exists among studies in the use of imaging for their participants. Descriptions of CT scan results vary in quality of interpretation, level of detail presented, and classification systems used for CRS diagnosis. Similar difficulties exist in interpreting and classifying endoscopic findings in CRS, as well as histologic results. Because of variation in all of these factors, misclassification of study participants is a major concern in studying genetic associations with CRS phenotypes. Another concern is the possibility of undiagnosed CRS among study control subjects. Given that individuals are generally not evaluated with endoscopy or imaging unless they have specific complaints, the possibility exists for inaccurate grouping of CRS patients as controls. The effect of the potential misclassification is that it can diminish study power, which often is already low in studies of genetic associations with CRS.

Besides phenotypic misclassification, other difficulties inherent to genetic studies create additional challenges. Although SNPs can directly cause disease, a study outcome may also be affected by the phenomenon of linkage disequilibrium. In this situation, nonrandom inheritance of two genes, only one of which may be causative for the disease, can lead to a false association between the noncausative SNP and the disease. A perceived association might also be actually due to undetected differences in ancestry proportions of the case and control groups and therefore unrelated to the CRS phenotype.[29] Another common risk in genetic studies is the possibility of type I statistical error. Failure to correct for multiple testing can create a falsely positive result, thereby leading an investigator to presume a statistically significant association that may not be real.[30] Given the lack of replication of genetic associations among studies involving CRS phenotypes, this is a distinct possibility.

FAMILIAL INHERITANCE PATTERNS OF RHINOSINUSITIS

Studies of familial inheritance patterns of CRS have identified not only an increased prevalence of CRS in individuals with positive CRS history, but also in increase in symptom

severity. The familial inheritance predisposition was first suggested by Grunberg in 1934. Since then, numerous studies have reported associations between family history and various incident CRS phenotypes. In 1973, Lockey et al. reported clustering of the aspirin triad (asthma, nasal polyps, aspirin-induced wheezing) in two separate families, demonstrating an autosomal recessive pattern. The individuals affected with the triad were presumably homozygotes.[8] Although they did not provide a hypothesis for the mode of transmission, Greisner and Settipane compared 50 patients with nasal polyps with 30 patients without nasal polyps and demonstrated a positive family history in 14% of patients with polyps as compared with 0% in the control group.[31] The difference was statistically significant, suggesting a hereditary factor for development of nasal polyps. In addition, Rugina et al. found a positive family history in more than half of 224 patients with nasal polyps.[32] A study of a series of French families by Delagrand et al. identified a 19.7% prevalence of polyps in family members of affected patients, as compared with an estimated 2.1% of the French population. This study also suggested an autosomal recessive pattern as the more likely mode of inheritance.[33] Delving deeper into the association between family history and incident CRS, Cohen et al. analyzed the association between severity of sinus disease and presence of CRS in family members. In a 2006 study, they demonstrated a significant correlation between the severity of sinonasal disease and the frequency of a positive family history in nasal polyposis, further supporting the hypothesis that incidence as well as severity of the disease process is proportional to the penetrance of the underlying genetic component.[34]

SYNDROMES ASSOCIATED WITH RHINOSINUSITIS

Some of the strongest evidence for a genetic basis for rhinosinusitis comes from work demonstrating associations between CRS and syndromes with strong genetic components. Several genetic syndromes have CRS as a common clinical manifestation (Table 25.3). In addition, individuals with genetic abnormalities indicative of these syndromes have also been shown to have sinonasal disease even without other symptoms common to those syndromes.

Cystic Fibrosis and Rhinosinusitis

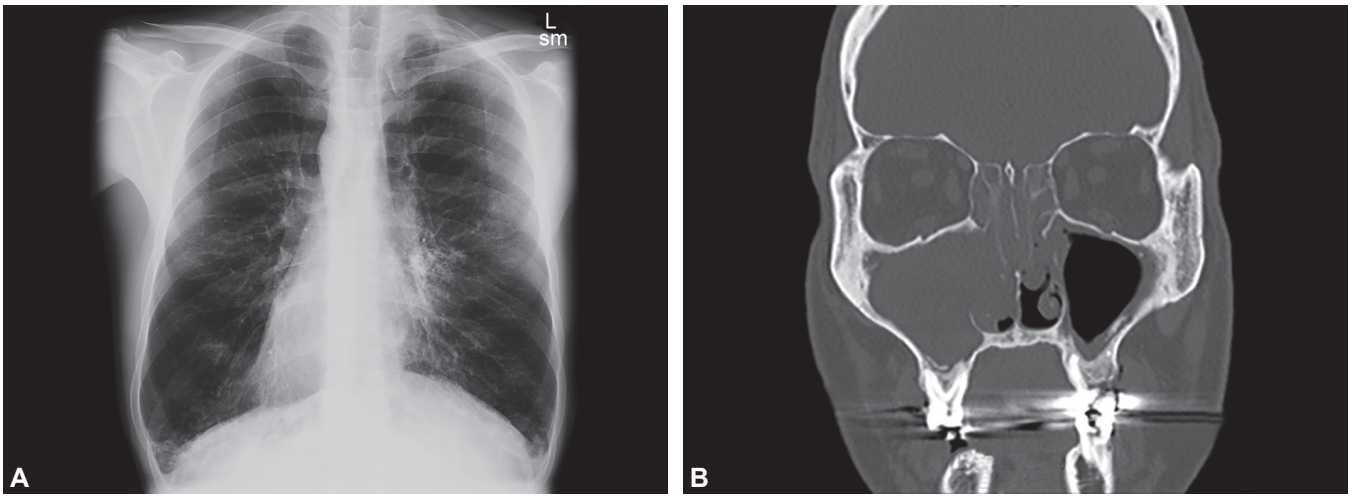
The CF is an autosomal recessive genetic disorder characterized by abnormal chloride and sodium transport that affects the lungs, pancreas, liver and intestine. These abnormalities in ion transport across mucosal epithelia lead to thick, viscous secretions. CF is caused by defects in the CF gene, which codes for a protein transmembrane conductance regulator (CFTR) that functions as a chloride channel regulated by cyclic adenosine monophosphate. Mutations in the CFTR are thought to be the genetic cause of CF.[35] The most common CFTR mutation in the United States is the ΔF508 mutation, but numerous potentially pathogenic CFTR mutations have been proposed, with frequencies varying by racial and ethnic groups.[36]

Table 25.3: Genetic syndromes with rhinosinusitis as a clinical manifestation

Genetic diseases associated with sinusitis
• Cystic fibrosis
• Primary ciliary dyskinesia (Kartagener syndrome)
• Young syndrome
• Churg-Strauss syndrome
• Bare lymphocyte syndrome
• Ataxia telangiectasia

Although the exact mechanism by which a malfunctioning CFTR gene affects the sinuses is not completely understood, a large proportion of patients with CF have severe CRSwNP. This relationship seems to hold true even in patients without other clinical features common to CF. A landmark study by Wang et al. found that patients with CRS were more likely to be CFTR carriers compared with those without CRS (7% vs 2%). The difference was small but statistically significant.[37] Subsequent studies have identified a statistically significant difference in prevalence of CF carriers in children with CRS (12%) compared with those without CRS (4%),[38] as well as a significant difference between prevalence of CRS among CF carriers (36%) as compared with those without CFTR abnormalities (13%).[37] Another study performed in the United States retrospectively evaluated patients with CRS who underwent full sequencing of CFTR and found that 38% of these individuals had mutations in CFTR.[39] The prevalence of CFTR mutations was even higher in patients with both CRS and asthma (42%) and even higher in those with CRSwNP (66%). In addition, a genome wide screen for CRS performed by Pinto et al. in 2008 identified a locus on chromosome 7 that may influence disease susceptibility, suggesting a link between the CFTR gene and CRS.[40]

Various mechanisms have been proposed to explain how CFTR dysfunction affects sinus disease in individuals



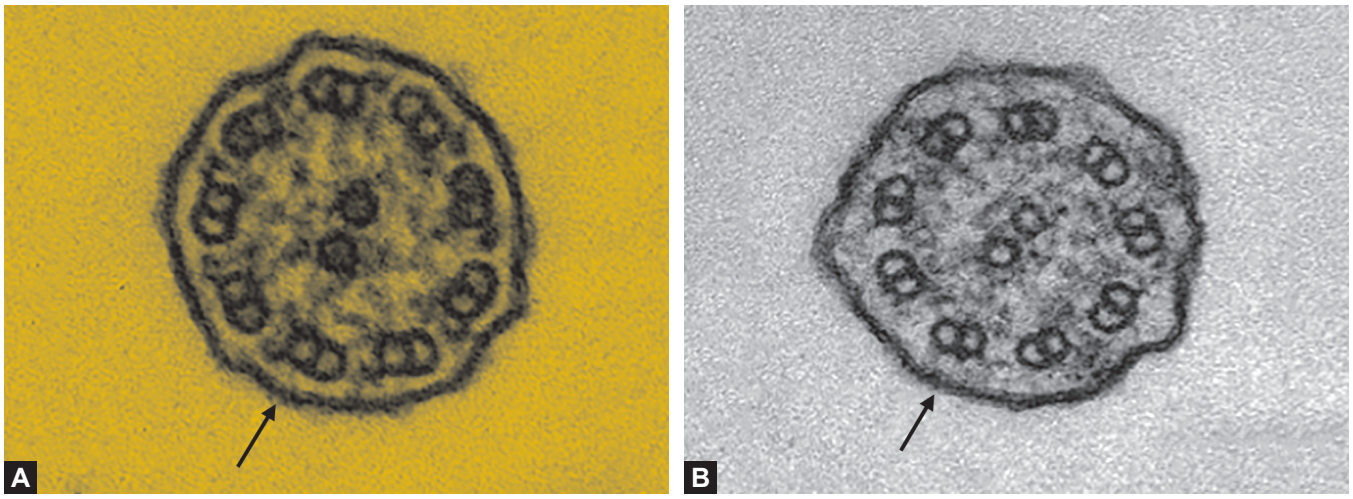
Figs. 25.1A and B: An anteroposterior chest X-ray of an individual with Kartagener syndrome, with the accompanying representative coronal cut of the maxillofacial computed tomographic (CT) scan. The X-ray demonstrates situs inversus, whereas the maxillofacial CT shows diffuse rhinosinusitis with polyposis.

with and without other manifestations of CF. Chloride ions are abnormally excreted, and sodium is excessively absorbed along with water, leading to altered viscosity of the mucus blanket and desiccation of the mucosal surface, which may lead to obstruction of sinus ostia.[41] Decreased mucociliary clearance has also been demonstrated. These features may predispose individuals with CFTR abnormalities to recurrent sinonasal infection and chronic inflammation.[10] Dysfunction in CFTR may also lead to abnormal sinonasal pH and decreased thiocyanate, an antioxidant with antimicrobial properties, transport into the airways.[42,43] In addition, the hyperviscous mucus of CF patients contains low oxygen tension, and this local hypoxia may be associated with biofilm formation seen in patients with CRS.[44]

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD), also known as "immotile ciliary syndrome" is a rare, genetically heterogeneous but typically autosomal recessive disorder associated with a defect in the ciliary lining of the respiratory tract.[45] When the ciliary disorder is accompanied by the combination of situs inversus, CRS, and bronchiectasis, it is known as Kartagener syndrome[11] (Figs. 25.1A and B). The term "immotile ciliary syndrome" is actually a misnomer, as the cilia have been shown to have movement, but that movement is inefficient or unsynchronized. The main direct consequence of impaired ciliary function is decreased mucus clearance from the respiratory mucosa, which leads to chronic recurrent respiratory infections, including infectious forms of rhinosinusitis, bronchitis, pneumonia, and otitis media. The damage from these infections may be progressive, beginning in childhood and becoming severe in adults.[46] The pulmonary effects can be severe, even requiring lung transplantation. In the head and neck, a common otologic manifestation is "glue ear," with variable responsiveness to insertion of tympanostomy tubes, and CRS with acute infectious exacerbations. Hyposmia is common, likely due to high production of thick mucus, as is bacterial superinfection.[47]

Recent studies have identified mutations in several genes encoding structural and/or functional proteins in respiratory mucosal cilia. Normally, the respiratory epithelium has the classic mobile peripheral microtubule doublets in the 9+2 pattern studded with dynein arms surrounding a central pair microtubule complex (Figs. 25.2A and B). The ciliary beat frequency normally ranges from 8 to 20 Hz and has a wave pattern. Dysfunction of ciliary structure has been linked to multiple conditions, including Kartagener, Bardet-Biedl syndrome, polycystic kidney disease, and several others.[48,49] The complexity of the axonemal structure presents multiple opportunities for protein abnormalities, which accounts for genetic heterogeneity of the disorders. Although this heterogeneity has made identifying family-based genome linkages difficult,[50] several candidate genes have been identified. The genes identified in PCD are *DNAI1, DNAH5, DNAH11, DNAI2, KTU, RSPH9, RSPH4A, and TXNDC3*.[11] These are responsible for the dynein chain structures (DNAI1, DNAH5, DNAH11, DNAI2,), microtubule binding (TXNDC3), cytoplasmic protein required for dynein complex assembly (KTU),



Figs. 25.2A and B: (A) Normal cilium with nine doublets around the periphery and two singlets in the center. The doublet indicated by the arrow shows clear inner and outer dynein arms. (B) Abnormal cilium from an infant with complete situs inversus. This cilium also has a "9 + 2" pattern of microtubules. However, the doublets all lack inner and outer dynein arms (arrow).

radial spoke structures (RSPH9, RSPH4A). While specific associations between the identified PCD genes and CRS have not been quantified, the prevalence of rhinosinusitis in individuals with PCD is nearly 100%,[47] which implies the likelihood of shared genotypic features.

Young Syndrome

Young syndrome, also known as sinusitis-infertility syndrome or azoospermia sinopulmonary syndrome, is a rare condition composed of bronchiectasis, rhinosinusitis, and reduced fertility.[51] Initially described in 52 men with obstructive azoospermia, of whom over half had pulmonary dysfunction, it is a disease of mucociliary clearance that is associated with recurrent respiratory tract disease.[52] Originally thought to be associated with CFTR mutations, this has now been shown to be a separate genetic entity from CF.[53] The mechanism of sinus disease associated with Young syndrome, however, includes abnormalities in mucociliary clearance and thickened mucus. Although the etiology has not yet been identified, this is thought to contribute to the frequent sinonasal recurrent infections in these patients.

Churg-Strauss Syndrome

Churg–Strauss syndrome (CSS), or eosinophilic granulomatosis with polyangiitis, is a rare syndrome that affects small to medium-sized arteries and veins. The syndrome has three phases—allergic rhinitis and asthma; eosinophilic infiltrative disease; and systemic medium and small-vessel vasculitis with granulomatous inflammation. The first phase of CSS is the allergic phase. This is marked by a number of conditions related to atopy, including asthma, allergic rhinitis and rhinosinusitis. A reported 97% of CSS patients develop asthma symptoms, which may precede the vasculitis by 10 years.[54] Allergic rhinitis is also common, and 61% get CRS. The CRS symptoms in these patients generally respond well to oral steroids.[55]

Multiple genetic polymorphisms have been associated with CSS. Abnormalities in the levels of the chemokine eotaxin-3 have been shown to be significantly associated with active CSS. SNPs in the gene for eotaxin-3 have also been demonstrated in asthma, allergic rhinitis, and rhinosinusitis.[56] Studies have also identified the expression of TNF-related apoptosis-inducing ligand receptor-3 as being higher on CSS patients' eosinophils compared with those from health individuals.[57] In addition, differences in coding for CD4+CD25+ T cells and CD4+CD25- T cells have been shown to be associated with the immunological tolerance that leads to the first phase of CSS.[58] Human leukocyte antigen (HLA) genes unique to CSS development have also been identified and have been shown to be strongly associated with vasculitis manifestations in CSS patients.[59]

Bare Lymphocyte Syndrome

Bare lymphocyte syndrome (BLS) is a rare autosomal recessive disorder of major histocompatibility complex (MHC) gene expression. The syndrome is classified into subtypes; type I, where the defect is in MHC class I expression, and type II, where the defect is in MHC class II

expression. Both classes are thought to be variants of severe combined immunodeficiency.[60] BLS I is more rare and is characterized by HLA class I deficiency. It is associated with abnormalities in transporters associated with antigen processing (TAP)1, TAP2, and TAP binding protein (TAPBP). BLS II is due to mutations in genes that code for transcription factors that normally regulate transcription of *MHC II* genes. Mutations in class II transactivator (CIITA), regulatory factor of the X box 5 (RFX5), RFX-associated protein (RFXAP), and RFX ankyrin repeats (RFXANK) are associated with BLS II.

Patients with BLS demonstrate upper respiratory manifestations of immunodeficiency, including rhinosinusitis and chronic bronchitis.[61] In a study of siblings with bronchiectasis, Donato et al. identified a strong association between BLS and pansinusitis with nasal polyposis.[62] The patients were found to have a single mutation in the *TAP2* gene, located in the class II region of the MHC, and encoding subunit 2 of the class I peptide transporter. The defect was transmitted in an autosomal recessive manner and did not lead to severe viral infections but was associated with bacterial infections of the respiratory mucosa. This suggested a mechanism for infectious rhinosinusitis associated with the genetic defect responsible for the syndrome.

Ataxia Telangiectasia

Ataxia telangiectasia is a rare autosomally recessive neurodegenerative disease caused by mutations in the ataxia telangiectasia mutated (ATM) gene on chromosome 11. The gene encodes P13 kinase, involved in the regulation of synaptic vesicle trafficking. Immunoglobulin deficiencies are common, affecting IgG4, IgA, IgG2, IgE, and IgG. Lymphopenia has also been demonstrated.[63] The affected individuals develop an increased number of respiratory tract infections, including pneumonia, and ear infections. Acute exacerbation of CRS has been shown to affect 27% of patients with ataxia telangiectasia.[63]

Ataxia telangiectasia is caused by defects in the ATM gene, located on chromosome 11.[64] The ATM codes for a protein of the same name that is responsible for the cell's response to stress. The ATM protein detects double-strand DNA breaks, fixes the breaks, and prevents the cell from transcription until repairs are made. The decreased ability to manage DNA breaks results in a reduced number of lymphocytes and impairs lymphocyte function, thereby leading to an increased number of infections. The decreased immunologic ability likely accounts for the sinus disease in these patients.

GENES ASSOCIATED WITH INDIVIDUAL PHENOTYPES OF RHINOSINUSITIS

Because of the varied nature of sinus disease manifestation, numerous genes are likely to contribute to normal and abnormal sinus function. The distinct phenotypic entities of rhinosinusitis are likely to have distinct genotypic features. This section addresses the individual rhinosinusitis phenotypes as separate disease entities and addresses the genotypic associations specific to each entity.

CRS with Nasal Polyposis

CRS with polyps is a complex, chronic disease characterized by severe mucosal inflammation with local eosinophil accumulation. The presence of nasal polyps often accompanies other upper respiratory and sinonasal disorders, such as aspirin hypersensitivity, CF, and allergic fungal sinusitis (AFS). CRSwNP without any of the associated conditions has also been referred to as CHES.[65] As the other entities associated with nasal polyposis are discussed elsewhere in this chapter, this section will concentrate on CHES. Diagnosis of CHES is by biopsy, with histochemical staining for eosinophils, demonstrating a marked increase in cells expressing cytokines, chemokines, and proinflammatory lipid mediators that mediate increased tissue eosinophilia.[66,67] Because the eosinophils also produce the mediators that act in their recruitment, CHES is a self-perpetuating condition with unrestrained inflammation.[68,69] The etiology of CHES has been elusive due to disease heterogeneity. Many, but not all, of the patients display allergic sensitization on skin prick IgE results. As the sinus cavities of CHES patients are often occluded, aeroallergens should not be able to readily access them. However, aeroallergen exposures have been shown to exacerbate eosinophil influx into the sinuses.[65] This may suggest systemic or local lymphatic recirculation of inflammatory cells.[70] An alternative hypothesis is that allergic sensitization to microbes colonizing the sinuses (such as in biofilms) might account for the inflammatory infiltration. As CHES patients share many of the immunologic and histologic features with asthma patients, the two conditions have been hypothesized to share similar immunologic processes leading to upper and lower airway inflammation.[71] This is further supported by the frequent coexistence of the two conditions.

Numerous genetic linkages have been established with CRSwNP. The inflammatory nature of the associated genes indicates a dysregulation in the inflammatory response of sinonasal mucosal epithelium in patients with polyps. Multiple studies have demonstrated significant associations between abnormalities in alleles coding for IL-1α and risk of polyp formation.[72,73] A polymorphism in the TNF-α gene was also associated with similar findings.[73] The C allele of the IL-4 promoter has been associated with increased risk of asthma and has now been found to also be associated with nasal polyposis in multiple studies.[74,75] Numerous other polymorphisms have also shown an association with inflammatory genes. These reported genes include IL-25, IL-33, eotaxin-3[76] IL-22 receptor α1, IL-33, IL-1ra, IL-1receptor-like1, and MMP9.[77] The human MHC has also been linked in genetic studies to the development of nasal polyps. In a 2000 study by Molnar-Gabor et al., participants carrying the HLA-DR7-DQA1*0201 and DQB1*0202 haplotype were found to have a two to three times higher odds ratio for developing nasal polyposis, compared with controls.[78] A 2006 study by Fajardo-Dolci also found that the HLA-DQA1*0201-DQB1*0201 haplotype conferred a 5.5 times increased risk of developing polyposis.[79] These findings suggest a link between genetic variability and defects in antigen presentation as a potential cause for nasal polyposis. In addition, CRSwNP has been associated with an excessively activated toll-like receptor (TLR)-mediated signaling pathway. The same study also demonstrated downregulation of the TLR-mediated pathway,[80] potentially demonstrating further links between genetic expression of inflammatory mediators and development of nasal polyps.

Chronic Rhinosinusitis without Nasal Polyposis

CRS without polyposis is the most common form of chronic sinusitis. The sinonasal edema and inflammation in these patients is multifactorial, with possible etiologies, including allergic disease, anatomic predisposition, and chronic or recurrent bacterial or viral infection. The sinus mucosa of these patients often does not demonstrate eosinophilia, and the inflammatory component consists more of a mononuclear cell infiltrate.[81]

As CRS without nasal polyps (CRSsNP) and CRSwNP are becoming increasingly recognized as distinct disease entities, differences in gene expression are also being discovered.[82] Although both conditions demonstrate tissue inflammation, the differential expression in the inflammatory mediators differs. While CRSwNP shows TH2 polarization with high levels of IL-4, IL-5, and IL-13, the inflammation in CRSsNP is characterized by a TH1 polarization with high levels of interferon-γ and tumor growth factor-β.[82] Differential expression of TLR pathway genes has also been demonstrated. CRSsNP is characterized by the downregulation of TLR-mediated signaling pathway, and such a deficiency within the innate immune system may contribute to the inflammatory process.[80] Specifically, expression of TLR4 and TLR7 was shown to be significantly decreased in patients with CRSsNP compared with controls.[80] Other associations have been demonstrated with polymorphisms coding for SPINK5 (a serine protease inhibitor and regulator of epithelial barrier maintenance),[83] and GILZ (an anti-inflammatory mediator)[84] in patients with CRSsNP. These associations provide further insight into the genetic underpinnings of local inflammatory and immune dysfunction in patients with this CRS.

Allergic Fungal Sinusitis

Fungal organisms, when present in the paranasal sinuses, can act as potent activators of innate immune pathways and produce a robust inflammatory response. AFS is a distinct disorder characterized by mucosal inflammation stemming from a pathogen-associated receptor-induced robust Th2 lymphocyte and eosinophilic inflammatory response. Numerous species of fungi are associated with AFS, including *Aspergillus*, *Alternaria*, *Penicillium*, *Cladosporium*, *Curvularia*, and *Bipolaris* species.[85] This form of chronic sinusitis occurs disproportionately in young, atopic, immunocompetent individuals and is characterized by IgE sensitization, as demonstrated by skin prick testing and serum immunoassays.[86]

Evidence is emerging for a genetic basis for AFS. While patients with CRSwNP have been shown to express a variation in the MHC class I phenotype, those with AFS have shown significant associations with variation in the coding for MHC class II phenotypes.[86] In a study of 74 individuals, 44 with AFS, a significant association was noted between the MHC class II beta chains HLA-DQB1*0301 and HLA-DQB1*0302 alleles and AFS. In addition, a DNA microarray study of AFS patients demonstrated differential expression in 38 different genes.[87]

Aspirin Exacerbated Respiratory Disease

Aspirin exacerbated respiratory disease (AERD), initially defined by the triad of NPs, asthma, and aspirin sensitivity[88] (Samter triad), is a disorder characterized by sensitivity to aspirin and other nonselective cyclo-oxygenase (COX) inhibitors, eosinophilia, pansinusitis with robust nasal polyposis, and severe asthma,[77] Aspirin intolerance occurs in up to 20% of adult asthmatic patients and up to 30% of asthmatic patients with CRS.[89] Patients with AERD tend to develop a severe nonallergic (IgE-mediated) reaction to ingestion of COX-inhibiting agents. These patients demonstrate a diminished prostaglandin (PG) E2 concentration at baseline, and ingestion of COX-inhibitors renders them increasingly susceptible to a massive inflammatory response because their eosinophils, basophils, and mast cells are dependent on the modest PGE2 concentrations to prevent their activation.[90] AERD patients also overproduce cysteinyl leukotrienes (CysLTs) at baseline and develop a surge in CysLTs with ingestion of aspirin and other nonselective COX inhibitors.

Studies have analyzed the association of genes involved with leukotriene synthesis or response and AERD. An A-to-C base exchange of the LTC4S (a rate-limiting enzyme in leukotriene synthesis) promoter has been shown to increase expression of that gene.[91] This base change has been found to be significantly associated with AERD in different populations.[91,92] Another variation, within the promoter of the 5-lipoxygenase gene, has been found to have an increased odds for development of AERD.[93] A second study found an association between a polymorphism in this gene and increased severity of airway hyper-responsiveness in patients with AERD.[94] Other genetic studies have also identified associations between polymorphisms in genes coding for CysLT1 and CysLT2 receptors and development of AERD.[95] Other potential genetic biomarkers contributing to the AERD phenotype include HLA-DPB1, LTC4S, ALOX5, CYSLT, PGE2, TBXA2R, TBX21, MS4A2, IL-10, ACE, IL-13, KIF3A, SLC22A2, CEP68, PTGER, and CRTH2.

Genes Associated with Therapeutic Effects of Steroids

Because of the inflammatory nature of rhinosinusitis, local and systemic glucocorticoids are some of the most effective available medications. These medication, however, are not uniformly effective in all sinusitis patients. The genomic and nongenomic effects of glucocorticoids may account for some of the variability in treatment effect. Glucocorticoids exert their effects by binding to glucocorticoid receptor molecules, which then induce changes in gene expression. The glucocorticoid receptor gene is located on the fifth chromosome and is composed of nine axons.

The glucocorticoids influence gene transcription and translation of genes encoding inflammatory mediators, antiapoptotic genes, and genes regulating cell proliferation.[96] Microarray studies of nasal polyps have examined the wide range of glucocorticoid actions. Fluticasone was shown to change the expression of 203 genes, most of which were associated with inflammation.[97] In nasal polyps, it downregulated proinflammatory genes and also upregulated anti-inflammatory genes. The most highly expressed gene was uteroglobulin, a protein which inhibits leukocyte chemotaxy, phospholipase activity, and pro-inflammatory cytokine activity. The activity of this gene is considerably decreased in untreated nasal polyps in comparison with the level of expression in healthy mucus membranes, and a significant increase in uteroglobulin expression with glucocorticoid treatment demonstrates a likely anti-inflammatory mechanism.[97] Changes in the expression of glucocorticoid receptor isoforms, GR-α and GR-β, have also been reported in nasal polyps treated with glucocorticoids. Although expression of GR-α was significantly reduced after glucocorticoid treatment, that of GR-β remained unchanged. The observations indicate that variations in the receptors may play a role in the inflammation associated with nasal polyps, and the ratio of the receptor types may affect the clinical response to glucocorticoid treatment.[98]

CLINICAL IMPACT ON PATIENT CARE

The study of the effects of genetics on rhinosinusitis has the potential to affect clinical care in multiple ways. One way is through improved identification and classification of disease mechanisms. As demonstrated above, the distinct sinus disease entities have genetic features unique to the individual phenotypes. Improved understanding of these genetic associations may allow for more accurate classification of disease features in sinusitis patients. This improvement in classification may assist researchers studying the disease pathophysiology and mechanisms, allowing for more accurate stratification of patients by disease subclass. As more of the associated genes are discovered, it is likely to have a self-perpetuating effect of

guiding researchers to other associated genes. This may aid in the discovery of previously unknown pathologic mechanisms of the disease process.

The goal of genetic research is that improvements in understanding of the genetic basis of sinus disease will allow for improved treatment of rhinosinusitis. Drug classes may directly target upstream mechanisms to eliminate expression of abnormal genes. In addition, defined genotypic subclassifications may help predict which individuals will have a more robust response to different treatment modalities. Genetic markers offer an important mechanism in enabling physicians to make these distinctions. Pharmacologic or surgical treatment may then be better tailored to improve outcomes in an evidence-driven fashion.

CONCLUSION

Current evidence has clearly demonstrated the substantial genetic contribution to sinus disease. Studies of familial inheritance patterns of rhinosinusitis have provided enticing evidence for the strong genetic component to sinus disease. Based on that evidence, specific genetic association studies have demonstrated numerous individual genes and gene classes associated with disease subtypes. With improved gene and disease classification, the precision of these associations continues to improve. The current mechanisms of studying genetic associations, including PCR and microarray technology, are also allowing for faster and more efficient studies of genetic associations with sinus phenotypes. Ultimately, these research efforts have the potential to provide individuals with rhinosinusitis with improved treatment modalities.

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CHAPTER

26 Immunologic Aspects of Rhinosinusitis

Songhui Ma

INTRODUCTION

Rhinosinusitis affects approximately one in seven adults in the United States.[1] The majority of these patients present with uncomplicated acute disease that resolves with appropriate medical therapy. However, some progress to develop refractory disease with chronic and recurrent presentations. Chronic rhinosinusitis is a heterogeneous group of conditions characterized by inflammation of the sinuses lasting greater than 12 weeks. Recurrent acute rhinosinusitis is defined as more than three to four acute episodes of rhinosinusitis per year with resolution of symptoms between episodes.[2] Environmental and host factors including allergy, anatomic abnormalities, and immunodeficiency contribute to the severity of sinusitis. The prevalence of immunodeficiency among patients with refractory sinusitis has been reported to range from 8% to 63%.[3] Immunodeficiency may be primary in origin or secondary to various underlying host conditions.

PRIMARY IMMUNODEFICIENCIES

Primary immunodeficiencies (PIDs) are a group of diseases in which there is an intrinsic defect in the host immune system. Affected individuals suffer from increased rate and severity of infections. In addition, impaired immune function and regulation may lead to increased rates of autoimmune disease and malignancy. In the 2011 International Union of Immunologic Societies, Classification of PIDs, over 150 separate entities have been listed.[4]

The prevalence of PIDs may be higher than previously considered. A Mayo Clinic population-based survey conducted over 30 years from 1976 to 2006 revealed an incidence rate of 4.6 per 100,000 person years.[5] However, there was a four- to fivefold increase in incidence from 2.4 per 100,000 person years from 1976 to 1980 to 10.3 per 100,000 person years from 2001 to 2006. This shift was coupled with decreased delay in diagnosis from 17.5 years after onset of symptoms among patients who presented before 1986 to 2.7 years for patients who presented after 1996 suggesting that the increased rate of diagnosis may be due at least in part to increased awareness and/or the availability of improved diagnostic tests. A 2007 telephone survey of 10,000 households reported a population prevalence of 1 in 1200 people in the United States.[6]

PIDs are often grouped by the arm of the immune system affected (Table 26.1).[7,8] Disorders of the adaptive immune system include antibody deficiencies, T-cell disorders, and combined B- and T-cell defects. Disorders of the innate immune system include phagocytic disorders and complement deficiencies. Clinical manifestations of individual PIDs can be attributed to the underlying immunologic impairment. For example, antibody deficiencies lead to susceptibility to extracellular bacteria and impaired T-cell function is associated with vulnerability to intracellular pathogens, fungi, and opportunistic infections. Deep-seated abscesses are characteristic of phagocytic disorders. Sinopulmonary infections, autoimmune disorders, and disseminated neisserial infections occur with complement deficiencies.

The most common PIDs are antibody deficiencies and include congenital agammaglobulinemia, common variable immunodeficiency (CVID), selective IgA deficiency (SIGAD), and IgG subclass deficiency (IGGSD). These

Table 26.1: Characteristic infections of PIDs

Immune defect	*Examples of specific disorders*	*Typical sites of infection*	*Common pathogens*
Antibody deficiencies	Congenital agammaglobulinemia Common variable immunodeficiency Hyper IgM syndrome Selective IgA deficiency IgG subclass deficiency Specific antibody deficiency with normal immunoglobulins	Sinopulmonary tract GI tract Joints CNS	Bacteria—*Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Mycoplasma* spp. Viruses—Enterovirus spp. Fungi—none Protozoa—*Giardia lamblia*
T cell defects	Severe combined immunodeficiency Common variable immunodeficiency Hyper IgM syndrome	Sepsis Pulmonary tract GI tract	Bacteria—as above, *Salmonella* spp., *Listeria monocytogenes, Mycobacteria* spp. Viruses—Cytomegalovirus, all others Fungi—*Pneumocystis jiroveci, Candida* spp., *Aspergillus* spp., *Cryptococcus* spp. Protozoa—Cryptosporidia spp.
Phagocytic defects	Chronic granulomatous disease Hyper-IgE syndrome Leukocyte adhesion deficiency	Skin infections Deep abscesses Lymphadenitis Osteomyelitis Gingivitis	Bacteria—*Staphylococci, Serratia marcescens, Burkholderia cepacia,* Klebsiella spp., *Escherichia coli, Salmonella* spp. Viruses—none Fungi—*Candida* spp., *Aspergillus* spp., *Nocardia* spp. Protozoa—none
Complement deficiencies	Deficiencies of individual components	Sinopulmonary tract Meningitis Systemic infections	Bacteria—*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides* Viral—none Fungi—none Protozoa—none

(GI: Gastrointestinal; IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG: Immunoglobulin G; IgE: Immunoglobulin E).
Data from Notarangelo[7] and Oliveira and Fleisher.[8]

deficiencies are estimated to constitute from approximately half and up to 78% of all cases.[5,9] The typical clinical presentation of antibody deficiencies includes recurrent sinopulmonary infections, chronic gastrointestinal infections, bacteremia, and/or meningitis. In the Mayo Clinic study discussed above, the most common presentation of PIDs was pneumonia in 43% of cases, followed by recurrent otitis media in 41% and chronic or recurrent sinusitis in 40%. Select PIDs leading to recurrent sinopulmonary infections and their immune defects are summarized in Table 26.2.

Among patients with refractory sinusitis, studies report significant prevalence of antibody abnormalities. At the Johns Hopkins University School of Medicine, CVID was diagnosed in 25% and SIGAD in 40% of patients with chronic sinusitis and PIDs.[10] These patients had a median age of 31 years and duration of sinus disease of 4 years. Previous sinus surgery was reported in 60%, otitis media in 25%, and pneumonia in 50%. The total number of patients screened was not reported. In a retrospective chart review of 78 adults with chronic rhinosinusitis and/or sinus surgery at the University of Iowa, CVID was diagnosed in 9.9% and SIGAD in 6.2%.[11] A follow-up of 67 similar patients by the same group found impaired antibody response to pneumococcal polysaccharide vaccine in over half.[12]

The management of patients with refractory sinusitis can be challenging and requires comprehensive evaluation of all underlying comorbid factors. Evaluation of immune function should be considered for all patients with unusually frequent or severe sinus disease, multiple sinus surgeries, family history of PID, bronchiectasis or other

Table 26.2: Laboratory findings of PIDs with recurrent sinopulmonary infections

Immunodeficiency	*Antibody levels*	*Specific antibody function*	*Lymphocyte counts and other cellular defects*
Congenital agammaglobulinemia	IgA, IgG, IgM markedly decreased	Impaired	B-cell counts undetectable or markedly decreased
Common variable immunodeficiency	IgG decreased, usually below 450 mg/mL IgA and/or IgM decreased	Impaired	B-cell counts variable T-cell function variable
Good syndrome	IgG decreased IgA and/or IgM decreased	Impaired	B-cell counts decreased T-cell function impaired
Hyper IgM syndromes	IgM normal or elevated IgG, IgA, and IgE decreased	Impaired	T-cell function impaired in type 1 and 3 T-cell function normal in type 2 and 5
Selective IgA deficiency	IgA undetectable	Not-applicable unless concomitant IgG subclass or selective antibody deficiency	Normal
IgG subclass deficiency	IgG subclass level decreased IgG, IgA, IgM normal	Impaired	Normal
Selective antibody deficiency with normal immunoglobulins	IgG, IgA, IgM normal	Impaired to polysaccharide antigens Normal to protein antigens	Normal
Wiskott–Aldrich syndrome	IgG, IgA, IgM variable	Impaired	T-cell counts decreased T and NK cell and macrophage function impaired
Ataxia-telangiectasia	IgA, IgG, IgG subclasses variably decreased	Variably impaired	B- and T-cell counts variably decreased T-cell function variably impaired
X-linked lymphoproliferative disease	IgG and IgA levels decreased IgM variable	Impaired	NK-cell counts decreased
Transient hypogammaglobulinemia of infancy	IgG decreased IgA variable IgM normal	Normal	Normal

(IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG: Immunoglobulin G; IgE: Immunoglobulin E).

concomitant infections such as frequent otitis media, pneumonia, or bronchitis. Additionally, because recurrent sinopulmonary infections are among the most common presentation of PIDs, otolaryngologists play a critical role in early recognition of these disorders. Early recognition and aggressive management may help minimize significant morbidity and prevent long-term sequelae. Rhinosinusitis guidelines of the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS), the American Academy and College of Allergy and Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology (AAAAI, ACAAI, JCAAI), and the European Academy of Allergology and Clinical Immunology (EAACI) societies recommend immunologic evaluation of patients with chronic or recurrent acute disease who have failed aggressive medical management and demonstrate recurrent or persistent purulent infections.[13-15] Published "Warning Signs of Primary Immunodeficiency" include two or more severe sinus infections or four or more sinopulmonary infections requiring antibiotics per year (Table 26.3).[16-19]

Evaluation of immunodeficiency in a patient with refractory sinus disease may include measurement of complete blood count (CBC) with differential, major

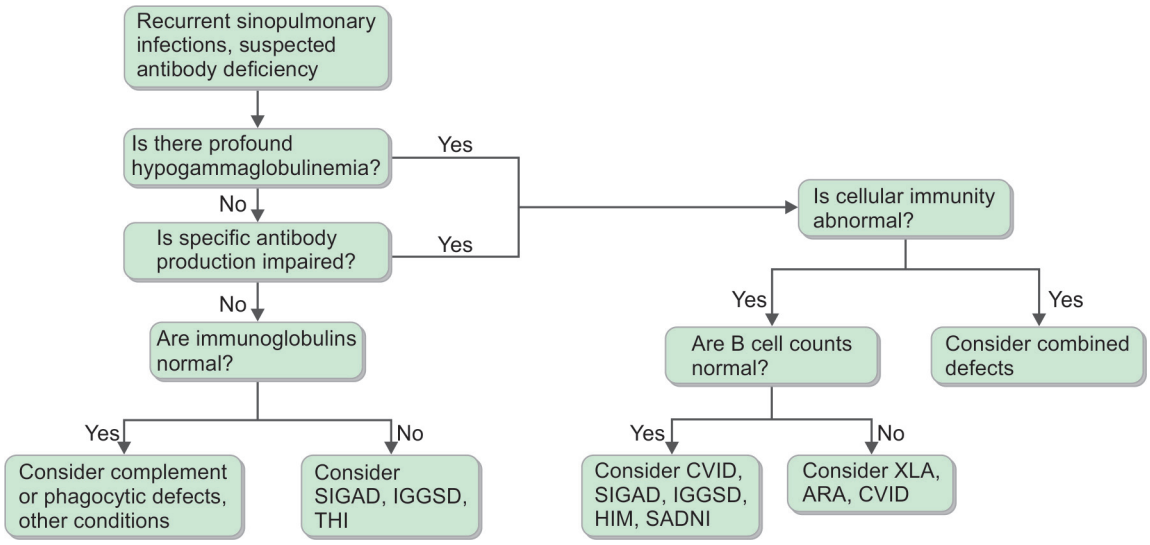
Table 26.3: Published warning signs of primary immunodeficiency

Criteria	*Jeffrey Modell Society*[14,15]	*Jeffrey Modell Society—For adults*[16]	*European Society for Immunodeficiencies—For adults*[17]
Otitis media	Four or more within 1 year	Two or more within 1 year	Four or more within 1 year (otitis, bronchitis, sinusitis, pneumonia)
Sinusitis	Two or more serious episodes within 1 year	Two or more serious episodes within 1 year, in the absence of allergy	Two or more serious episodes within 1 year
Pneumonia (radiologically proven)	Two or more within 1 year	One per year for more than 1 year	Two or more within 1 year
Other bacterial infections	Need for intravenous antibiotics to clear infections Two or more months of antibiotics with little effect	Recurrent deep skin or organ abscesses	Two or more deep-seated infections, including septicemia
	Recurrent, deep abscesses of the skin or internal organs	Recurrent, deep abscesses of the ski or internal organs	
	Two or more deep-seated infections including septicemia		
Unusual infections	Persistent thrush or fungal infection on skin or elsewhere	Persistent thrush or fungal infection on skin or elsewhere	Persistent thrush in mouth or fungal infection on skin
		Infection with normally harmless tuberculosis-like bacteria	
Other infections	Not mentioned	Recurrent viral infections (colds, herpes, warts, condyloma)	Not mentioned
Other manifestations	Failure of an infant to gain weight or grow normally	Chronic diarrhea with weight loss	Failure of an infant to gain weight or grow normally
Family history of PID	Yes	Yes	Yes

(PID: Primary immunodeficiencies).
Data from references 16-19.

immunoglobulin isotypes (IgG, IgA, and IgM), and functional antibody studies. CBC is used to evaluate for possible neutropenia or lymphopenia. Lymphocytosis may be suggestive of hematologic malignancy and eosinophilia with various hypereosinophilic conditions. Among patients with hypogammaglobulinemia, the differential diagnosis includes PID as well as secondary immunodeficiencies such as hematologic malignancy, nephrotic syndrome, or protein-losing enteropathies. Functional antibody studies include evaluation of specific antibody titers to protein and polysaccharide antigens. Typical protein antigens are tetanus and diphtheria toxoids and polysaccharide antigens are the differing pneumococcal capsular antigens. Pre- and postvaccination titers are employed to assess immune competency and are essential to confirm the presence of a clinically significant antibody defect in cases of normal or mildly decreased total antibody levels or decreased IgG subclass levels (Flowchart 26.1).[9] Additional testing may include HIV testing, lymphocyte subset analysis, complement studies, flow

Flowchart 26.1: Algorithm for the evaluation of suspected antibody deficiencies. Adapted from the Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology.[9]



(SIGAD: Specific IgA deficiency; IGGSD: IgG subclass deficiency; THI: Transient hypogammaglobulinemia of infancy; CVID: Common variable immunodeficiency; HIM: Hyper IgM syndrome; SADNI: Specific antibody deficiency with normal immunoglobulins; XLA: X-linked agammaglobulinemia; ARA: autosomal recessive agammaglobulinemia).
From Bonilla FA, Bernstein IL, Khan DA, et al.[9]

cytometry, and/or genetic analysis. Secondary causes of immunodeficiency must be ruled out. Specific immunodeficiencies with prominent sinopulmonary manifestations are addressed individually below.

Congenital Agammaglobulinemia

Congenital agammaglobulinemia is a PID characterized by significantly decreased levels of all major classes of immunoglobulins and circulating B cells.[9,20,21] Specific antibody responses are impaired. Tonsils and lymphoid structures are absent. Affected individuals most commonly present with recurrent bacterial infections in the first year after loss of maternally derived immunoglobulin. Approximately 85% of cases are due to X-linked mutations in the Bruton's tyrosine kinase (BTK) gene.[22] The remaining cases are assumed to be due to a variety of autosomal recessive mutations. In 5–10% of cases, a defect has not yet been identified. Definitive diagnosis requires analysis for known mutations or impaired expression of the relevant proteins.

X-linked agammaglobulinemia (XLA) has a minimum estimated prevalence of 1:379,000 in the United States.[23] Typically, males are affected with the disorder and female carriers are asymptomatic. BTK is a protein tyrosine kinase that transmits signals from the B-cell receptor and plays an integral role in early B-cell maturation (Fig. 26.1).[19] Over 500 different mutations have been identified and some mutations may be associated with milder phenotypes.[24] Family history is positive in approximately half with sporadic mutations accounting for the remainder. Atypical presentations have been reported including higher than expected concentration of immunoglobulins, immunoglobulin profiles compatible with SIGAD, CVID, or specific antibody deficiency with normal immunoglobulins (SADNI), delayed diagnosis into adulthood, and significant survival without immunoglobulin replacement.[25,26] Rarely, female carriers may develop clinical disease due to extreme skewed X inactivation.[21]

In a US registry of 201 patients, 50% of patients with XLA were clinically symptomatic by 1 year of age and 90% by 5 years.[23] Half were diagnosed with agammaglobulinemia/hypogammaglobulinemia by 2 years of age. The most common infections were otitis media in 70%, pneumonia in 62%, and sinusitis in 59%. Chronic/recurrent diarrhea occurred in 23%, meningitis/encephalitis in 12%, sepsis in 10%, and arthritis in 7%. Neutropenia, usually in the setting

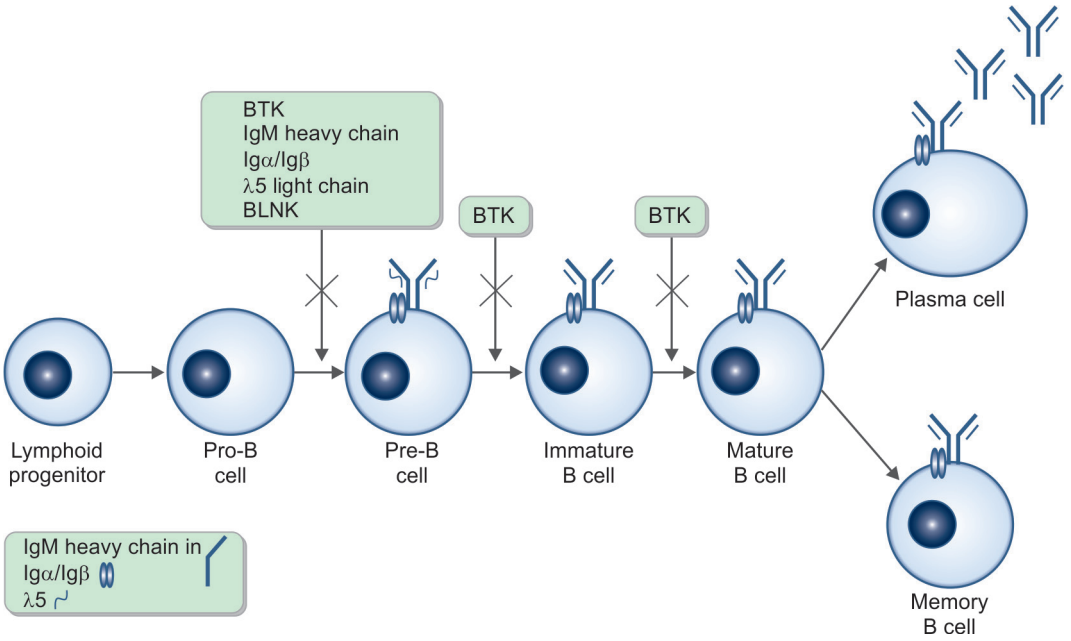


Fig. 26.1: B-cell maturation blocks in congenital agammaglobulinemia. In XLA, BTK mutations lead to incomplete blocks at multiple stages of early B-cell differentiation. ARA mutations affect expression of the pre-B-cell receptor or its signaling and consequently inhibit development of the pro-B cell to the pre-B cell. IgM heavy chains, Igα and Igβ, are components of the B-cell receptor, which are first expressed in the pre-B cell. γ 5 is a component of the pre-B-cell receptor that is subsequently replaced by its mature counterpart. BLNK is a protein kinase integral to pre-B-cell receptor signaling.
(XLA: X-linked agammaglobulinemia; BTK: Bruton's tyrosine kinase; ARA: Autosomal recessive agammaglobulinemia; BLNK: B-cell linker protein).
Data from Gaspar and Kinnon.[21]

of severe infection, was found in 15%. Encapsulated bacteria including *Streptococcus pneumoniae* and *Haemophilus influenza*e were the most common cause of infections overall. Other common causes of the infections that were noted include *Giardia* (chronic diarrhea), *S. pneumoniae* and *Enteroviruses* (CNS infections), *Pseudomonas* and *S. pneumonia* (sepsis), and mycoplasma (arthritis). Paralytic polio following live vaccination occurred in two patients. The most common cause of death was disseminated enteroviral infections followed by chronic lung disease. Mortality was estimated at approximately 1% per year.

Bronchiectasis and chronic sinusitis are major complications of XLA. In an Italian cohort of 73 patients with XLA, 68.5% had respiratory infections involving the upper and lower respiratory tracts.[25] At diagnosis, 38.5% of patients with lower respiratory tract infections had chronic lung disease and 20.5% of all patients had chronic sinusitis. Half of all patients with chronic sinusitis also had concomitant chronic lung disease. During mean follow-up duration of 10 years and despite intravenous immunoglobulin (IVIG) replacement, chronic lung disease developed in an additional 9 patients and chronic sinusitis in an additional 20 patients. The risk of having chronic lung disease by the time of diagnosis increased with older age of diagnosis and of subsequent development of chronic lung or sinus disease correlated with duration of follow-up despite treatment with IVIG. The risk of developing chronic lung disease was estimated to be 90% after 25 years.

Autosomal recessive agammaglobulinemia (ARA) is due to mutations in the IgM heavy chain in 20–30% of cases.[20] Other identified mutations include those affecting Igα, Igβ, B-cell linker protein (BLNK), and γ5. Similar to the BTK mutations, each of these mutations also causes a block in early B-cell differentiation. Early B-cell development requires signaling through the pre-B-cell receptor. The IgM heavy chains, Igα, Igβ, and γ5, are each components of the pre-BCR that then activates BLNK and BTK. A mutation in the leucine-rich repeat-containing protein 8 gene has also been reported. Clinical characteristics are similar to XLA but tend to present earlier and be more severe.[26]

Congenital agammaglobulinemia is a pure B-cell immune deficiency and treatment centers on immunoglobulin replacement. IVIG replacement with minimum serum IgG levels of 500 mg/dL have been shown to be effective in preventing bacterial infections.[27] In a retrospective study of 31 patients started on IVIG within 3 months of diagnosis and continued for a minimum of 4 years, the incidence of bacterial infections requiring hospitalization decreased from 0.40 to 0.06 per patient per year. However, in accordance with the findings in the Italian cohort, IVIG was less effective in preventing progressive respiratory disease. At the onset of IVIG replacement, bronchiectasis was documented in two patients. Recurrent bronchitis continued in 15 and bronchiectasis developed in an additional four patients. Chronic sinusitis was documented in 4 children at onset of treatment and 20 patients at follow-up. It has been postulated that prevention of chronic pulmonary and sinus disease may require higher doses of IVIG. Similarly, IVIG levels of 500 mg/dL may not be adequate in preventing enteroviral infections. In this study, enteroviral infections were diagnosed in three patients during IVIG therapy and resolved with increased doses of IVIG in two of the three patients. The third patient did not survive. An alternative explanation for the lack of improvement in respiratory tract infections with IVIG therapy is the importance of secretory IgM and IgA in mucosal immune defenses.

Common Variable Immunodeficiency

CVID is a heterogeneous and polygenic group of diseases characterized by hypogammaglobulinemia and impaired antibody production.[9,20,28] Among Caucasians, its prevalence is estimated to be up to 1:30,000.[29] It is considered rare among Asians and blacks. Age of diagnosis can range from 4 to 80+ years, but most commonly occurs in the third decade of life. With earlier diagnosis and more aggressive management, mortality has decreased from 25% over 7 years among patients followed from 1973 to 1999 to 6% over 11 years among patients followed from 1999 to 2005.[30,31]

Diagnosis of CVID is one of exclusion. Diagnostic laboratory criteria include markedly decreased (at least two standard deviations below the mean for age) levels of IgG and at least one of the other two major immunoglobulin isotypes, IgA and IgM. Over 85% of patients have IgG levels lower than 450 mg/mL at diagnosis.[28,30] The majority has decreased levels of IgA and approximately half have decreased IgM. Antibody production to proteins and polysaccharide antigens is poor. B-cell numbers range from low to markedly elevated. T-cell function is frequently impaired. Variability in IgM levels and B-cell numbers underscores the heterogeneity of underlying defects with similar immunologic profiles that may fall under the diagnosis of CVID. Normal or elevated IgM levels suggest a possible hyper IgM syndrome (HIM) or other class switch defect. Low B-cell numbers may indicate early B-cell maturational defects in young children and Good syndrome in older adults. Elevated B-cell numbers raise the possibility of lymphoid malignancy. To exclude other causes of congenital hypogammaglobulinemia and secondary hypogammaglobulinemia due to malignancy, age should be greater than 4 years and an observation period of 2 years following identification of hypogammaglobulinemia is necessary. The differential diagnosis of hypogammaglobulinemia includes other PIDs such as XLA, ARA, HIM, X-linked lymphoproliferative (XLP) disease, and Good syndrome. Secondary causes of hypogammaglobulinemia include malignancy, nephrotic syndrome, protein losing enteropathy, and medications.

Nearly all patients suffer from recurrent infections. In a US cohort of 248 patients with CVID, recurrent bronchitis, sinusitis, and otitis were found in 98% followed by pneumonia in 76.6%.[30] Encapsulated bacteria including *S. pneumoniae* and *H. influenzae* are responsible for the majority of respiratory infections. Recurrent and/or severe infections may lead to chronic sinusitis and/or bronchiectasis. In an Italian cohort of 224 patients, chronic sinusitis was found in 36.6% and chronic lung disease in 33% of patients at diagnosis.[31] Similar to findings in XLA, immunoglobulin replacement significantly decreased the frequency of respiratory infections but not the development of chronic sinus and lung disease that increased to 54% and 46.4%, respectively, at follow-up. Other significant infections and infectious sequelae included fibrotic bladder following recurrent UTI due to ureaplasma uraelyticum, joint and bronchial destruction due to mycoplasma, meningoencephalitis and dermatomyositis due to enterovirus, and enteropathy due to chronic giardiasis. As in other disorders with impaired T-cell function, opportunistic and unusual infections with *Pneumocystis jiroveci,* cytomegalovirus (CMV), other viruses, and fungi also occur.[30,32]

A European registry started in 1996 highlights the diverse spectrum of CVID.[32] The range of complications included autoimmune manifestations, lymphoproliferative disorders, and malignancy (Fig. 26.2). Noninfectious complications consistent with impaired T-cell function leading to immunologic dysregulation and lymphoid proliferation occur in over half of patients. Cytopenias were the

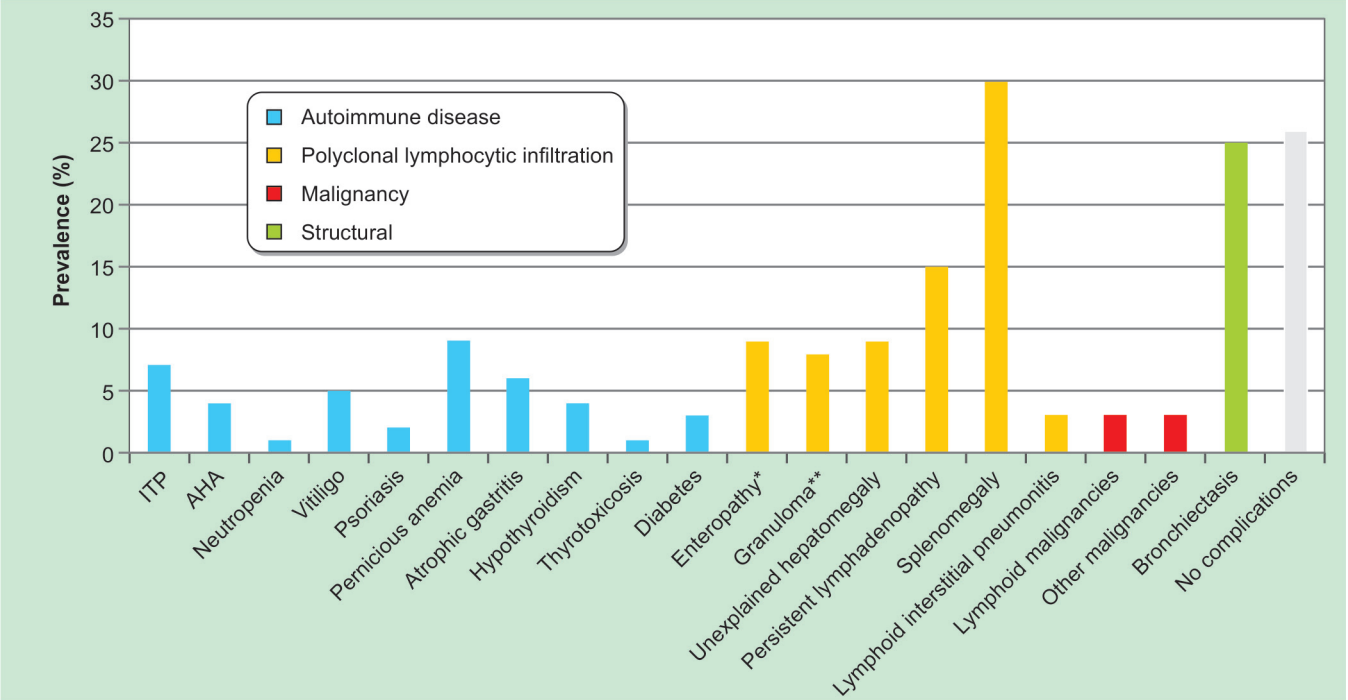


Fig. 26.2: Noninfectious manifestations of CVID. Noninfectious complication reported by the European Common Variable Immunodeficiency Disorders registry included autoimmune diseases, polyclonal lymphocytic processes, and malignancies. Individual patients may have had more than one complication. *Gluten insensitivity enteropathy. **Does not include Crohn disease.[30]
(CVID: Common variable immunodeficiency; ITP: Idiopathic thrombocytopenic purpura; AHA: Autoimmune hemolytic anemia).
Data from Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112:277-86.

most common autoimmune manifestation, occurring in 12% of patients. Polyclonal lymphocytic infiltration including granulomatous disease occurred in 8%, enteropathy in 9%, persistent lymphadenopathy in 15%, and splenomegaly in 30%. Lymphoid malignancies occurred late in the course disease and typically in the setting of polyclonal lymphocytic infiltration. IgM level was found to positively correlate with eventual development of polyclonal lymphocytic infiltration or a lymphoid malignancy and elevated CD8 T cells were inversely associated with autoimmunity. Polyclonal lymphocytic infiltration and lymphoid malignancies as well as bronchiectasis were associated with increased mortality.

Approximately 10% of patients with CVID have a family history of primary antibody deficiency, usually SIGAD. Advances in genetic research underscore the polygenic nature of CVID. Class switch defects may account for up to 12% of cases.[28] Analysis of families with several affected members has shown a homozygous deficiency of ICOS, a protein involved in immunoglobulin class switching, as the cause of one form of CVID. Polymorphisms of TNFRS13B that codes for TACI a protein associated with B-cell survival, differentiation, and immunoglobulin class switching have been associated with increased risk of both CVID and SIGAD as well as autoimmune and lymphoproliferative complications. Polymorphisms of MSH5 that codes for a DNA repair protein involved in class switching have also been linked with CVID and SIGAD. Other genetic mutations associated with CVID include mutations of the CD19 complex including CD81, CD20, and BAFF-R. Disease-modifying polymorphisms associated with specific clinical phenotypes are also being studied.

Management of CVID centers on immunoglobulin replacement, rapid recognition, and aggressive treatment of breakthrough infections and monitoring for associated complications. Autoimmune and lymphoproliferative complications may be treated with steroids and other immunosuppressive medications. Malignancies are treated according to standard chemotherapy protocols. Live vaccines should be avoided. Prophylactic antibiotics may have a role in patients with bronchiectasis. In patients with

hypogammaglobulinemia, serologic and other indirect assays for diagnosis of disease or infection are unreliable. For example, the diagnosis of celiac disease is dependent on production of IgA and antibody testing for diagnosis of infections in a patient receiving IVIG replacement will measure antibody levels in the gamma globulin replacement only. Accurate diagnosis in these patients requires direct testing methods such as biopsy, culture, or polymerase chain reaction. Patients with absent IgA may develop anti-IgA antibodies and be at risk of anaphylactic reactions to IgA containing blood products. IgA-depleted products should be used in these patients when possible.

Thymoma with Immunodeficiency (Good Syndrome)

Good syndrome is an adult onset immunodeficiency that occurs in 3–6% of individuals with thymoma and presents between the ages of 40 and 70 years.[9,20,33] The immunologic defect includes hypogammaglobulinemia, impaired T-cell function, and decreased peripheral B cells. CD4 lymphopenia may also be present. The majority of thymomas are benign and well-encapsulated masses. Surgical removal or debulking may be indicated for the treatment of malignancy or localized obstruction. However, resection of the thymoma has not been shown to reverse the immunodeficiency. The pathogenesis of the immunodeficiency is unknown.

Reflecting both underlying antibody and cell defects, patients have increased susceptibility to recurrent bacterial and opportunistic infections as well as autoimmune diseases including myasthenia gravis, neutropenia, red blood cell aplasia, and anemias. In a review of 51 patients, the diagnosis of thymoma preceded the diagnosis of hypogammaglobulinemia with an interval of 3 months to 23 years in 35% and followed the diagnosis of the immunodeficiency with an interval of 3 months to 20 years in 57%.[34] Recurrent infections of the upper and lower respiratory tract were reported in 78% and diarrhea in 43%. Bronchiectasis developed in 14%. Opportunistic infections included *Candida* in 24%, CMV in 10%, and *Pneumocystis pneumoniae* (PCP) in 6%. Treatment includes immunoglobulin supplementation, prophylaxis of opportunistic infections, and management of associated autoimmune disorders.

Hyper IgM Syndrome

HIM are a heterogeneous group of genetic diseases characterized by elevated or normal levels of IgM with decreased levels of IgG, IgA and IgE, and impaired specific antibody production.[9,20] HIMs may be characterized by genetic subtype.[35] As a group, all patients have defective antibody class switching from initial production of IgM to secondary production of the other isotypes. Type 1 HIM is caused by an X-linked defect in CD40 ligand (CD154) found on activated T cells that interact with CD40 on B cells and antigen presenting cells. Types 2, 3, and 5 are caused by autosomal recessive defects in activation-induced deaminase (AID), CD40, and uracil N glycosylase (UNG), respectively. AID and UNG are B cells proteins that work downstream of the CD40 receptor. Type 4 refers to HIM due to as yet unidentified mutations. The minimum prevalence of type 1 HIM is estimated to be 1 in 500,000 live male births.[36]

Normal maturation of B cells leads to the production of naïve B cells that develop into IgM secreting plasma cells.[35] IgM antibody is an early antibody capable of recognizing various pathogens. Alternatively, T cells activated by antigen presenting cells can induce B cells to switch to production of IgG, IgA, or IgE antibodies. Unlike IgM, these antibodies are produced during the secondary adaptive immune response, are highly antigen specific, and participate in immunologic memory. This second pathway requires intact CD154–CD40 interaction. Subsequent B cell signaling via CD40 leads to immunoglobulin class switching and somatic hypermutation, a related process that then fine tunes the B cells to produce antibodies with progressively higher affinity for their respective antigens (Fig. 26.3).[37]

The X-linked defect in CD154 accounts for at least 70% of cases of HIM.[35] Because CD154 on T cells is integral to antibody production via interaction with B cells and cell-mediated immunity via its interaction with macrophages, dendritic cells, and other antigen presenting cells, patients present with characteristics of both antibody and cellular immunodeficiency. In addition to the expected bacterial infections of the respiratory and gastrointestinal tracts, opportunistic infections are prominent. In a US registry of 79 patients, over half presented with symptoms in the first year of life and the majority by age 4 years.[36] Two patients presented in adolescence. The most common infections were pneumonia in 81% of patients, sinusitis and/or recurrent otitis media in 49%, and recurrent protracted diarrhea in 34%. Other infections included CNS infections, sepsis, skin infections, hepatitis, and sclerosing cholangitis. *Pneumocystis jiroveci* was the most common opportunistic pathogen, responsible for 59% of cases of

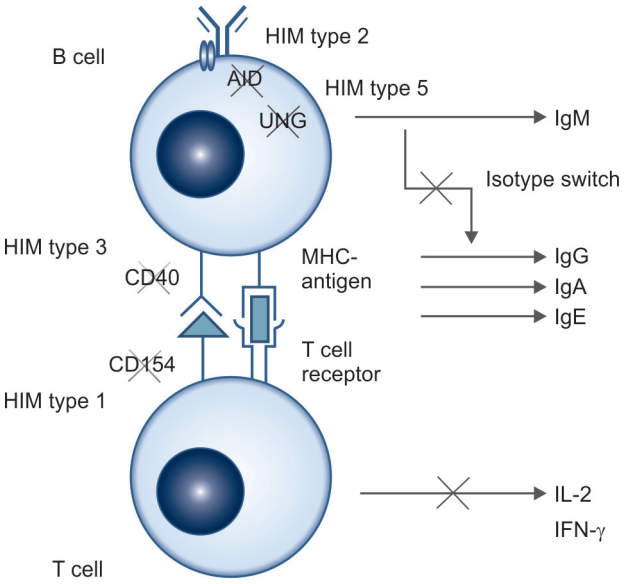


Fig. 26.3: Class-switch mutations in HIM syndromes. HIM types 1 and 3 mutations affect CD154 and CD40 respectively, directly impair T- and B-cell interaction and lead to both cell-mediated and humoral immune defects. Patients present with both infections due to extracellular bacteria characteristic of antibody deficiency and opportunistic infections typical of T-cell defects. HIM types 2 and 5 impair class switch mechanisms downstream of CD154-CD4, are limited to B cells and lead to humoral deficiencies only. (HIM: Hyper IgM; MHC: Major histocompatibility complex; AID: Activation-induced deaminase; UNG: Uracil N glycosylase; IL-2: Interleukin 2; IFN-γ: Interferon gamma).
Data from Sorenson and Moore C.[37]

pneumonia. *Cryptosporidium* was the most common cause of chronic diarrhea and sclerosing cholangitis. The most common noninfectious complication was neutropenia in over 60% of patients. Anemia, thrombocytopenia, and malignancies of the gastrointestinal tract were also reported.

The autosomal recessive deficiency in AID accounts for the majority of other cases. In a series of 29 patients, the median age at first clinical manifestation was 2 years (range 0.3–12.9) and at diagnosis of immunodeficiency was 3.8 years (range 0–44.3).[38] Respiratory infections were most common with pneumonia in 59%, upper respiratory and sinus infections in 93%, and bronchitis in 72%. Bronchiectasis and chronic sinusitis occurred in two and six individuals, respectively, at diagnosis. Lymphoid hyperplasia with persistent B-cell activation was found in 69%. Autoimmune and other inflammatory disorders including Crohn disease, autoimmune hepatitis, and cytopenias affected 21%. Unlike in CD40 ligand deficiency, the immune defect in these patients is limited to B cells and opportunistic infections were not seen.

Less common are autosomal recessive defects in the genes encoding for the CD40 receptor and UNG. Characteristics of patients with UNG deficiency are similar to those with AID deficiency and lymphoid hyperplasia is prominent.[35,39] Similar to patients with CD40 ligand defects, patients with CD40 receptor defects are vulnerable to opportunistic infections. Autosomal dominant mutations of AID, multiple uncharacterized B-cell defects, X-linked and autosomal dominant defects in NF-κB signaling, and an uncharacterized defect leading to high rates of autoimmunity have also been reported. HIM patterns of immunodeficiency can also be found in a subset of patients with CVID, XLP, and ataxia-telangiectasia (AT).

Treatment is dependent on the type of defect. For those patients with B-cell limited defects, immunoglobulin replacement is effective in decreasing the frequency of infections and lymphoid hyperplasia as well as suppression of elevated IgM secondary to ongoing chronic infections. In the series of patients with AID deficiency, followed for a median 6.5 years (range 1.4–21) since initiation of IVIG, all patients were alive except the oldest who died at the age of 63 years from septicemia.[38] Autoimmune disorders are managed accordingly. Among patients with CD40 ligand defects, immunoglobulin replacement, PCP prophylaxis, hygienic measures, and G-CSF to treat neutropenia to prevent *Cryptosporidium* infection are initial treatment options but do not fully address the cell-mediated defect. Survival rates as low as 20% at 25 years has been reported.[40] The most common cause of death was opportunistic infection and hepatobiliary disease. Bone marrow transplant can be curative for patients with CD40 ligand defects. Among patients without pre-existing hepatobiliary disease, success rates up to 72% have been reported.[41]

Selective IgA Deficiency

SIGAD is a primary humoral immunodeficiency with variable presentation. Prevalence estimates range from 1 in 300 to 1 in 700 in the Caucasian population.[9] Up to 85–90% of patients are asymptomatic. Symptomatic patients develop frequent sinopulmonary and gastrointestinal infections, autoimmune and other gastrointestinal diseases, and atopic disorders. IgA deficiency may occur in association with other immune defects such as IGGSD, SADNI, and AT. Up to 25% of affected individuals have a family history of either SIGAD or CVID and a subset of patients may progress to develop CVID.[42,43]

IgA constitutes over 70% of total immunoglobulin in the body.[44] It is concentrated in mucosal secretions of the

nasal, pulmonary, gastrointestinal, and genitourinary tracts as well as in saliva, tears, and breast milk. IgA exists in two forms. Monomeric IgA is found in the serum. Dimeric IgA is found in secretions and participates in mucosal defense by coating organisms and preventing colonization and/or penetration of mucosal surfaces. The absence of frequent infections in the majority of individuals with IgA deficiency may be explained by redundant immunoprotective mechanisms including compensation by secretory IgM. The specific defect in SIGAD unknown but leads to a terminal block in the maturation of B lymphocytes to become IgA secreting plasma cells.

The diagnosis of SIGAD requires IgA level <0.07 g/L in the setting of normal levels of IgG and IgM in an individual greater than 4 years of age.[9,20] IgA levels in younger children may be low due to physiologic delayed immune maturation and therefore unreliable. The term partial IgA deficiency has been used for individuals with low but detectable IgA levels. A functional antibody deficit is not required for diagnosis of SIGAD. However, because SIGAD is associated with other defects such as IGGSD and SADNI, functional antibody studies are recommended. The differential diagnosis includes other PIDs and secondary IgA deficiency due to medications. Medications known to cause IgA deficiency include anticonvulsants (phenytoin, valproic acid, carbamazepine), D-penicillamine, captopril, sulfasalazine, gold, fenclofenac, and thyroxine.

Recurrent infections have been reported in 50–94% of symptomatic patients.[45,46] In an Iranian series of 37 patients with SIGAD ranging from 4 to 32 years of age (median age 9 years), 73% of patients presented with recurrent infections and during an average 3.5 years of follow-up, 94% developed recurrent infections.[46] Sinusitis was reported by 78% followed by pneumonia in 46%, otitis media in 38%, bronchitis in 35%, and chronic diarrhea in 19%. Bronchiectasis developed in 11%. When grouped by presence or absence of concomitant IGGSD or specific antibody deficiency, increased frequency and severity of infections as well as all cases of bronchiectasis were found in the group with additional immune defects. Encapsulated bacteria are responsible for the majority of respiratory infections and *Giardia* was a common cause of chronic diarrhea. Increased susceptibility to sinopulmonary compared with gastrointestinal infections may be due to higher levels of secretory IgM in the gastrointestinal tract.[47,48]

Noninfectious complications are common and may be due to immune dysregulation, impaired mucosal clearance of foreign antigens, or other independent underlying genetic defects. Autoimmune disorders have been reported in 20–30% and celiac disease in up to 8% of symptomatic individuals.[49] IgA deficiency occurs in up to 4.6% of patients with systemic lupus erythematosus and 4.3% of patients with juvenile rheumatoid arthritis.[50] Other autoimmune and gastrointestinal disorders associated with IgA deficiency include idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune thyroiditis, inflammatory bowel disease, and nodular lymphoid hyperplasia. Allergic disorders have been reported in 13–84% of cases.[45,46]

Treatment of IgA deficiency centers on management of associated diseases. Prophylactic antibiotics can be considered for patients with recurrent infections, and noninfectious complications are managed accordingly. Immunoglobulin supplementation is reserved for a subset of patients with concomitant IgG subclass or specific antibody deficiency. Because individuals with undetectable IgA may develop anti-IgA antibodies and be at risk of anaphylactic reactions, IgA-depleted blood products should be used when necessary. Serologic testing for celiac disease is dependent on IgA antibodies and therefore unreliable in patients with SIGAD. Ongoing monitoring of immune function is necessary to identify children in whom IgA deficiency can resolve and others in whom there may be progression to CVID. Overall prognosis depends on the severity of complications.

IgG Subclass Deficiency

IGGSD refers to decreased serum concentration of one or more subclasses of IgG in an individual with normal total IgG.[9,20] It may occur as an isolated abnormality or in combination with other immunodeficiencies such as SIGAD, SADNI, or AT. The majority of people with an isolated defect are asymptomatic and therefore the significance of decreased IgG subclass levels is controversial.[51,52] The diagnosis of a clinically significant IGGSD requires evidence of antibody dysfunction with recurrent infections and poor antibody response to vaccinations. When present, infections primarily affect the upper and lower respiratory tracts and may lead to chronic sinusitis and/or bronchiectasis.[9,37]

IgG is the most abundant intravascular immunoglobulin isotype. It is produced during the secondary adaptive immune response and is responsible for immunologic memory and long-term immune protection. IgG has four subclasses and normal levels vary by age.[53] IgG1

accounts for 60–70% of total IgG. Its deficiency generally results in hypogammaglobulinemia, may occur in combination with IgG3 deficiency, and may precede the development of CVID. IgG2 accounts for 20–30% of total IgG and the majority of antibodies to polysaccharide antigens. It is therefore considered to be primarily responsible for protection against encapsulated bacteria. It may occur in combination with IgG4 or IgA deficiency and has been associated with multiple autoimmune disorders, autoimmune cytopenias and Sjögren syndrome, and secondary immunodeficiencies including HIV infection.[54-56] IgG3 accounts for 10–15% total IgG. IgG4 deficiency is asymptomatic.

Management of IGGSD includes management of comorbid conditions that may predispose to infections such as allergic rhinitis and asthma and prompt recognition and antibiotic treatment of infections. In select individuals, prophylactic antibiotics or IVIG supplementation may be considered. All individuals who do not respond appropriately to polysaccharide vaccines should receive the conjugated pneumococcal vaccine. Children should be monitored routinely for normalization of subclass levels. Individuals with persistent deficiency should be monitored for worsening immunodeficiency or progressive end organ damage.

Specific Antibody Deficiency with Normal Immunoglobulins

SADNI describe individuals with impaired antibody responses to polysaccharide antigens and otherwise intact immune function.[9,20,37] Overall immunoglobulin levels and response to protein antigens are normal. It is among the most commonly diagnosed PIDs and affected individuals have increased incidence of bacterial respiratory tract infections and development of chronic sinusitis and/or bronchiectasis. Prevalence estimates range from 6% to 23% of children with recurrent infections, 8% of adults with recurrent pneumonia, and 12–51% of adults with chronic sinusitis.[12,57-60] Poor antibody response to polysaccharides may occur in isolation or in association with other primary or secondary immunodeficiencies such as SIGAD, IGGSD, Wiskott–Aldrich syndrome (WAS), HIV infection, or asplenia. Progression to CVID has been reported.[61]

Diagnosis of SADNI typically relies on antibody titers specific for pneumococcal capsular antigens and evaluation of the strength of the immunologic response to the pneumococcal polysaccharide vaccine. IgG titers to specific pneumococcal serotypes are checked at baseline and 4–6 weeks after vaccination with the 23 valent pneumococcal polysaccharide vaccine. Because the immune system of infants and young children may not be able to amount an adequate response to polysaccharide antigens, the diagnosis can be made only in individuals over 2 years of age and the defect may be transient in children between 2 and 5 years of age.[62]

The normal immune response to pneumococcal capsular antigens is controversial. Consensus guidelines of the AAAAI and ACAAI define normal response as postimmunization IgG concentration to individual serotypes of at least 1.3 mg/mL or a fourfold increase in baseline levels.[9] Healthy children between 2 and 5 years of age are expected to mount an appropriate response to at least 50% and older individuals to at least 70% of serotypes tested. Table 26.4 summarizes recent recommendations

Table 26.4: Response phenotypes to 23 valent pneumococcal polysaccharide vaccine (PPV23)

*Phenotype**	*PPV23 response, age > 6 years*	*PPV23 response, age < 6 years*	*Notes*
Severe	≤ 2 protective titers (≥ 1.3 μg/mL)	≤ 2 protective titers (≥ 1.3 μg/mL)	Protective titers present are low
Moderate	< 70% of serotypes are protective (≥ 1.3 μg/mL)	< 50% of serotypes are protective (≥ 1.3 μg/mL)	Protective titers present to ≥ 3 serotypes
Mild	Failure to generate protective titers to multiple serotypes or failure of a twofold increase in 70% of serotypes	Failure to generate protective titers to multiple serotypes or a failure of a twofold increase in 50% of serotypes	Twofold increases assume a prevaccination titer of less than cutoff values[†]
Memory	Loss of response within 6 months	Loss of response within 6 months	Adequate initial response to ≥ 50% of serotypes in children < 6 years of age and ≥ 70% in those > 6 years of age

*All phenotypes assume a history of infection.
[†]Cutoff values represent serotype-specific absolute preimmunization values above which a significantly increased response would not be expected. Values varies between serotypes and ranges from 4.4 to 10.3 mg/mL.
From Orange JS, Ballow M, Stiehm R, et al.[63]

of the AAAAI in evaluating the response to the 23 valent pneumococcal polysaccharide vaccine.[63] Impairment is characterized as mild, moderate, or severe based on adequate responses to number of serotypes. A fourth category describes patients who have initial good response to pneumococcal vaccination followed by loss of protective titers within 6 months–2 years.

A retrospective study of 75 adults with SADNI found that 92% had greater than four documented infections per year for at least 2 years.[64] Mean age at presentation was 35 years and a diagnosis was 43 years. The most common infection was sinusitis in 81% followed by pneumonia in 52%, bronchitis in 25%, and otitis media in 24%. Meningitis, sepsis and abscesses were also reported. Bronchiectasis occurred in 12% and autoimmune disorders in 8%. Family history of malignancy was found in 72%. Otitis media and chronic otorrhea was reported to be the most common manifestation in young children.[57]

Two recent studies evaluated the prevalence and characteristics of polysaccharide nonresponsiveness among patients with medically refractory sinusitis and using current diagnostic methodology with the 23 valent unconjugated pneumococcal vaccine. In a study of 69 patients with refractory chronic sinusitis, a low level of one of the major immunoglobulin isotypes occurred in 27%.[12] Unconjugated pneumococcal vaccine was administered in 51 patients and impaired response occurred in 67% of vaccinated patients. However, the prevalence of impaired polysaccharide response among patients with otherwise normal versus decreased immunoglobulin levels was not reported separately. There was a trend toward increased number of sinus surgeries and frequency of pneumonia as well as a lower incidence of nasal polyposis, asthma, and positive allergy skin tests among patients with poor compared with normal response to pneumococcal vaccination.

A subsequent study of 129 patients with refractory chronic sinusitis that excluded all patients with other known primary or secondary causes of immunodeficiency reported low baseline pneumococcal antibody levels in 72%.[60] Pneumococcal vaccination was administered in 69 and impaired response occurred in 22% of the vaccinated patients. Difference in prevalence estimates between two studies may be due to methodologic differences including exclusion criteria, proportion of patients lost to follow-up, and definition of normal immune response. These two studies defined "normal" differently, further highlighting existing controversies regarding normal immune response to polysaccharide antigens. In the first study, normal response was defined as a fourfold increase in antibody levels for 7 of 14 serotypes. The later study defined normal immune response as IgG level ≥1.3 mg/mL for 7 of 14 serotypes.

Treatment is similar to that of symptomatic IGGSD and includes management of comorbid conditions predisposing to respiratory infections, prompt recognition, and treatment of infections and administration of the conjugated pneumococcal vaccine. Prophylactic antibiotics and IVIG supplementation can be considered in select cases.

Transient Hypogammaglobulinemia of Infancy

Transient hypogammaglobulinemia of infancy (THI) describes an abnormally protracted period of low immunoglobulin levels due to delayed onset of immunoglobulin synthesis.[9,20,37] It has an estimated incidence of 1 in 20,000–50,000 live births and affected infants are predominantly male (60–80%).[65] Infants are found to have low IgG levels either during evaluation of recurrent infections or during screening evaluation, often while asymptomatic, for those with family histories of PID. IgA level may be decreased and B-cell numbers are normal. Specific antibody responses are generally normal. Atopic disease has been reported in up to 63% of cases.[66] Spontaneous resolution occurs usually between 2 and 4 years of age but may be delayed until adolescence.[67]

In infants, maternally derived IgG antibodies transferred through the placenta during the third trimester of pregnancy account for the majority of antibodies at birth.[68] These antibodies decline after birth and are progressively replaced by infant-derived antibodies. IgM antibodies are the first to develop and rapidly increase during the first month. IgG antibody production increases between the first 3 and 6 months of age and normally reach 60% of adult levels at 1 year of age. IgA antibodies increase variably with up to 20% of adult levels at 1 year. Due to the combination of maternal IgG loss and delayed infant antibody production, there is a nadir in immunoglobulin levels between 3 and 6 months of age. Infants with THI have abnormally delayed antibody production resulting in accentuation of their "physiologic hypogammaglobulinemia." The cause of the delay is unknown.

Definitive diagnosis of THI can only be made retrospectively after immune defects resolve. The differential diagnosis includes XLA, ARA, and CVID. Infants with XLA or ARA may be differentiated by exceptionally low antibody levels to all isotypes, inability to mount specific

antibody responses, and absent B cells. However, unless known mutations are demonstrated, atypical presentations cannot be ruled out. CVID can present in childhood and is associated with impaired functional antibody responses.

THI has a relatively benign course and severe infections such as sepsis, meningitis, or other invasive infections are unusual.[69] In a study of 40 children with hypogammaglobulinemia and no evidence of other immunodeficiency, upper respiratory tract infections occurred in 70%, lower respiratory tract infections in 11%, otitis media in 22%, and gastroenteritis in 12%.[70] Two were treated with IVIG and there were no life-threatening infections. Antibody levels were normalized by 36 months of age in 83% of patients. The presence of invasive infections is suggestive of persistent immunodeficiency and lower respiratory tract infections may be more common with lower IgG levels.[71,72]

Supportive therapy and appropriate antibiotic treatment of infections are usually adequate. However, prophylactic antibiotics may be considered and select patients with severe or refractory infections may benefit from temporary immunoglobulin supplementation.

Wiskott-Aldrich Syndrome

WAS is an X-linked PID due to mutations in the WAS protein (WASP) gene.[9] Symptomatic WASP mutations occur in approximately 1 in 100,000 live births, and affected individuals can be categorized into three major groups: classic WAS, X-linked thrombocytopenia (XLT), and X-linked neutropenia (XLN).[29,73] Approximately 50% of affected individuals exhibit the classic symptoms of WAS including eczema, microthrombocytopenia, and recurrent infections. The majority of the remainder develops XLT, characterized primarily by thrombocytopenia. Mutations leading to absent or expression of a truncated WASP are associated with the classic phenotype, whereas mutations leading to decreased expression of full-size WASP are associated with XLT.[73,74] Clinical manifestations of WAS/XLT may be present shortly after birth. In a retrospective study, average age at diagnosis was 21 months with a range up to 25 years of age.[75] A distinct mutation leading to XLN has also been characterized.[76]

WASP is a cytoplasmic protein expressed exclusively in hematopoietic cells.[77] Its function includes relaying signals from cell membrane receptors to the actin cytoskeleton and organization of actin filaments leading to effective chemotaxis, phagocytosis, and cell–cell interactions between T and B cells and cytotoxic cells and their targets. Thus, WASP mutations can cause global immunologic defects affecting both innate and adaptive immune mechanisms. The most common laboratory abnormality is microthrombocytopenia. IgG is generally normal, IgM may be decreased, and IgA may be elevated. Antibody response to polysaccharide antigens is consistently impaired and antibody response to protein antigens depressed in 50% of cases. T-cell lymphopenia develops progressively and is common by first 6–8 years. As expected, T- and NK-cell function and migration and trafficking of macrophages and dendritic cells is impaired.

In a study of 50 individuals with WASP mutations, expression of the full-size WASP correlated with the risk of infection.[73] Recurrent and/or life threatening infections occurred in over 90% of patients who did not express WASP and were over four times more common compared with patients with XLT. Recurrent upper and lower respiratory infections are common with otitis media reported in 78% of patients, sinusitis in 24%, and pneumonia in 45%. PCP has been reported in 9%, viral infections including recurrent herpes simplex in 12%, and fungal infections predominantly due to *Candida* in 10%. PCP and fungal infections were reported only among patients who did not express WASP.

The majority of patients with WAS/XLT have history of bleeding including petechiae, epistaxis, hematemesis, and melena.[75] Life-threatening hemorrhages of the gastrointestinal tract and CNS occur in 30% of patients. If the diagnosis is known prenatally, C-section may be preferable to than vaginal delivery to avoid intracranial bleeding. Moderate-to-severe eczema develops in the first year in classic WAS. If present, it is usually mild in XLT. Eczema may be due to colonization with *Staphylococcus* rather than atopy and responds to antimicrobial treatment. Autoimmune manifestations occur in 40% of both WAS and XLT patients and include hemolytic anemia, vasculitis, renal disease, Henoch-Schönlein purpura and inflammatory bowel disease. Malignancies primarily lymphoreticular in origin occur later with a peak in the third decade among patients with classic WAS.

Treatment is supportive and includes prompt diagnosis, antibiotic prophylaxis, and treatment of infections and IVIG supplementation for the underlying antibody deficiency. Platelet transfusions are indicated for severe bleeding. However, due to the underlying T-cell defect, platelets and other lymphocyte containing blood products should be irradiated to prevent graft versus host disease and tested for CMV. Splenectomy can increase platelet

counts and decrease the risk of bleeding. However, it is not routinely indicated due to markedly increased risk of septicemia.[78] Classic WAS is fatal in childhood with an average life expectancy of 6.5 years.[79] However, individuals with milder variants frequently survive into adulthood. Bone marrow transplant is curative and indicated for all patients with WAS and some with XLT.

Ataxia-Telangiectasia

AT is an autosomal recessive disorder with a prevalence ranging from 1 in 20,000–100,000 live births.[80] Up to 2% of Caucasians Americans are heterozygote carriers. The disorder is due to a mutation in the ataxia-telangiectasia-mutated (ATM) gene.[81] ATM is a protein kinase involved in recognition of DNA damage regulation of cell cycle progression. In the presence of double-stranded DNA breaks such as caused by damage due to ionizing radiation or physiologic production of reactive oxygen species or during immunoglobulin and T-cell receptor recombination processes, ATM delays cell division to allow for appropriate repair of the break. In its absence, progressive accumulation of somatic mutations leads to increased frequency of cancer and aberrant immune maturation leads to increased frequency of infections. Other functions of ATM include mitochondrial homeostasis. Mitochondrial dysfunction with excessive production of reactive oxygen species is associated with aging and neurodegeneration.

The hallmark features of AT include progressive degenerative neurologic changes, ocular and cutaneous telangiectasias, and immunodeficiency.[9,81] Other features are pulmonary disease, malignancies, insulin resistance, premature aging, sensitivity to oxidative stresses, and premature aging. Ataxia occurs after the first year of life and is followed by progressive deterioration of gross and fine motor skills, visual performance, speech, and swallowing. Telangiectasias develop between 3 and 5 years of age. After age of 10 years, patients are progressively wheelchair bound and malignancies, mostly hematologic, develop in 10–20%. Alpha-fetoprotein is elevated. A variant form with milder clinical features has been described. Heterozygote carriers may have a higher incidence of malignancy or cardiovascular disease.

Recurrent respiratory infections occur in 83% of cases, and chronic bronchitis leading to possible bronchiectasis occurs in 52%.[82] Immune defects are variable and affect both the humoral and cell-mediated arms of the immune system. In a study of 100 patients at the Johns Hopkins Ataxia-Telangiectasia Clinical Center, low levels of IgG4 were found in 65%, IgA in 63%, IgG2 in 48%, and total IgG in 18%.[83] Among patients with IgA deficiency, concomitant IgG or IGGSDs were found in 76%. Lymphopenia occurred in 71%, low CD19 B-cell counts in 75%, and low CD3 T-cell counts in 57%. Response to immunizations and T-cell function was variably decreased. Hypergammaglobulinemia, was also common with elevated IgM in 26%, IgG in 13%, and IgA in 7%. Monoclonal gammopathy was found in 11%. Clinically, recurrent sinopulmonary infections were common with otitis media in 46%, sinusitis in 27%, bronchitis in 19%, and pneumonia in 15%. Upper respiratory tract infections occurred with similar frequency in all age groups, but lower respiratory tract infections increased with age. Severe viral and opportunistic infections included extensive/refractory warts (7%), severe varicella requiring hospitalization (5%), *Candida* esophagitis (3%), and viral meningitis (2%).

Median age of death is 25 years and the primary causes of death are chronic lung disease due to recurrent infections and malignancy.[84] Management of AT includes treatment of acute infections. For patients with recurrent infections or hypogammaglobulinemia, prophylactic antibiotics or immunoglobulin replacement may be helpful. Other measures include chest clearance techniques and noninvasive ventilation for respiratory failure, measures to minimize aspiration risk, and physical and occupational therapy to maximize level of function. X-rays and other diagnostic procedures utilizing ionizing radiation should be avoided whenever possible.

X-Linked Lymphoproliferative Disease

XLP disease affects approximately 1 in 1 million boys characterized by enhanced susceptibility to Epstein-Barr virus (EBV) infection and absent NK cells.[9,85] In 80% of familial cases, there is a mutation in the Src homology 2 domain containing gene 1A (SH2D1A) with encodes for signaling lymphocytic activation molecule (SLAM)-associated protein (SAP).[86] A mutation in the BIRC4 gene that encodes for X-linked inhibitor of apoptosis has been identified in the majority of the remaining patients. A third defect involving an intracellular tyrosine kinase (ITK) has also been reported. The defects are thought to cause impaired function of NKT cells but are not yet fully understood.

An XLP registry was formed in 1978, and as of December 2000, 89 families with 309 affected individuals were represented.[87,88] Clinical presentation was variable. The most common manifestation was fulminant EBV infection

occurring in 63% of affected individuals and leading to massive polyclonal lymphocytic infiltration of the bone marrow, liver, spleen, thymus, lymph nodes, and intestinal tract. Dysgammaglobulinemia with varying degrees of hypogammaglobulinemia, primarily affecting IgG levels, developed in 30%. Increased IgM suggestive of a class switch disorder and IGGSDs was also reported. Lymphoma or other lymphoproliferative disease occurred in 28%. Aplastic anemia and vasculitis were less common with a prevalence of 6% and 1%, respectively. Median age of development of fulminant and lymphoproliferative disease was 3 years, of dysgammaglobulinemia 9 years, and lymphoma or other lymphoproliferative disease 6 years. Age of presentation of each clinical phenotype ranged from infancy to 40 years and individual patients could develop more than one phenotype in succession over time.

Despite the severity of EBV infection in the majority of individuals with XLP, nearly 40% of individuals with EBV infection did not develop fulminant disease and roughly half of individuals with dysgammaglobulinemia or lymphoproliferative disease had no evidence of preceding EBV infection. Prognosis was worst for patients with fulminant EBV infection with median survival of 2 months, intermediate for those with lymphoma, and best among patients with dysgammaglobulinemia, particularly if treated with IVIG. Among those with lymphoma, prognosis is better among those without EBV infection compared with those who were EBV positive. Overall mortality was 70% by 10 years of age.

Bone marrow transplant is curative. Chemotherapeutic regimens can control fulminant infection pending bone marrow transplant or induce remission of lymphoma. Immunoglobulin supplementation to prevent bacterial and viral infections is indicated for patients with dysgammaglobulinemia. However, in the absence of curative treatment, patients inevitably relapse or develop additional manifestations of XLP.

SECONDARY IMMUNODEFICIENCIES

Secondary immunodeficiencies may be due to infections, medications, malignancy or other underlying systemic disease.[89,90] Similar to the PIDs, individuals develop recurrent infections with general characteristics relatable to the nature of the immune defect. These individuals may also be at higher risk of malignancies and autoimmune disease. Secondary causes of immunodeficiency include infection, medications, malignancies, and other systemic diseases (Table 26.5).

Infections

Profound immunosuppression secondary to HIV has been well characterized and will be discussed in further detail below. More common in the developing world, measles infection by direct infection of T cells can lead to T-cell lymphopenia and loss of T-cell function resulting in marked immunosuppression and mortality from secondary superinfection.[91] EBV, CMV, parvovirus B19, and congenital rubella may lead to secondary hypogammaglobulinemia.[90]

Human Immunodeficiency Virus

Human immunodeficiency virus infection has affected an estimated 1.1 million persons in the United States and an estimated 405,926 persons were living with AIDS at the end of 2003.[92] Due to aggressive antiretroviral management, survival of infected persons has dramatically increased over the past 30 years. Sinusitis is a common problem among individuals with HIV infection and affects up to 68%.[93,94] Its presentation is dependent on the stage of HIV infection. Factors that increase the severity of sinus disease include underlying immune defects, presence of unusual pathogens, and worsening allergic rhinitis. Drug hypersensitivity may also complicate treatment.

Immune defects of HIV include both the hallmark cell-mediated defect and an antibody defect. Acute HIV infection is associated with a mononucleosis like syndrome with fever, lymphadenopathy, sore throat, rash, arthralgias, and myalgias.[89] Infection progresses to a latent stage with minimal symptoms. In some patients, persistent lymphadenopathy due to polyclonal B-cell activation may be present. Without treatment, ongoing immune activation leads to hypergammaglobulinemic and impaired specific antibody production. Immune response to vaccination including influenzae and pneumococcus may be attenuated or the responses may be unsustained with rapid loss of immune protection.[95] Progressive attrition of CD4+ T cells lead to cell-mediated immunodeficiency and further depression of humoral immune responses. Pediatric patients, in particular infants who acquired HIV infection transplacentally or via transfusion may present with marked hypogammaglobulinemia.[96]

Among individuals with intact immune function, sinusitis presents similarly to the general population with the characteristic symptoms of nasal congestion, purulent nasal discharge, headache, and facial pain.[93,97] Common pathogens include the usual respiratory bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae*,

Table 26.5: Secondary causes of immune deficiency

Category	*Examples*
Extremes of age	Prematurity Advanced age
Malnutrition	Hypoproteinemia Nutrient deficiencies
Infection	HIV Measles CMV, EBV Congenital rubella
Metabolic diseases	Diabetes mellitus Uremia Cirrhotic liver disease
Malignancy	Chronic lymphocytic leukemia Multiple myeloma
Protein loss	Nephrotic syndrome Protein losing enteropathies
Genetic syndromes	Down syndrome Turner syndrome
Immunosuppressive medications	Corticosteroids Calcineurin inhibitors—cyclosporine, tacrolimus m-TOR inhibitors—sirolimus Antimetabolites—mycophenolate mofetil, methotrexate, azathioprine, 6-mercaptopurine Alkylating agents—cyclophosphamide, chlorambucil, melphalan
Immunomodulatory biologics	Polyclonal antibody B and T cells—anti-thymocyte globulin Monoclonal antibodies to B cells—rituximab, ofatumumab Monoclonal antibodies to T cells—OKT3, alemtuzumab CD28 antagonist—abatacept IL2 receptor antatonist—basiliximab, daclizumab IL6 receptor antagonist—tocilizumab TNF inhibitors—infliximab, etanercept, others
Medication-induced hypogammaglobulinemia	Immunosuppressive medications—glucocorticoids, gold, D-penicillamine, sulfasalazine Anticonvulsants—carbamazepine, chlorpromazine, lamotrigine, oxcarbazepine, phenytoin, valproic acid, zonisamide Others—captopril
Miscellaneous	Splenectomy Trauma, burns Ionizing radiation

and *Moraxella catarrhalis* in acute sinusitis and *Staphylococcus*, gram-negative bacilli, and anaerobes in chronic disease. However, individuals with advancing HIV infection and progressive loss of immune function may not be able to mount the expected inflammatory responses. These patients present atypically with cough, weight loss or fever of unknown origin. With CD4 counts below 200 cells/mm^3, infections become increasingly refractory and with 50 cells/mm^3, unusual and opportunistic pathogens including *Pseudomonas aeruginosa, Legionella pneumophila, Klebsiella pneumonia, Listeria monocytogenes, Mycobacterium avium, Aspergillus fumigatus, Mucoraceae, Candida albicans,* CMV, *Pneumocystis jiroveci, Acanthamoeba,* and microsporidium become increasingly responsible.

Nasopharyngeal lymphoid hypertrophy and allergic rhinitis are local host factors predisposing to sinusitis. Early in HIV infection, nasopharyngeal lymphoid hypertrophy due to polyclonal B-cell activation has been reported in up to 88% of cases and decreases with worsening immune function.[98] Atopic disease is common and allergic rhinitis may be twice as common among

HIV-infected individuals compared with the general population.[99] Additionally, HIV-infected individuals may have thicker and more tenacious mucus with decreased mucociliary clearance.[100] In some populations, higher rates of smoking and cocaine use may occur.

Initial treatment of sinusitis among HIV-infected patients is similar to the general population. Among patients with partial responses to antibiotics, chronic disease, or CD4 counts below 200 cells/mm^3, antibiotic coverage should be expanded to include *Pseudomonas, Staphylococcus,* and anaerobes. Patients who fail to improve with empiric therapy, present with severe symptoms, or have CD4 counts below 50 cells per mm^3 should undergo sinus CT and endoscopic evaluation with sinus culture to evaluate for resistant or unusual organisms or underlying malignancy. Pediatric patients with hypogammaglobulinemia may benefit from immunoglobulin replacement.

Medications

Iatrogenic causes include immunosuppressive medications following transplant or for the treatment of autoimmune disease, chemotherapeutic agents for hematologic malignancies, biologic agents with immunomodulatory properties, and medications associated with secondary hypogammaglobulinemia.[89,90] The severity of adverse immune effects is dependent on the specific activity, dosage and duration of the drug, other concomitant immunosuppressive medications, and host factors including the nature of the underlying disease being treated and other medical comorbidities. For drug-induced hypogammaglobulinemia, the defects are generally mild and reversible if the medication can be discontinued.

Malignancies

Secondary hypogammaglobulinemia is common among individuals with lymphoproliferative disorders and plasma cell dyscrasias, specifically chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). Infections are a major cause of morbidity and mortality and due to both immune defects inherent to the underlying disease process as well as immune suppression due to chemotherapeutic regimens necessary to treat the disease. Consistent with other antibody deficiencies, infections associated with the underlying disease process are predominantly due to encapsulated bacteria and affect the sinopulmonary tract.[101,102] However, with increasingly potential chemotherapy regimens, severe infections with gram-negative organisms and opportunistic infections are seen. The hypogammaglobulinemia has been attributed at least in part to progressive B-cell dysfunction. T- and NK-cell abnormalities contribute to the overall immune dysfunction. Among patients with hypogammaglobulinemia, immunoglobulin replacement has been shown to decrease infections.[103,104] However, its effect on overall mortality remains controversial.[105]

Chronic Lymphocytic Leukemia

CLL is a generally indolent disorder characterized by clonal expansion of B cells.[106] It accounts for 30% of all leukemias in the United States.[107] It has a median age of diagnosis of 70 years and survival can be greater than 10 years for those with early stage disease. Ten percent present before 50 years of age. The majority of patients are asymptomatic in early disease and diagnosis is commonly made by the finding of lymphocytosis on laboratory testing requested for an unrelated problem. Infection accounts for up to 60% of deaths in CLL.[106]

Hypogammaglobulinemia as well as poor specific antibody production progressively develop in virtually all patients with CLL and their magnitude correlates to disease duration and stage, frequency of infections, and survival. In a study of 109 CLL patients with stored prediagnostic samples, immunoglobulin abnormalities were noted up to 10 years before diagnosis.[108] A natural history study of 247 patients with CLL reported hypogammaglobulinemia at diagnosis in 20%.[109] IgG levels < 600 mg/dL were found in 5% of patients with early disease and increased to over 20% with advancing disease. Similarly low IgA levels were found in 23% with early disease and increased to nearly 50% of patients. Decreased survival was associated with worsening IgG and IgA levels. Increased severity of infections has been shown with decreasing IgG levels with no infections in 58% of patients with normal immunoglobulin levels having no infections and severe infections in 47% of patients with IgG between 4 and 6.5 g/L and 100% of patients with IgG less than 4 g/L.[101] Progressively impaired responses to pneumococcal and influenza vaccination have been reported to correlate with advancing disease.[110,111]

Multiple Myeloma

MM is a plasma cell malignancy that accounts for 15% of all hematologic malignancies in the United States.[107,112] It has a median age of diagnosis of 69 years and at death 74 years. Less than 5% of patients present before 40 years

of age. When symptomatic, MM typically presents with bone pain due to clonal expansion in the marrow as well as invasion into surrounding bone and fatigue due to anemia. Plasma cells in nearly all patients produce a monoclonal immunoglobulin that may obscure the underlying antibody deficiency. There is concomitant suppression of the uninvolved immunoglobulins and poor antibody responses to vaccinations. In a review of 1027 patients with MM, hypogammaglobulinemia was present in 8%.[113] However, 90% had decreased levels of one or more of the unaffected immunoglobulin classes (IgG, IgA, or IgM) and 73% had decreased levels of both unaffected immunoglobulin classes. Poor response of pneumococcal vaccination has been associated with maximum benefit from IVIG replacement.[104]

Systemic Diseases and Other Underlying Host Factors

Malnutrition is the most common cause of immunodeficiency worldwide and leads to global immune suppression in proportion to the severity of hypoproteinemia and affecting both cell-mediated and antibody functions.[89] Deficiencies of zinc, iron, folate, pyridoxine, and vitamins A and D may further suppress immune function.[114-116] Extremes of age, pregnancy, and severe stress are also associated with immune dysfunction

Metabolic diseases including diabetes and chronic renal disease lead to phagocyte and T-cell dysfunction due to toxic effects of hyperglycemia and uremia.[89] Cirrhotic liver disease and decreased hepatic function lead to elevated levels of endogenous glucocorticoids and hypocomplementemia. Splenectomy is associated with marked susceptibility to infections by encapsulated bacteria.

Nephrotic syndrome leads to hypogammaglobulinemia associated with increased protein loss in the urine.[90] Infections are a leading cause of mortality among children but adults appear less susceptible. Similarly, hypogammaglobulinemia may develop in individuals with protein losing enteropathies including celiac disease, inflammatory bowel disease, and intestinal lymphangiectasia. Despite hypogammaglobulinemia, production of antibodies is thought to remain functional and the role of immunoglobulin supplementation is controversial.

CONCLUSION

Refractory sinusitis is a common disorder with marked morbidity. Varied host factors including anatomic abnormalities, allergy, and other environmental exposures as well as underlying immunodeficiency contribute to its severity. Immunodeficiency encompasses a vast spectrum of disorders, due to intrinsic disorders of the immune system and secondary to conditions such as nutritional status, infections, medications, or various systemic diseases. Among patients with severe sinus disease, immunologic evaluation may provide critical information regarding optimal management of the sinusitis. Additionally, early recognition of underlying immune problems can prevent or minimize further deterioration of health. Guidelines of when to consider underlying immunodeficiency have been published and screening evaluation is benign. There remains controversy regarding when screening for immunodeficiency should be initiated. Further research will be necessary to determine optimal protocols.

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CHAPTER

27

Acute Rhinosinusitis

Yan W Ho, Satish Govindaraj

CLASSIFICATION AND DIAGNOSIS OF ACUTE RHINOSINUSITIS

Rhinosinusitis encompasses a broad range of diseases all characterized by inflammation of one or more paranasal sinuses. The diagnosis of acute rhinosinusitis is based on subjective and objective findings of sinusitis that lasts up to 4 weeks after the onset of symptoms. Depending on the duration of symptoms, it is important to distinguish acute rhinosinusitis from recurrent-acute, subacute, and chronic rhinosinusitis.

Acute-recurrent rhinosinusitis: Four or more episodes of acute rhinosinusitis with symptom-free periods in between

- Subacute rhinosinusitis: 4–12 weeks of symptoms
- Chronic rhinosinusitis: 12 weeks or more of symptoms.

When diagnosing acute rhinosinusitis, it is also important to distinguish between viral and bacterial etiologies. Efforts to distinguish between viral and bacterial acute rhinosinusitis based on symptomatology alone have been largely unsuccessful. As a result, recent guidelines have encouraged the use of disease severity and time-course as a way to distinguish viral versus bacterial etiologies. According to the clinical practice guidelines, all acute rhinosinusitis symptoms should be diagnosed as viral if the duration of symptoms is less than 10 days and if they are not worsening. However, if the symptoms persist beyond 10 days or worsen after initial improvement, then the diagnosis of acute bacterial rhinosinusitis (ABRS) is applicable. [1]

Symptoms that are most sensitive and specific for acute rhinosinusitis include mucopurulent drainage (anterior or posterior), nasal obstruction/congestion, and facial pressure/pain/fullness. Other symptoms include hyposomia or anosmia, headache, fever, cough, malaise, fatigue, dental pain (maxillary), ear fullness, or otalgia. Various diagnostic criteria have been proposed by a number of groups including the Rhinosinusitis Initiative, the Joint Task Force on Practice Parameters, and most recently the Clinical Practice Guidelines: Acute Sinusitis.

In 2004, a collective statement called the Rhinosinusitis Initiative (RI) was published. The five national groups include The American Academy of Allergy, Asthma and Immunology (AAAAI), The American Academy of Otolaryngic Allergy (AAOA), The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), The American College of Allergy, Asthma and Immunology (ACAAI), and the American Rhinologic Society (ARS). According to their recommendations, rhinosinusitis should be diagnosed based on a series of major and minor symptoms as listed in Table 27.1. Any patient with at least two major symptoms or one major symptom with two minor symptoms probably has a diagnosis of rhinosinusitis.[2]

The most recent guidelines from the clinical practice guideline on adult sinusitis, however, do not distinguish between major and minor symptoms, but instead focus on the three cardinal symptoms of rhinosinusitis: mucopurulent drainage, nasal obstruction, and facial discomfort. Specifically, the diagnosis requires the presence of purulent nasal discharge *and* either nasal obstruction or facial pain–pressure–fullness (Table 27.2).

As with other disease processes, an accurate diagnosis also includes measurement of vital signs and a full head and neck physical examination. This will be discussed in greater detail later in this chapter.

Table 27.1: Symptoms associated with rhinosinusitis[2]

Major symptoms	*Minor symptoms*
Purulent anterior nasal drainage	Headache
Purulent-discolored posterior nasal drainage	Ear pain–pressure–fullness
Nasal obstruction blockage	Halitosis
Facial congestion fullness	Dental pain
Facial pain–pressure–fullness	Cough
Hyposmia–anosmia	Fever (all nonacute)
Fever (acute only)	Fatigue

Table 27.2: Clinical practice guidelines diagnostic criteria of acute rhinosinusitis[1]

Term	*Definition*
Acute rhinosinusitis	Up to 4 weeks of purulent nasal drainage (anterior, posterior, or both) accompanied by nasal obstruction, facial pain–pressure–fullness, or both: (a) Purulent nasal discharge is cloudy or colored, in contrast to the clear secretions that typically accompany viral upper respiratory infection, and may be reported by the patient or observed on physical examination (b) Nasal obstruction may be reported by the patient as nasal obstruction, congestion, blockage, or stuffness, or may be diagnosed by physical examination (c) Facial pain–pressure–fullness may involve the anterior face, periorbital region, or manifest with headache that is localized or diffuse.
Viral rhinosinusitis (VRS)	Acute rhinosinusitis that is caused by, or is presumed to be caused by, viral infection. A clinician should diagnose VRS when: (a) Symptoms or signs of acute rhinosinusitis are present less than 10 days and the symptoms are not worsening.
Acute bacterial rhinosinusitis (ABRS)	Acute rhinosinusitis that is caused by, or is presumed to be caused by, bacterial infection. A clinician should diagnose ABRS when: (a) Symptoms or signs of acute rhinosinusitis are present 10 days or more beyond the onset of upper respiratory symptoms, or (b) Symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement (double worsening).

EPIDEMIOLOGY AND IMPACT OF ACUTE RHINOSINUSITIS

According to data gathered through the National Health Interview Survey for calendar years 1997–2006, the annual disease prevalence of sinusitis was 15.2%. In the United States, it is estimated that approximately 20 million cases of ABRS occur annually.

Acute rhinosinusitis is a major contributor to office visits in the primary care office. In the United States, from 1999 to 2002, there were an estimated 3,116,142 visits annually due to acute rhinosinusitis, representing 0.30% of all ambulatory visits.[3] In 1985–1992, sinusitis was the 5th most common diagnosis for prescribing antibiotics, and in 1996, sinusitis led to $3.5 billion US dollars in healthcare expenditures.[4]

The burden of acute rhinosinusitis on patient quality of life is also substantial. Patients with sinusitis are significantly more likely to visit the emergency room, spend over $500 annually on healthcare, and see a medical specialist. Also, patients with sinusitis missed an average of 5.67 workdays annually versus 3.74 workdays for those without. Comparatively, healthcare expenditures due to sinusitis far exceeded those of ulcer disease, acute asthma, and hay fever.[5]

Surveys have been developed in order to objectively measure the burden of disease on patient's quality of life.[6] Based on the sinonasal outcome tests (SNOT-20, SNOT-22), a modified SNOT-16 survey has been developed specifically to address the impact of acute rhinosinusitis on quality of life of patients. Patients are asked to rate the severity and frequency of their symptoms from a

Table 27.3: Modified SNOT-16[8]

Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Mild or Slight Problem	Moderate Problem	Severe Problem	5 Most Important Items
1. Need to blow nose	0	1	2	3	○
2. Sneezing	0	1	2	3	○
3. Runny nose	0	1	2	3	○
4. Cough	0	1	2	3	○
5. Postnasal discharge	0	1	2	3	○
6. Thick nasal discharge	0	1	2	3	○
7. Ear fullness	0	1	2	3	○
8. Headache	0	1	2	3	○
9. Facial pain/pressure	0	1	2	3	○
10. Wake up at night	0	1	2	3	○
11. Lack of a good night's sleep	0	1	2	3	○
12. Wake up tired	0	1	2	3	○
13. Fatigue	0	1	2	3	○
14. Reduced productivity	0	1	2	3	○
15. Reduced concentration	0	1	2	3	○
16. Frustrated/restless/irritable	0	1	2	3	○
Please mark the most important items affecting your health (maximum of 5 items)_____↑					

scale of 0 to 3, and then are asked to check their five most important symptoms. The final score is an average of the 16 symptoms[7] (Table 27.3). This is a useful tool not only for initial evaluation but also for subsequent monitoring of symptoms after treatment.

PATHOGENESIS

The pathophysiology of acute rhinosinusitis commonly involves predisposing factors that can be divided generally into three categories: (1) environmental, (2) anatomical and (3) systemic. They commonly occur at the same time, and can predispose patients to not only acute infections, but also contribute to development of chronic sinusitis.

Environmental

Viral Infection

Acute bacterial rhinosinusitis is often preceded by an acute viral upper respiratory tract infection. After the first 10 days of a viral upper respiratory tract infection, approximately 0.5% of patients will go on to develop a bacterial acute rhinosinusitis. The most common bacterial organisms are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. However, there is evidence that *Staphylococcus aureus* is becoming a major contributor to the development of acute rhinosinusitis.[9] If these acute infections are not resolved or become recurrent, *S. aureus*, anaerobic, and Gram-negative organisms such as pseudomonas aeruginosa become predominant.[10] The progression of rhinosinusitis from viral to bacterial is illustrated in Figure 27.1.

The transition between viral and bacterial acute rhinosinusitis has been studied extensively, and is thought to be secondary to altered mucociliary clearance and colonization of bacteria. The inflammation from the viral illness temporarily stuns the cilia, mucus remains trapped in the sinuses, and bacteria proliferate. Multiple studies have shown that bacterial cultures from the sinonasal tract are more likely to be positive in patients suffering from

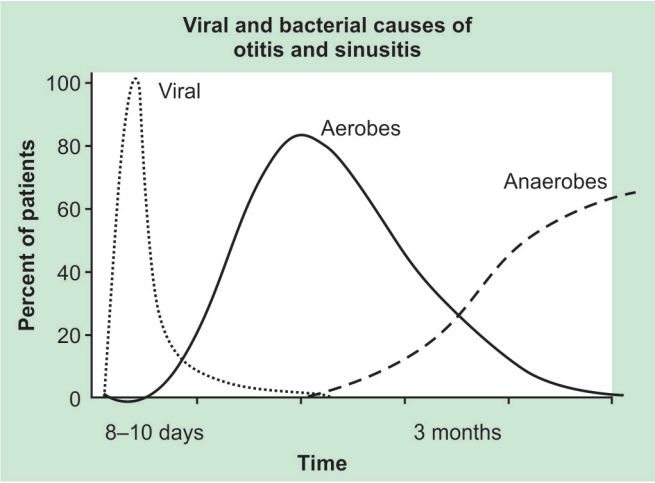

Fig. 27.1: The progression from viral to bacterial rhinosinusitis. Redrawn from Brook.[9]

an acute viral rhinosinusitis. In one study, osteomeatal complex (OMC) cultures in patients with viral URI are five times more likely to be positive for bacteria than in healthy patients. Nasal cavity cultures in ill patients are also positive significantly more often than well patients.[11]

Allergic Rhinitis

The association between allergic rhinitis and sinusitis has long been recognized, and has been attributed to decreased mucociliary clearance and mucus retention in the sinuses. The inflammation caused by the allergic response causes mucosal membranes to become edematous, thereby obstructing the outflow of mucus through sinus ostia. This leads to a buildup of mucus within sinus cavities, oxygen stores are depleted, and bacteria proliferate in this acidic environment.[12] Most believe that the inflammation caused by allergic reaction causes obstruction of the sinus ostia, but in addition, some believe that the allergic response itself also causes an influx of eosinophils in the nasal cavity and the maxillary sinuses.[13] The use of technetium-labeled rhinoscintigraphy has also demonstrated decreased mucociliary clearance in patients with allergic rhinitis.[14]

Cigarette Smoke

Tobacco exposure in the form of smoking or second-hand smoke has been shown to increase bacterial and viral infections.[15,16] In a study comparing the microbiology of ABRS found that smokers were more likely to have cultures positive for *S. aureus*, methicillin-resistant *S. aureus* (MRSA), and β-lactamase producing bacteria.[17]

Pollution/Exposures

The link between pollution and other exposures to acute rhinosinusitis is less defined, but nonetheless, a correlation has been shown. In a study following rescue and recovery workers who were exposed to the 9/11 World Trade Center bombings were found to have more frequent upper respiratory tract infections and rhinosinusitis in the short term.[18] Long-term studies are currently being conducted.

Anatomical

Sinonasal Anatomy

Abnormal sinonasal anatomy may contribute to the development of acute rhinosinusitis and if left untreated, recurrent acute, subacute, or chronic sinusitis. The presence of septal deviation, septal spurs, turbinate hypertrophy, Haller cells, Agger nasi cells, or an obstructive mass, like a tumor or polyp, can all pose as barriers to proper mucociliary clearance. Arguably, the impairment of mucociliary function due to local or systemic disease can also be considered as an anatomical predisposition to the development of acute rhinosinusitis. (This will be discussed in greater detail under systemic disease section). When comparing computed tomography (CT) scans of patients with refractory acute rhinosinusitis and patients without sinonasal disease, patients in the first group were statistically more likely to have septal deviation toward the affected side.[19] Patients with recurrent acute rhinosinusitis were significantly more likely to have Haller cells and smaller infundibular widths (mean of 0.591 mm vs. 0.823 mm in unaffected individuals). They also were more likely to have concha bullosa and impinging septal spurs, although the difference was not statistically significant.[20]

Dental anatomy, particularly its relation to the maxillary sinus, can predispose patients to maxillary sinusitis. Depending on the development of the maxillary sinus, the maxillary teeth may be positioned very close to the inferior boundary of the sinus. Dental caries or gingivitis can easily spread into the maxillary sinuses and cause an acute maxillary sinusitis. Despite the fact that a minority of patients with acute maxillary sinusitis may have radiographs showing intrusion of maxillary dentition, the clinician should not assume that an incidental finding of dental intrusion is the cause of the sinusitis. In fact, dental intrusion into the maxillary sinus on radiographs does not correlate reliably with the manifestation of rhinosinusitis.[19] The same anatomic abnormalities contribute

to persistent and recurrent rhinosinusitis and will be discussed in greater detail in those chapters.

Ciliary Dysfunction

In many cases of rhinosinusitis, acute and chronic, ciliary dysfunction is thought to play a role in the pathophysiology. Most often, it is caused by environmental, infectious, or inflammatory factors, but in rare cases, a congenital disorder including Kartagener syndrome or another type of primary ciliary dyskinesia is involved.[21] Primary ciliary dyskinesia is a disorder with an autosomal recessive inheritance affecting the function of cilia. It is estimated to affect 1 in 7,000 to 1 in 60,000 people. Manifestations include chronic otitis media, subfertility, and chronic rhinosinusitis.[22] Usually, the workup of these diseases is not indicated unless acute rhinosinusitis develops into recurrent acute or chronic rhinosinusitis.

Systemic Disease

Immunodeficiencies (Congenital or Acquired)

It is important to recognize the role of immunodeficiencies in patients who have recurrent or chronic rhinosinusitis. The workup of acute rhinosinusitis should not routinely prompt an extensive immunological workup unless indicated by other signs and symptoms. The most common congenital immunodeficiencies that present with recurrent rhinosinusitis include selective IgA deficiency, common variable immunodeficiency, Wiskott–Aldrich syndrome ataxia telangiectasia, hypogammaglobulinemia, myelokathexis syndrome, and caspase-8 deficiency.[12] Commonly acquired and iatrogenic types of immunodeficiencies include HIV/AIDS, chemotherapy, transplantation, and the use of immunomodulating medications. (The workup and treatment options will be discussed in another chapter.)

GERD/Laryngopharyngeal Reflux

Reflux disease is increasingly being implicated as a contributor to chronic rhinosinusitis, but its effects on the development of acute rhinosinusitis have yet to be studied.

Cystic Fibrosis

This disorder is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7. This results in the abnormal transport of chloride ions leading to altered viscosity of mucous secretions. CF is not as relevant in isolated cases of acute sinusitis but should be part of the workup for chronic rhinosinusitis especially in patients with polyps.

Asthma

The association between asthma and chronic rhinosinusitis has long been recognized, but a causal relationship has yet to be illuminated. Although the evidence is focused primarily on the effect of asthma on chronic rhinosinusitis, this phenomenon is also seen in acute rhinosinusitis. Patients who are suffering from viral upper respiratory tract infections are more likely to experience asthma exacerbations and have more severe attacks.[23] Recently, multiple individuals also propose a "united airway disease" or "global airway disease" that links upper and lower airway diseases including allergy, sinusitis and asthma.[24] The evidence linking asthma and chronic rhinosinusitis will be discussed in further detail in another chapter.

CLINICAL FINDINGS

In addition to a complete history, an accurate diagnosis requires a full, comprehensive physical examination. A good physical examination can help to narrow the differential diagnosis as well as detect complications of acute rhinosinusitis. During the basic head and neck examination, the examiner should focus on the forehead, maxilla, and periorbital region to detect erythema, swelling, or tenderness to palpation in those areas overlying the sinuses. Facial cellulitis may be an indication that an acute rhinosinusitis has spread outside of the sinuses. A thorough ophthalmologic examination with extraocular movements and visual acuity should be performed because it may reveal changes in vision or extraocular movement secondary to subperiosteal or intraorbital abscess. Tenderness to palpation of the temporomandibular joint (TMJ) may guide the clinician toward an alternate cause for facial or ear pain. A good intraoral examination, specifically of dentition, might reveal oroantral fistulas or dental causes for sinusitis or facial pain. A complete neurologic examination may be necessary to detect or exclude complications such as meningitis, encephalitis, intracranial abscess, or nerve palsies.

Perhaps the most relevant finding of all is the detection of purulent fluid in the nasal cavity or posterior nasopharynx.[25] This clinical finding has been shown to have diagnostic value because it correlates with radiographic evidence of sinus disease[26] as well as positive cultures from the maxillary antrum.[1]

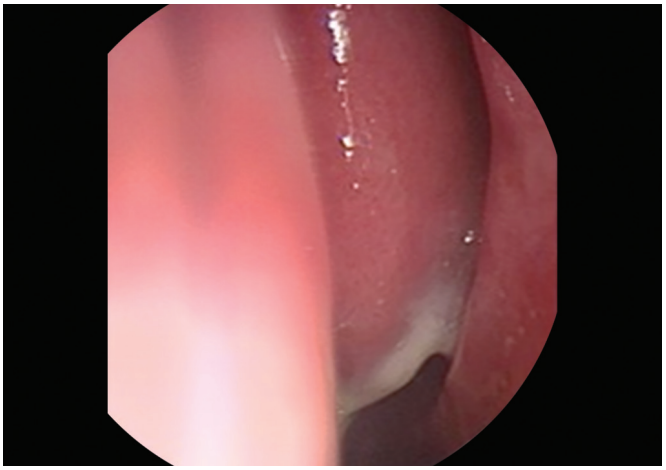

Fig. 27.2: Nasal endoscopy of left middle meatus with purulent drainage noted in infundibulum. Patient had an acute maxillary sinusitis.

Since both nasal endoscopy and radiographs have similar specificity and sensitivity for detecting acute rhinosinusitis, if nasal endoscopy is available, some believe that it should be done as a first line diagnostic tool.[27] Clinicians who are equipped with nasal endoscopes have a particular advantage of visualizing the nasal passages. After giving local decongestants and/or anesthetic agents, nasal endoscopy can be used to provide direct visualization of the turbinates, nasal septum, OMC, nasopharynx, and eustachian tube orifices. Any anatomic abnormalities may also be detected at this time. During acute rhinosinusitis, nasal mucosa may be edematous or erythematous, and purulent material may be draining from the sinus ostia or pooling within the nasal passages (Fig. 27.2). Although cultures are not required for the diagnosis of acute rhinosinusitis, nasal endoscopy provides a particularly useful tool for culture-directed antimicrobial therapy.

FURTHER DIAGNOSTIC MODALITIES

Nasal Cultures

Obtaining nasal cultures can facilitate culture-directed antimicrobial treatment, but the routine use of nasal cultures has not been proven to be useful or cost-effective for acute rhinosinusitis. If patients are immunocompromised or if there is concern of drug resistance, nasal cultures may be performed to help direct therapy. Traditionally, cultures from the OMC or middle meatus are preferred under direct vision. However, there is evidence that cultures of the nasopharynx correlate well with cultures of the middle meatus under direct endoscopic visualization, and may be useful in the primary care setting.[28] In light of the fact that *S. aureus* is becoming more of a major organism in acute rhinosinusitis and the three traditional organisms are becoming more drug resistant,[29] nasal cultures may become a more important tool in the workup of acute rhinosinusitis.

Laboratory Testing

Routine use of laboratory tests is deemed to be unnecessary in cases of acute rhinosinusitis. The diagnosis can be established solely by a good history and examination. However, if the disease is refractory to initial treatment or becomes recurrent or chronic, further workup to rule out immunodeficiencies, CF, Wegener granulomatosis, sarcoidosis, Churg-Strauss disease, or other autoimmune diseases may be necessary.

Allergy or Skin Testing

In patients with evidence of atopy or allergy, skin and laboratory testing can be conducted to investigate if allergy to environmental exposures may be contributing to the severity or frequency of rhinosinusitis. This may also lead to treatments that can help decrease the severity and frequency of sinus disease.

IMAGING

Given that acute rhinosinusitis can be diagnosed based on the history and physical examination, imaging is not a cost-effective method in the diagnosis of acute rhinosinusitis. In complicated or recurrent cases, however, it may be an adjunctive diagnostic tool.

Radiographs

X-rays in the four traditional views (Water's, Caldwell's, lateral, and submental) may be useful in uncertain or recurrent cases of acute rhinosinusitis. Water's view (Fig. 27.3), with the occiput tipped down and patient's chin and nasal tip against the plate, has good visualization of the maxillary sinuses with a positive predictive value of 82.5% and negative predictive value of 76.9%.[31] Caldwell's view, with the forehead and nasal tip against the plate, provides a good view of the ethmoid and frontal sinuses. The lateral and submental views allow visualization of the sphenoid and posterior ethmoid sinuses. A normal X-ray, especially in the frontal or maxillary sinuses, has a good negative predictive value (90–100%) but has a poor positive predictive value (as low as 80%).[32]

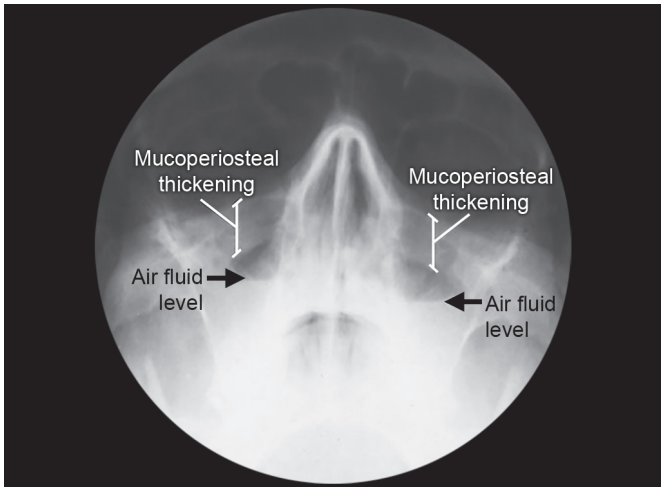

Fig. 27.3: Water's view of acute sinusitis. Mucoperiosteal thickening can be seen as well as air-fluid levels bilaterally.[30]

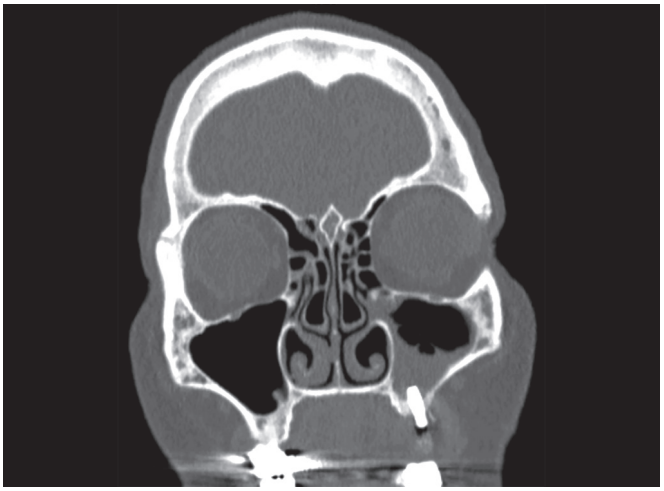

Fig. 27.4: Noncontrast CT scan of the sinuses with an acute left odontogenic maxillary sinusitis. Patient has an air fluid level in the left maxillary sinusitis with a dental implant placed into the floor of the maxillary sinus. Patient required maxillary antrostomy to clear the infection.

Ultrasound

The use of ultrasound in the diagnosis of acute rhinosinusitis is not mentioned as part of the clinical practice guidelines. However, in the setting of the primary care office, there is some preliminary evidence to support the use of an office ultrasound device that can be used to detect air-fluid levels in the maxillary sinus. Diagnosis of maxillary sinusitis using ultrasound in addition to history and physical examination had a sensitivity of 87% and negative predictive value of 85%.[33]

Computed Tomography

Computed Tomography (CT) of the paranasal sinuses is not recommended as part of the routine workup for acute rhinosinusitis. In cases with severe disease, immunocompromised state, or suspected complications, several guidelines including the rhinosinusitis initiative and the clinical practice guidelines advocate CT without IV contrast as the preferred imaging technique.[34]

According to the ACR Appropriateness Criteria proposed by the American College of Radiology, CT is the imaging method of choice for inflammatory sinonasal diseases. Coronal CT without contrast provides good anatomic detail of the paranasal sinuses. Contrast is not generally needed for routine sinus imaging. The application of cone-beam CT has recently expanded to sinonasal disease and although this technique offers some advantages like convenience of office use and reduction in radiation dosage, its routine use has not been well studied in cost-effectiveness and efficacy. Similarly, single-photon-emission CT has not been shown to be useful in the diagnosis of acute rhinosinusitis.[35]

Common findings in a CT sinus include air-fluid levels and mucosal thickening (Fig. 27.4). The latter finding usually is an indicator of chronic rhinosinusitis, but may be seen in acute rhinosinusitis. The absence of periosteal thickening and sclerosis may direct the clinician away from a diagnosis of chronic sinusitis.[36]

Magnetic Resonance Imaging (MRI)

Similar to all of the other aforementioned imaging modalities, MRI is not used routinely for acute rhinosinusitis unless there are signs of aggressive disease or cases with complications. MRI provides better soft tissue information (useful for intracranial, intraorbital, and extrasinonasal manifestations of rhinosinusitis), especially when differentiating malignant and inflammatory causes of rhinosinusitis. In addition, it does not pose a radiation exposure concern. The indications for CT with or without contrast and MRI are outlined in Table 27.4.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute rhinosinusitis is broad (Table 27.5). Aside from distinguishing it from recurrent acute, subacute, and chronic sinusitis as defined above,

Table 27.4: Comparing CT and MRI in rhinosinusitis[11]

Modality	*Indications*
CT without contrast (coronal views with bone windows)	Images bone, sinus anatomy, ostiomeatal complex, and shows soft tissue-air-bone contrast Indications: • Recurrent acute sinusitis • Chronic sinusitis • Preoperative for sinus surgery • Nasal polyposis • Persistent nasal congestion obstruction • Immunocompromised patient with fever • Dentomaxillary pain • Facial pressure headache unresponsive to medical therapy • Anosmia after appropriate workup
CT with contrast (coronal and axial views)	Allows for some degree of differentiation of soft tissue opacification Indications: • Complications of sinusitis (periorbital edema, subperiosteal abscess) • Sinonasal tumor
MRI with contrast (need to specifically request coronal views)	Provides excellent soft tissue differentiation (e.g. tumor vs. retained volume) but does not image bone or the bony anatomy required for surgery. Images the nasal cycle and thus might be oversensitive for sinusitis Indications: • Skull base dehiscence with opacification • Unilateral sinonasal opacification (on CT) • Sinonasal process with cranial extension • Expansile sinonasal mass with bony erosion (remodeling) • Sinonasal mass with orbital extension • Biopsy-proved tumor • Fungal sinusitis

Table 27.5: Differential diagnosis of acute rhinosinusitis

- Allergic rhinitis
- Nonallergic rhinitis
  - Infectious rhinitis
  - Vasomotor rhinitis
  - Eosinophilic nonallergic rhinitis
  - Rhinitis medicamentosa
  - Rhinitis due to pregnancy, hypothyroidism, Horner syndrome
- Temporomandibular joint disease
- Headache (migraines)
- Trigeminal neuralgia
- CSF rhinorrhea
- Sinus neoplasms
- Nasal polyposis
- Autoimmune disease
  - Wegeners granulomatosis
  - Sarcoidosis
- Odontogenic diseases

acute rhinosinusitis has to be differentiated from a number of other disease processes that can produce similar symptoms.

Rhinitis (Allergic and Nonallergic)

It is often very difficult to distinguish sinusitis from rhinitis based on history alone. The constellation of symptoms including rhinorrhea, congestion, postnasal drip, sneezing, and ocular or nasal pruritus can often occur in acute rhinosinusitis as well. Rhinitis can be divided into two basic groups: allergic and nonallergic. Allergic rhinitis is, by definition, an IgE-mediated sensitivity to an allergen, and can be diagnosed via skin prick testing or serum testing. Nonallergic rhinitis includes atrophic, vasomotor, nonallergic rhinitis with eosinophilia, gustatory, and drug induced.[37]

The features that most distinguish acute rhinosinusitis from rhinitis are part of the physical examination. In acute rhinosinusitis the nasal mucosa might be red and swollen

but in allergic rhinitis, the turbinates are boggy and pale. In acute rhinosinusitis, nasal discharge may be clear at first, but will often change into gray, yellow, or green. In allergic rhinitis, the discharge usually is watery and clear, and sometimes yellow. On anterior rhinoscopy or endoscopy examination, purulent material may be seen in the nasal passages or in the OMC, confirming the diagnosis of acute rhinosinusitis. In rhinitis of all types, treatment consists of anti-inflammatory medications as opposed to primarily antimicrobials for acute rhinosinusitis.

Temporomandibular Joint Disease

Similar to acute rhinosinusitis, patients with TMJ disease may present with facial pain. The key aspect to identifying pain due to TMJ is the location, which tends to be preauricular, radiating to the temple or neck. It is usually triggered by movement of the jaw or by palpation of the joint or masticator muscles. There might even be an audible click on jaw opening.[38] The etiology of TMJ pain may be myogenous or arthrogenous, which may require a combination of nonsurgical (analgesics, occlusive splints, physical therapy) or even surgical therapy (arthroscopy).[39]

Headache

Headache is a common complaint in the primary care office. A good history can help guide the clinician in differentiating a headache caused by an acute rhinosinusitis from other various types of headaches. Depending on which sinuses are affected, the pain can be referred to various regions of the head, or can be diffuse. Maxillary sinusitis usually refers to the cheek, palate, maxilla, or upper dentition, while ethmoid sinusitis refers to the area between the eyes. Frontal sinusitis can project to the frontal and orbital regions, whereas sphenoid sinusitis may refer to any region of the head or diffusely.[38]

It is important to distinguish headache from acute rhinosinusitis from the entity known as sinus headache, which is actually a type of migraine headache. Patients with sinus headaches often complain of facial pressure or pain over the cheeks, forehead, and around the eyes, which may be accompanied by nasal congestion, lacrimation, rhinorrhea, or eyelid edema. Their constellation of symptoms poses a striking resemblance to rhinosinusitis. However, workup of these patients reveals minimal to no sinus disease, and the severity of symptoms does not correlate with endoscopic or radiologic findings. Upon empiric treatment with triptans, a medication commonly used for migraine, many of these patients experience an improvement in symptoms.[40]

Trigeminal Neuralgia

Although some patients with acute rhinosinusitis may complain of facial pain as their primary symptom, facial pain can also be caused by trigeminal neuralgia, also called "tic douloureux." This disease is characterized by brief, repetitive, lancing facial pain that is unilateral. The distribution of pain can be any one or more of the three distributions of the trigeminal nerve. When divisions 1 or 2 are involved, it can often be mistaken for sinus pressure or pain. Unlike facial pressure caused by acute rhinosinusitis, these painful attacks can be triggered by a cutaneous stimulus, including chewing, shaving, and wind blowing on the face. Medical treatment, usually with carbamazepine, oxcarbazepine, or other anticonvulsants are the first line of treatment, followed by surgical therapy, which involves either transecting a branch of the trigeminal nerve or performing a microvascular decompression of the nerve.[41]

Sinus Neoplasms

When acute rhinosinusitis is refractory to medical treatment or when an abnormality is found on physical examination, the possibility of a sinus neoplasm should be considered. Various imaging modalities are available to assist in distinguishing neoplasms. CT scans can give bony detail, but MRI is better at distinguishing inflammatory causes from neoplastic causes of rhinosinusitis.[36] The most common neoplasms in the sinonasal tract are squamous cell carcinoma, adenoid cystic carcinoma, and adenocarcinoma. Others include neuroectodermal (melanoma, olfactory neuroblastoma), sinonasal undifferentiated carcinoma, and metastatic lesions.[42]

Odontogenic Diseases

Odontogenic causes of maxillary rhinosinusitis are relatively uncommon, although it causes an estimated 10–12% of all cases of maxillary rhinosinusitis.[43] In the evaluation of a patient with acute rhinosinusitis, it is prudent to look for an odontogenic source for the infection. Any history of an infected tooth or recent dental surgery should trigger a detailed dental examination. However, patients who have odontogenic disease without acute rhinosinusitis

may still complain of similar symptoms, and it is prudent to consider this possibility. Common dental infections that may be seen include dental caries, periodontal disease, and gingivitis.[44]

MEDICAL TREATMENT

In the management of acute rhinosinusitis, the clinician must take into account the duration of illness, the severity of the symptoms, and the reliability of the patient. According to the clinical practice guidelines, if symptoms are present within 10 days of onset and are not worsening, the presumptive diagnosis is acute viral rhinosinusitis. The treatment of acute viral rhinosinusitis is mainly symptomatic, with the use of antipyretics and analgesics. Topical or oral decongestants may be used for patients who complain of nasal congestion. In addition, mucolytics and expectorants may be useful adjunctive treatments in certain patients.

There is limited evidence to recommend the use of systemic or topical steroids and antihistamines in treating acute viral rhinosinusitis. However, there is growing evidence that they may have a role in treatment to relieve nasal congestion and facial pain, especially if a patient has underlying allergic rhinitis. When patients have worsening disease or double worsening that persists longer than 10 days, the diagnosis can then be considered ABRS.

At this point, watchful waiting without the use of antibiotics is considered a valid option if the patient is reliable, and has mild disease. (Mild disease involves mild pain and temperature of less than 101° F.)[1] In addition, the length of time for watchful waiting should not exceed 1 week. If the patient cannot be reliably contacted, or cannot return for follow-up visit, the clinician should consider initiating antibiotic treatment. This is one of many reasons why it is important to take into account patient reliability and access to care in the treatment of rhinosinusitis.

The mainstay of treatment for ABRS is the use of antibiotics but a number of additional adjunctive therapies are commonly used and have been shown to be effective in alleviating symptoms and improving recovery times. These include analgesics and antipyretics, steroids, irrigations, decongestants, mucolytics, and allergy management. Each of these will be discussed below.

Antibiotics

Choosing the right type of antibiotic for the treatment of ABRS can be challenging, but recent guidelines have been developed to help in this decision making. These guidelines help to provide adequate coverage of organisms with low cost and low side effect profile while attempting to mitigate the development of drug resistance. Additional recommendations are provided based on a number of different considerations for the patient, including whether or not the patient has an allergy to penicillin, whether the patient had recent antibiotic use (within 4–6 weeks), or if the patient has close contacts with nursing homes or daycare facilities.

Most guidelines advocate for the use of amoxicillin or amoxicillin–clavulanate as a first line of treatment based on its efficacy, low cost, and low side effect profile. Amoxicillin–clavulanate can be used in communities with a prevalence of β-lactamase producing bacteria. Those with an allergy to penicillin may be given macrolides or trimethoprim-sulfamethoxazole. The adequate duration of therapy is still under investigation. Some studies show that 3–5 days of therapy is enough, although most studies are performed with 10 days of therapy.[1,12] There are many studies comparing these antibiotic choices with cephalosporins, fluoroquinolones, and other antibiotics, but these have specific applications that will be discussed in another chapter.

Analgesics and Antipyretics

Among the many symptoms of acute rhinosinusitis, facial pressure, facial pain, headache, or toothache are often the chief complaints. However, some patients may not be as forthright about having pain. Therefore, many of the current recommendations highlight the importance of inquiring about pain as well as treating pain in acute rhinosinusitis. The choice of analgesic can range from acetaminophen or nonsteroidal anti-inflammatory drug to opioids depending on the pain level expressed by the patient. Similar to acute viral rhinosinusitis, the use of antipyretics may be indicated in febrile patients for symptomatic relief.

Steroids

The role of oral or topical steroids in the treatment of ABRS is still under investigation, although there may be some benefit of using intranasal topical steroids for the treatment of some patients with or without allergic rhinitis. Adjunctive therapy using systemic steroids can theoretically help to decrease discomfort related to nasal congestion and facial pain. The effectiveness of this approach is still under debate and under investigation. In 2011,

a Cochrane review was published which suggested that oral steroids may provide short-term relief of symptoms when used in conjunction with oral antibiotics.[45] Since then, however, there have been randomized, double-blinded clinical trials showing that although systemic steroids had low risk of side effects (gastrointestinal disturbance, mood changes, sleep disturbance), there was no significant improvement in symptoms compared with the placebo group.[46] The decision whether or not to use systemic steroids in the treatment of ABRS has to take into consideration the comorbidities of the patients, especially in the setting of diabetes and the risk of hyperglycemia, obesity and the risk of weight gain, and osteoporosis and the risk of bone fractures.

In the past, the use of intranasal corticosteroids has been recommended for patients who had underlying allergic rhinitis, but recent evidence may suggest that it has some benefit in most patients with ABRS regardless of underlying atopic disease. A Cochrane view of double-blinded, placebo-controlled trials comparing treatment with or without intranasal corticosteroids showed that those treated with topical steroids (alone or in combination with antibiotics) had a statistically significant improvement or resolution of symptoms compared with placebo. This effect was also shown to be dose dependent.[47] In fact, the Canadian clinical practice guidelines, published in 2011, gave a strong recommendation of using intranasal corticosteroids as a monotherapy for mild-to-moderate acute rhinosinusitis.[48] For more in-depth discussion on systemic and topical therapies, please refer to Chapter 36.

Nasal Irrigations

This category of treatments encompasses a large variety of delivery methods (sprays, squeeze bottle, neti pots), concentrations (isotonic or hypertonic), and additives (antibiotic ointments), but most of these methods are applied in the setting of chronic rhinosinusitis. In many of the studies on acute rhinosinusitis, the delivery method is low pressure via squeeze bottles or gravity flow using neti pots, and the solution is either isotonic or hypertonic with no additives.

Although nasal saline irrigations have been extensively shown to be effective in the management of chronic rhinosinusitis, there has yet to be conclusive evidence showing its efficacy in acute rhinosinusitis.[49] There was a randomized controlled study comparing hypertonic and isotonic irrigations with no irrigations, which showed a mild benefit in the use of saline irrigations in decreasing days of symptoms, but the difference was not statistically significant.[50] Despite the paucity of evidence showing the efficacy of nasal saline irrigations, given its low cost and low side effect profile, it remains a useful adjunctive therapy in the symptomatic relief for acute rhinosinusitis.[51]

Decongestants and Mucolytics

This group of medications can help to target specific symptoms that patients may have in acute viral or bacterial rhinosinusitis. Systemic or topical decongestants (pseudoephedrine, phenylephrine, oxymetazoline) are useful in patients who complain of nasal obstruction or congestion. Topical decongestants have the advantage of acting directly on the mucosa of the nasal cavity but do not typically reach the sinuses themselves. Also there is a potential for rebound effect, or rhinitis medicamentosa, in prolonged usage when the mucosa becomes more edematous after treatment is stopped. Most clinicians advise patients to stop using topical decongestants such as oxymetazoline after 3 days.

There is insufficient evidence to support the routine use of expectorants, or mucolytics, in patients with acute rhinosinusitis. But in certain cases where patients have thickened mucus and difficulty with clearing these secretions, medications such as guaifenesin may be given.

Allergy Management

Allergy management can be helpful in patients who have an underlying component of allergic rhinitis. Allergy management usually combines allergen avoidance, mechanical reduction in allergen via irrigations, and also medication. Common medications include systemic or intranasal steroids (such as fluticasone, mometasone), antihistamines (loratadine, cetirizine), or leukotriene receptor antagonists (montelukast). In general, allergy management is immensely helpful in treating chronic rhinosinusitis, but its application in acute rhinosinusitis is inconclusive. Antihistamines have not been shown to be effective in acute rhinosinusitis due to its drying effect on nasal mucosa and resultant nasal congestion. However, there is limited evidence that it can reduce sneezing and nasal congestion in patients with allergic rhinitis and ABRS.[1] As discussed previously, there is growing evidence that intranasal corticosteroids are beneficial in patients with acute rhinosinusitis regardless of whether or not they have underlying allergic pathology. Currently, there is no evidence on the use of leukotriene receptor antagonists in the setting of acute rhinosinusitis.

FAILURE OF MEDICAL THERAPY

The clinical practice guidelines recommend that after 7 days of treatment, if patients fail to improve or worsen, then the clinician should search for complications or another diagnosis. Signs and symptoms that the disease has spread intracranially or intraorbitally include proptosis, visual changes, severe headache, abnormal extraocular movements, changes in mental status, periorbital inflammation, edema, or erythema (*see* Chapter 34).

Another reason that patients may have failed initial antibiotic therapy is because the organisms are resistant to the first antibiotic or are, in fact, not bacteria. In these cases, another antibiotic can be prescribed, but there are insufficient data on any particular choice of antibiotic.[1]

SURGICAL TREATMENT

Surgical interventions are not usually necessary in cases of acute rhinosinusitis unless patients are refractory to medical treatment or there are complications including intracranial extension, orbital complications, or abscess in the extrasinus tissues. According to the Joint Task Force, antral puncture and irrigation can be safely done in the office in cases of acute rhinosinusitis refractory to medical therapy. Maxillary sinus puncture can be performed via the canine fossa or inferior meatus and allows for drainage of sinus contents to alleviate pressure. Cultures obtained from sinus puncture can also be used to direct antimicrobial therapy, especially in patients who are immunocompromised.

SUMMARY POINTS

- Acute rhinosinusitis affects millions of people in the United States annually, or 15.2% of the population each year. The burden of disease includes lost workdays, increased healthcare costs, and increased doctor's visits.
- The accurate diagnosis of acute viral or bacterial rhinosinusitis depends on symptoms, the duration of symptoms, and disease progression.
- The diagnosis of rhinosinusitis is based on three cardinal symptoms: mucopurulent drainage, nasal obstruction, and facial discomfort.
- The physical examination is helpful in detecting possible intracranial or ocular complications, and endoscopy is helpful for confirmation of diagnosis.
- There are many predisposing factors for ABRS that include preceding viral infection, smoking, allergic rhinitis, asthma, anatomic obstruction, and immunodeficiency. Many of these also predispose to chronic rhinosinusitis.
- Routine nasal cultures, laboratory testing, and imaging are not indicated unless disease is refractory to medical treatment or if there are complications.
- The preferred imaging of acute rhinosinusitis is CT sinus without contrast. However, CT with contrast can highlight abscesses and MRI can highlight soft tissue or nerve involvement.
- The mainstay of treatment of acute viral and bacterial rhinosinusitis is supportive, with the addition of antibiotics for ABRS. There is some evidence supporting the use of intranasal corticosteroids and decongestants, but less convincing evidence on steroids, irrigations, mucolytics, and allergy management.
- Failure of medical treatment should prompt further consideration into possible drug-resistant organisms or complication.
- Surgical therapy is rarely necessary. Maxillary sinus puncture may be indicated for select cases, and more extensive sinus surgery is reserved for intracranial or ocular complications.

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CHAPTER

Bacteria in Rhinosinusitis: Infection, Biofilms, and Superantigens

28

Raewyn G Campbell, James N Palmer

INTRODUCTION

The underlying pathophysiology of rhinosinusitis is unknown. Proposed mechanisms include microbial pathogens (viruses, bacteria, fungi), allergy, osteitis, biofilms, superantigens, and immunologic abnormalities. Whether bacteria are a causative factor in chronic rhinosinusitis (CRS) or merely an exacerbating factor is yet to be determined. However, it is likely that bacteria are a cofactor in a multifactorial disease. This chapter will focus on the role of bacteria in rhinosinusitis. The majority of upper respiratory tract infections, including rhinosinusitis, are viral in origin. However, approximately 0.5% will progress to develop an acute secondary bacterial infection due to facultative aerobic bacteria.[1]

Most of these infections resolve, however, if resolution does not occur, anaerobic bacteria predominate and CRS develop.[1,2] Whether the initial viral infection precedes, or is concurrent with, the bacterial infection is unknown. However, an evolution from viral to aerobic to anaerobic infections has been documented over the course of sinus infections.[2] The mechanisms behind the progression from an acute viral infection to chronic bacterial rhinosinusitis (CBRS) are also unknown; however, theories exist. These theories include microbial synergy, local inflammation causing occlusion of sinus ostia, increased bacterial attachment to sinus epithelium, and interruption to local immunity.[1] Certainly, mucosal thickening, increased secretions, and ostial occlusion have been documented on CT scans, MRI scans, and plain X-rays of adults and children with viral upper respiratory tract infections.[3-5] Mucociliary clearance (MCC) is also impaired during viral rhinosinusitis and epithelial injury can occur that can enhance bacterial adherence.[1,6]

Nonpathogenic bacteria with the ability to interfere with the growth of pathogenic bacteria, termed "bacterial interference," have been demonstrated to exist in the nasopharynx.[7-9] These bacteria produce bactericidal proteins called bacteriocins and include *Streptococcus mitis, Streptococcus sanguis, Prevotella melaninogenica,* and *Peptostreptococcus anaerobius*.[10,11] Therefore, colonization of the nasopharynx and/or nasal cavity with these bacteria may be protective against rhinosinusitis. Smoking, viral infections, and antimicrobial therapy can alter the normal flora of the nasopharynx and nasal cavity, predisposing the individual to infection with pathogenic bacteria.[12-14] Therefore, ostial occlusion, impaired MCC, epithelial injury, and disruption of bacterial interference due to viral infection may all contribute to a secondary bacterial infection and the progression to bacterial rhinosinusitis.

INFECTION

In determining the microbiology of rhinosinusitis, many confounding issues have resulted in inconsistent findings. These issues include variations in culture techniques and transport, contamination of samples as they enter the nasal cavity or sinuses, the variety of sinuses and/or areas of the nasal cavity sampled, antibiotic use, differing patient populations, and variation in the presence or absence of contributory pathology such as polyps.[1,15] To date, obtaining maxillary sinus cultures via an antral tap has been described as the "gold standard."[16,17] However,

endoscopically guided cultures of the middle meatus have been shown to have a 60–90% concordance with direct maxillary sinus cultures (antral tap or intraoperative culture),[18-20] a sensitivity of 80.9–85.7%, a specificity of over 90%, and an accuracy of over 89%.[21] Concordance is stronger (up to 100%) for anaerobic bacteria.[20] Endoscopic cultures are also less invasive and are associated with less morbidity. A positive culture and the presence of a large number of white blood cells associated with a high bacterial density [i.e. $>10^3$ colony forming units (CFU)/mL] further support the presence of a bacterial infection.[16] Endoscopic cultures are not accurate in children as the middle meatus of healthy children has been shown to be colonized with the same pathogens commonly recovered from children with rhinosinusitis.[22] Recently, Ikeda et al. demonstrated recovery of anaerobic bacteria from the maxillary sinus in patients with CRS undergoing balloon sinuplasty using a catheter-based approach.[23] Finally, when endoscopic cultures and sinus aspirates fail to identify bacteria where clinical suspicion is high, a sinus mucosal biopsy may be required.[16]

The origin of pathogenic organisms that infect the sinuses is the nasal cavity.[1] Bacterial flora of the healthy nasal cavity includes *Staphylococcus aureus, Staphylococcus epidermidis,* α- and γ-*Streptococci, Propionibacterium acnes,* and aerobic diphtheroids.[24-26] Pathogenic bacteria, such as *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes, Peptostreptococcus* spp. and *Prevotella* spp., are rarely isolated from healthy nasal cavities.[24-26] In patients with sinusitis, the flora of the nasal cavities differs from healthy cavities and includes *S. pneumoniae, H. influenzae, S. pyogenes,* and *M. catarrhalis*.[1]

Whether healthy sinuses contain bacterial flora is controversial. Many studies have cultured both anaerobic (*Prevotella, Porphyromonas, Fusobacterium, Peptostreptococcus* spp.) and aerobic (*S. pyogenes, S. aureus, S. pneumoniae, H. influenzae*) bacteria in healthy sinuses.[27-30] In one study, 20 patients undergoing maxillary repositioning, maxillary sinus samples were collected and included part of the anterior bony wall, an aspirate, and a swab via an antral window.[29] Only 20% of patients demonstrated bacterial growth and this growth was negligible.[29] Those specimens with bacteria present also demonstrated a more acute inflammatory response compared with those with sterile sinuses.[29] Su et al. compared cultures from 48 patients with chronic maxillary sinusitis with 7 healthy controls.[28] They found anaerobic bacteria only in inflamed sinuses and concluded anaerobes were the most important pathogen in chronic maxillary sinusitis.[28] However, Brook cultured anaerobes in all specimens cultured from the noninflamed maxillary sinuses of patients undergoing nasal septal surgery.[27] In 58%, aerobes were also cultured.[27] In contrast, Sobin et al. failed to culture any bacteria via antral puncture, irrigation, and aspiration in 12 healthy patients.[31]

ACUTE BACTERIAL RHINOSINUSITIS

The most consistent major pathogens recovered in acute bacterial rhinosinusitis (ABRS) are *Streptococcus pneumoniae, H. influenzae* and *Moraxella catarrhalis, Streptococcus pyogenes,* and *S. aureus*.[1,32-34] In approximately one-third of patients, the infection is polymicrobial.[1] The distribution of organisms can differ between sinuses when multiple sinuses are infected.[35] Anaerobic bacteria are not commonly encountered unless the infection is of odontogenic origin.[36,37] Gram-negative rods, such as *Pseudomonas aeruginosa,* are common in nosocomial infections, immunocompromised patients, cystic fibrosis, and HIV infections with a CD4 count less than 50 cells/mm.[31,38,39]

CHRONIC BACTERIAL RHINOSINUSITIS

While the pathogenesis of CRS is uncertain, it is possible that CRS is a consequence of unresolved ARS that favors persistent inflammation and an environment suited to anaerobic bacterial growth.[1] This environment arises secondary to mucosal edema (which reduces blood supply), a low oxygen tension, and acidity of the sinus due to oxygen consumption by aerobic bacteria.[1,40] The likelihood of a bacterial infection in CRS increases in the following circumstances: immune deficiency, the presence of sinus opacification without polyps, purulent secretions draining from sinus cavities, or the presence of gram-negative or resistant organisms.[41]

Polymicrobial infection is common in CRS, which explains the ineffectiveness of narrow-spectrum antibiotics.[42] The predominant bacteria in CRS are *S. aureus, S. epidermidis,* and anaerobic bacteria such as *Peptostreptococcus* spp, *Prevotella* spp, *Porphyromonas* spp, *Propionibacterium acnes,* and *Fusobacterium* spp.[1,43,44] Overall, anaerobes have been cultured in 8–93% of studies and are more common in patients who have not undergone surgery.[45] Immunoglobulin E (IgG) antibodies to anaerobes have been detected in sinus aspirates in CRS.[44] These antibodies were noted to decrease in patients who responded

to treatment, yet levels did not change in those with recalcitrant disease.[44] As in acute sinusitis, bacteria differ between sinuses when multiple sinuses are infected.[35] Anaerobic and beta-lactamase producing bacteria (BLPB) (e.g. *S. aureus, H. influenzae, M. catarrhalis, Prevotella* spp, *Porphyromonas* spp, and *Fusobacterium* spp) are more commonly isolated in CRS with multiple sinus involvement when compared with acute infections.[35] BLPB resist β-lactam antibiotics; however, they also may provide protection to β-lactam-sensitive bacteria by secreting β-lactamase into the infected tissue, a phenomenon known as shielding.[46,47] The increased incidence of BLPB in CRS is likely due to therapy with β-lactam antibiotics. The incidence of recovery of methicillin-resistant *S. aureus* (MRSA) in rhinosinusitis has increased and this must be considered, especially in recalcitrant disease.[45,48] Gram-negative bacilli, including *P. aeruginosa*, are more commonly isolated in patients who have undergone sinus surgery, received systemic steroid therapy, those who used sinus irrigations and in those with recalcitrant disease.[45,49] *S. epidermidis* is likely a colonizing bacteria.[1,22,50,51]

Osteitic bony changes are often noted on CT scans of patients with CRS. It is thought that these changes are due to intraosseous bacterial infection, similar to osteomyelitis. Bacterial gram-positive microcolonies have been detected in the sphenoid bone of a small number of CRS patients; however, they were also found in healthy controls and the difference was not significant.[52] Further, intraosseous bacteria did not correlate with the increased bone thickness or density seen on CT scans.[52] It is, therefore, unlikely that bacterial microcolonies are the cause of the osteitic bony changes seen in CRS. These changes are more likely due to generalized upper airway tissue remodeling secondary to inflammatory cytokines released by inflamed mucosa overlying the bone. Osteitis is associated with greater disease severity and less chance of postoperative improvement.[53]

Chronic Rhinosinusitis with Nasal Polyposis

The most common bacteria in CRS with nasal polyposis (CRSwNP) in adults and children include *S. aureus, H. influenzae, S. pneumoniae, Prevotella,* and *Peptostreptococcus*.[20,54] The bacterial flora in eosinophilic CRSwNP does not differ from neutrophilic CRSwNP.[55] Bacteria cultured in CRSwNP and CRS without nasal polyposis (CRSsNP) also does not differ.[20,55]

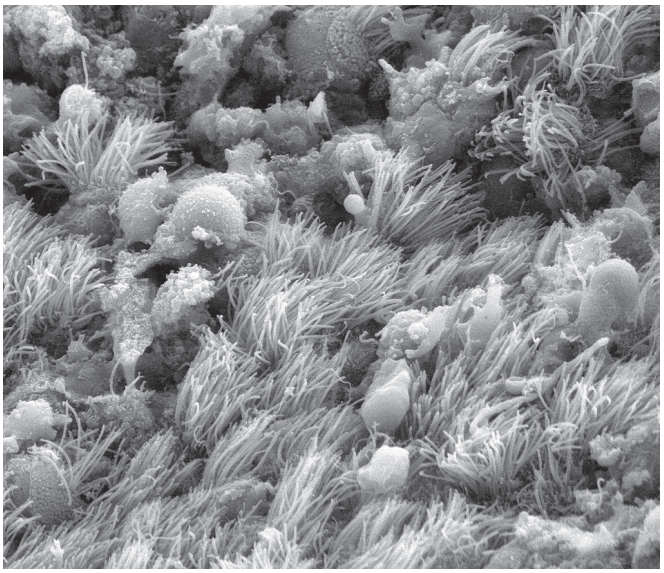

Fig. 28.1: Scanning electron microscope photograph of a *Staphylococcus aureus* biofilm in a patient with chronic rhinosinusitis.

Nosocomial Rhinosinusitis

Patients at risk of nosocomial rhinosinusitis are those requiring extended nasotracheal or nasogastric intubation, particularly those intubated for longer than 5 days.[56] Factors contributing to rhinosinusitis in these patients include impaired immunity, prolonged antibiotic courses, impaired MCC, and the presence of a foreign body in the nasal cavity that may also obstruct sinus ostia. Infections are often polymicrobial[57] and the most common pathogens include gram-negative enteric organisms such as *P. aeruginosa, Klebsiella pneumoniae, Enterobacter* spp, *Proteus mirabilis, Serratia marcescens,* and gram-positive cocci (e.g. *Streptococcus* spp and *Staphylococcus* spp.).[56,57]

BIOFILMS

Bacterial biofilms are complex, highly organized communities of bacteria embedded in a protective extracellular matrix that consists of polysaccharide, nucleic acids, and extracellular polymeric substances (Fig. 28.1). This matrix can comprise up to 90% of the biofilm.[58] The majority of bacteria exist as biofilms. In fact, over 80% of microbial infections are due to biofilms.[59] Biofilms are involved in many head and neck pathologies such as otitis media,[60] chronic tonsillitis,[61] adenoiditis, cholesteatoma,[62] infections of implanted devices (such as cochlear implants, tympanostomy tubes, frontal sinus stents, and tracheostomy tubes),[63-66] and CRS.

The bacteria in biofilms are phenotypically distinct from planktonic bacteria. Biofilms develop in several stages. Initially, planktonic bacteria attach and adhere to an inert or biologic surface and form microcolonies. Cell-to-cell signaling occurs between bacteria and, at a certain critical population density, this cross-talk, termed "quorum sensing,"[67] activates genes involved in biofilm phenotypic differentiation. The bacteria then grow, express virulence factors, excrete, and form an extracellular matrix and mature into three-dimensional mushroom-like structures. These structures are composed of bacterial towers separated by water channels, or interstitial voids, which act as a primitive circulatory system, delivering nutrients and removing metabolic waste from the biofilm. Finally, the biofilm can shed bacteria in planktonic form, causing intermittent acute infections at remote sites.[58]

The bacteria within biofilms are more resistant to host defense mechanisms such as antibodies, desiccation, environmental fluctuations (such as pH), phagocytosis, antibiotic penetration through the extracellular matrix, and complement activity. Some biofilm bacteria have upregulated efflux pumps that pump antibiotics into and directly out of the cell. Biofilms also have a lower metabolic and growth rate further reducing antibiotic susceptibility.[59] Finally, biofilms can share DNA via horizontal transfer that can result in mutations favoring antibacterial resistance.

Biofilms are very difficult to culture via traditional staining techniques due to their slow metabolic rate. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are not ideal techniques due to difficulties with fixation. SEM and TEM are also not able to distinguish between bacterial species. Confocal laser scanning microscopy (CLSM) with fluorescent in situ hybridization (FISH) is a noninvasive and nondisruptive technique that does not require fixation, provides a three-dimensional image of the biofilm, and can differentiate between bacterial species.[68]

Biofilms and Disease

Biofilm presence is associated with multiple host immune function defects. First, lactoferrin, an antibacterial peptide that prevents bacterial attachment and aggregation, is downregulated in biofilm-associated CRS.[69] MUC-7, an antibacterial glycoprotein, is also downregulated.[70] Additional adherence targets are provided by the overexpression of sialic acid glycoproteins and sialyltransferase genes.[70] Therefore, host innate immunity against bacteria and their attachment is impaired. Biofilms are associated with epithelial destruction and loss of cilia.[71-73] Therefore, the mucous blanket and MCC are impaired, promoting further adherence and preventing clearance of bacteria. Biofilms have been associated with a T-helper type 1 (Th1) local inflammatory response in the mucosa of patients with CRS; however, biofilm species were not identified.[74] When species have been identified, *S. aureus* biofilms were found to be associated with a T-helper type 2 (Th2) immune response in CRS patients.[75]

The Role of Biofilms in Chronic Rhinosinusitis

The pathogenesis of CRS is likely a manifestation of multiple host and environmental factors interacting with microorganisms in a genetically predisposed host.[76] Mounting evidence supports the contributory role of bacterial biofilms in recalcitrant CRS.[45,66,70,77-79] Biofilm-related diseases share common, unique characteristics with CRS and biofilms are found in up to 70% of CRS patients.[75] These characteristics include: chronicity with repeat acute exacerbations, variable culture rates and antibiotic resistance.[75]Animal models have demonstrated the development of biofilms in sinuses inoculated with *S. aureus* and *P. auruginosa*.[68,80] In CRS, the most common bacterial species forming biofilms include: *P. aeruginosa, S. aureus,* coagulase-negative *Staphylococcus* and *H. influenzae*.[81-83] Fungal biofilms have also been found in up to 64% of CRS patients, particularly in those with *S. aureus* infections[83-87] indicating synergism. It may be that fungal biofilms require the *S. aureus* biofilm matrix for growth. *S. aureus* has also been noted to elevate levels of alternatively activated macrophages (M2s) that are immunosuppressive and impair phagocytosis.[88]

Biofilms have been found to confer worse preoperative symptoms and radiologic appearances and worse postoperative outcomes in sinus surgery, particularly *S. aureus* biofilms.[75,86,89-92] In fact, CRS patients with successful postoperative outcomes have been shown to have a lower biofilm burden than their recalcitrant counterparts.[90] Further, *H. influenzae* biofilms are associated with less severe disease, supporting the role of *S. aureus* biofilms in CRS severity.[86] Interestingly, one study found that biofilms associated with CRSwNP were less developed with less adhesion when compared with biofilms in CRSsNP.[93] Clinical factors associated with bacterial biofilm formation include positive culture results, prior sinus surgery, and nasal steroid use within 1 month of sample collection.[94]

Interestingly, biofilm formation was not associated with nasal polyposis, allergy, Samter's triad, sleep apnea, smoking, age, or gender.[94] Biofilms have also been detected in control subjects[82,95] supporting the likelihood that biofilms are a cofactor in the pathogenesis of CRS.

Biofilm Therapy

Biofilms are up to 1000 times more resistant to antibiotics compared with their planktonic counterparts and would, therefore, require toxic concentrations of some antibiotics for successful eradication.[59,96] The minimal biofilm eradication concentration (MBEC) for *P. aeruginosa* has been found to be 60-fold greater than the minimum inhibitory concentration (MIC) for gentamicin and over 1000-fold greater for ceftazidime and piperacillin.[97] The MBEC for ciprofloxacin was also found to lie outside the acceptable MIC range. Only tobramycin and amikacin were found to be effective against the biofilm at concentrations within the susceptible MIC range.[97] For *S. aureus,* the MBEC was 100- to 1000-fold greater than the MIC for planktonic *S. aureus* populations for penicillin, oxacillin, cefazolin, ciprofloxacin, clindamycin, and vancomycin.[97] Only gentamicin was effective against the *S. aureus* biofilm within the susceptible MIC range.[97] Furosemide demonstrated a reduction in *P. aeruginosa* biofilm size by 50% using the Calgary Biofilm Device.[98]

Topical antibiotics have been studied as an alternative method to deliver the required concentrations of antibiotics to the sinus mucosa without any associated systemic toxicity. Ha et al. demonstrated that topical mupirocin was effective in eradicating 90% of a *S. aureus* biofilm mass in an in vitro study.[99] In a prospective, double-blind, placebo-controlled study, 1 month of twice-daily mupirocin sinonasal rinses achieved microbiological clearance of *S. aureus* in 88.9% of recalcitrant CRS patients.[100] Immediate post-treatment endoscopic appearance also demonstrated statistically significant improvement. Symptom and quality of life scores improved; however, these improvements were not significantly different to control patients who rinsed with saline.[100] Further, while cultures remained negative in 85.7% of patients at delayed follow-up (mean 89 days), improvements in endoscopic and symptom scores were not sustained.[100] The lack of significant improvement in symptoms and the rebound of endoscopic disease, despite microbiological clearance, once more suggest a multifactorial disease process. Finally, when mupirocin or gentamicin was added to a topical surfactant, complete bacterial elimination was noted for *MRSA* and *P. aeruginosa* biofilms in vitro.[101] Long-term (i.e. 3 months) macrolide therapy has been shown to improve symptoms and endoscopic appearance in patients with CRS 3 months post-treatment.[102] Azithromycin has been found to inhibit quorum sensing in *P. aeruginosa* in vitro.[103]

Mupirocin resistance has been reported in up to 13.2% in selected patient populations.[104,105] Further, macrolide resistance rates of up to 69.7% have been reported.[106-109] Approximately, 19% of *S. aureus* species are MRSA,[109] 27% of *P. aeruginosa* spp are quinolone resistant, and 36% of *P. aeruginosa* spp are aminoglycoside resistant.[110] Therefore, alternative topical therapies have also been studied. Manuka honey contains a phenol compound, methylglyoxal (MGO), which confers antibacterial activity against a broad spectrum of gram-positive and gram-negative bacteria including *S. aureus* and *P. aeruginosa*.[111-113] In vitro attempts to induce resistance to manuka honey have been unsuccessful.[114] A 16.5% manuka honey nasal lavage solution augmented with MGO has been demonstrated to be bacteriocidal against *S. aureus* and to be at the upper limit of tolerability for patients.[112] Further clinical studies are required to investigate manuka honey in the management of CRS.

Surfactants are molecules that are solvent in both water and in organic substrates. One percent baby shampoo nasal irrigation has been shown to disrupt *P. aeruginosa* biofilm formation; however, it did not eradicate preformed *P. aeruginosa* biofilms.[115] In a prospective, nonrandomized study, 46.6% of postoperative, recalcitrant CRS patients reported improved symptoms after twice daily sinonasal lavage with 1% baby shampoo for 4 weeks.[115] Olfaction also improved in 7 out of 11 (63.6%) patients.[115] A sinonasal surfactant solution diluted in bicarbonate buffered saline recently demonstrated a transient increase in ciliary beat frequency (CBF) with no evidence of cilial toxicity.[116] Finally, a hydrodynamic saline lavage was found to be successful in reducing biofilm cell counts in vitro and warrants further studies involving living tissue and in animal models.[117] Photodynamic therapy has been shown to reduce 99.9% of *P. aeruginosa* and MRSA biofilms in the maxillary sinus in vitro.[118,119] Further research in this promising area is required.

Lactoferrin is an iron-binding glycoprotein abundant on airway mucosal surfaces, in tears, breast milk, and in the secretory granules of neutrophils.[120-122] Lactoferrin possesses antibacterial, antifungal, antiviral, antineoplastic, immune-regulatory, and anti-inflammatory actions.[121,123] Bacteria require a higher level of iron to

form biofilms.[122] Lactoferrin is an iron chelator that deprives pathogens of nutrients and stimulates a specialized form of pili-driven surface motility, termed "twitching," causing the bacteria to move across the surface rather than aggregate in clusters and form biofilms.[122] Lactoferrin can also bind lipopolysaccharide and disrupt and permeate bacterial membranes.[124] Lactoferrin has been shown to inhibit *P. aeruginosa* biofilm formation in vitro.[122] Finally, lactoferrin enhances the bacteriocidal actions of certain antibiotics[125] and has been used clinically, in conjunction with antibiotics and antiviral agents, to treat antibacterial resistant *Helicobacter pylori* infections and hepatitis C infections.[126,127] Lactoferrin has also been used in combination with antifungal agents to treat *Candida* species infections in vitro.[128-130]

Psaltis et al. have demonstrated that patients with CRS have lower levels of lactoferrin expression relative to controls, particularly in biofilm-positive patients.[78] Patients with genetic, transcriptional, or translational deficiencies in lactoferrin synthesis may be predisposed to biofilm formation and recalcitrant CRS.[78] Lactoferrin is, therefore, a broad-spectrum antimicrobial peptide, and has been investigated as an alternative class of antibiotic.[131] Bacteria do not appear to develop resistance to antimicrobial peptides.[132] Oral lactoferrin has been used to treat gastrointestinal tract and urinary tract infections.[133,134] However, the systemic administration of antimicrobial peptides in general has been limited to date due to their toxicity at effective doses.[135] This area is under current development.

Topical lactoferrin-based agents have also been investigated. A combination wound dressing consisting of lactoferrin, xylitol, and silver has been shown to reduce biofilm viability in vitro.[136] The addition of xylitol inhibits the ability of certain biofilms to respond to the lactoferrin-induced iron restriction.[137] Lactoferrin may serve as a topical agent in the management of CRS, as a single agent or in combination with topical antibiotics as a synergistic tool to enhance their activity, particularly against resistant strains. This area requires further investigation. Technetium-99m-labeled lactoferrin derivatives have been developed to distinguish between bacterial infection and aseptic inflammation. This is particularly useful determining the nature of an infection associated with an implanted device.[138-140]

Endoscopic sinus surgery does not completely eradicate biofilms; however, it does reduce the biofilm load, allow cultures to be collected to confirm the presence and type of biofilm, and permit access for topical therapies to infected sinuses. Future therapies for eradication of biofilms may include microbiota-targeted therapies that focus on the ecology of the sinonasal microbiota. These bacteriotherapies aim to replace a pathogenic bacterial community with new microbiota that restores the bacterial flora to a more normal state. Microbiota-targeted therapies have already been used successfully in resistant enterocolitis in the form of fecal transplants.[141-144] This technique would aim to alter the pathogenic flora of the sinuses, nasal cavity, and nasopharynx that may have originally seeded the sinuses with pathogenic bacteria. This area has not been explored in rhinologic research.

SUPERANTIGENS

Superantigens are a class of antigen that causes nonspecific polyclonal T-cell activation of up to 30% of the T-cell population, 1000–30,000 times the normal response, resulting in massive cytokine release. Superantigens have been implicated in a variety of diseases including atopic dermatitis, Kawasaki disease, asthma, and rheumatoid arthritis. Superantigens are produced by bacteria, viruses, and mycobacteria have been implicated in the pathophysiology of CRSwNP.

Superantigens are able to bypass the usual antigen-specific antigen presenting cell (APC) processing pathway by binding directly to the major histocompatibility complex (MHC) class II proteins via the T-cell receptor (TCR) beta-chain in a region outside the conventional variable region binding site. Superantigens are not internally processed by APCs and do not require CD4 or CD8 as coreceptors.[145] This binding results in severe inflammation involving the polyclonal activation of B cells and recruitment of eosinophils.[146] The eosinophilic inflammation associated with superantigens, is characteristic of CRSwNP, a Th2 biased inflammatory process involving interleukin-5 (IL-5) and eotaxin.[75,147] This process contrasts with CRSsNP, which is a Th1 biased process involving interferon-γ (IFN-γ) and transforming growth factor-β (TGF-β).[148] Superantigens also alter nasal epithelial cell salt and water entry that may then progress to polyposis.[149] Superantigens may contribute to glucocorticoid insensitivity in CRSwNP via overexpression of the β-glucocorticoid receptor subtype that inhibits the functional α-subtype.[150] This finding may contribute to the recalcitrance typified by CRSwNP. Finally, superantigens may concurrently behave as conventional antigens, stimulating a specific immunoglobulin E (IgE) response as well as a polyclonal B-cell activation.[151]

In CRSwNP, the most common pathogen cultured is *S. aureus*.[83,152] In fact, the group with the highest rate of *S. aureus* culture positivity is those with Samter's triad.[152] *S. aureus* produces exotoxins that behave as superantigens. These superantigens include staphylococcal exotoxin A, B, C, D and Q, and toxic shock syndrome toxin-1 (TSST1). *S. aureus* superantigens are disease modifiers in CRSwNP and illustrate the interaction between the local immune system and bacteria.[151] Superantigens are found in 20–58% of CRSwNP patients, yet are rarely found in CRSsNP patients or in controls.[75,151,153] IgE antibodies to *S. aureus* enterotoxins have been found in nasal polyp tissue from patients with CRSwNP compared with CRSsNP patients.[75,154] The association between *S. aureus* superantigens and CRSwNP is further supported by Guven et al. who noted a higher proportion of *S. aureus* exotoxins in the tissue from patients with CRSwNP when compared with controls.[155] El Fiky et al. noted a higher proportion of TSST1 in patients with CRSwNP when compared with CRSsNP and controls.[156] *S. aureus* superantigens have been shown to shift the cytokine pattern toward a Th2-type response.[157] Foreman et al. reported an elevated level of Th2 cytokines in association with superantigen-specific IgE in CRSwNP patients, particularly in those with *S. aureus* biofilms.[75] Further, the number of T cells expressing the TCR β-chain variable region has been found to be increased in CRSwNP when compared with CRSsNP and controls.[152] Total IgE and myeloperoxidase (MPO) have been found to be the most important predictors of superantigen status.[75] Eosinophilic cationic protein (ECP), IL-5, and TGF-β are the most important predictors of S. aureus biofilm status.[75]

S. aureus can reside intracellularly, intramucosally, and in biofilms on the mucosal surface.[158] The association between *S. aureus* biofilms, superantigens, and a Th2-dominant inflammatory response in CRSwNP may suggest that *S. aureus* biofilms act as a reservoir for the release of planktonic bacteria and superantigens into the sinuses.[75] However, *S. aureus* biofilms and superantigen-specific IgE are not universally found in CRSwNP. This further supports the multifaceted theory of CRSwNP.

CONCLUSION

Bacteria are just one arm in the pathogenesis of rhinosinusitis, a multifaceted disease. The increasing prevalence of drug resistance undermines the efficacy of empiric antibiotic therapy and highlights the importance of endoscopically guided culture-directed treatment. The role of biofilms and superantigens in the pathogenesis of CRS contributes to our further understanding of the recalcitrance of this disease and drives the desire to investigate and develop more effective therapeutic options beyond conventional systemic antibiotic therapy.

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CHAPTER

29

Nasal Polyposis

Stella Lee, Berrylin J Ferguson

INTRODUCTION

Nasal polyps (NPs) are benign hypovascular outgrowths from the nose and sinus cavities, recorded as early as 2000 BC in Egyptian writings and 1500 years later, referred to as "polypus" by Hippocrates for their resemblance to sea polyps, a term that has persisted into the English language today. In ancient times, NPs were thought to be due to viscous bodily humors, and later from damp weather, allergies, and infection. Recently several different potential studies have evaluated the cellular and inflammatory composition. NPs commonly occur in patients with asthma, chronic rhinosinusitis (CRS), aspirin-exacerbated respiratory disease (AERD), and cystic fibrosis (CF). Most NPs are eosinophil-rich, with the exception of those associated with infection as seen in CF or antral-choanal polyps (ACPs). A wide variety of etiologies have been proposed that trigger this inflammation, including fungal hypersensitivity, superantigen-mediated, bacterial infection, and defects of the innate immune system. Regardless of cause, most NPs are responsive to steroids and recur if medical therapy is not continued.

TERMINOLOGY

Increased evidence suggests that the underlying cause of nasal polyposis is quite diverse and due to a variety of immunologic mechanisms that result in inflammation. CRS is divided broadly into CRS without NP (CRSsNP) or CRS with NP (CRSwNP). It is estimated that 20% of patients with CRS have NP and the inflammation can be characterized by a Th2-mediated eosinophilic response, but ethnic and geographic variations have been reported as discussed in the following section.

EPIDEMIOLOGY

NPs occur in approximately 1–4% of the population and the incidence increases with age and in the presence of asthma. Six percent of adult asthmatics have NP. Asthmatics over 40 years of age are four times more likely to have NP than asthmatics less than 40 years. Average age of onset is in the 5th decade and NP before the age of 20 are unusual and should lead to an investigation of possible CF or primary ciliary dyskinesia (PCD). While women more commonly develop AERD, characterized by the triad of aspirin hypersensitivity, NP and asthma, other forms of NP in most studies are slightly more common in men. The highest rates of NP are in the Scandinavian studies and the lowest rates from the Korean literature. Identification of NP usually requires nasal endoscopy and in a small Danish autopsy series (n = 15), over 40% of cadavers had evidence of small NP in the sinuses or nose. Allergic fungal rhinosinusitis (AFRS) is a subcategory of CRS characterized by eosinophilic mucin and fungal hyphae. AFRS is usually seen in younger patients and is more common in regions with warm climates. Eosinophilic inflammation can also be seen in patients with a systemic vasculitis such as Churg-Strauss syndrome (CSS) that is associated with eosinophilia >10%, asthma, neuropathy, pulmonary infiltrates, and rhinosinusitis. NP can be an early indicator of disease in patients with CSS and present in up to 60% patients. ACPs are unilateral NPs that are thought to represent the unrestrained expansion of a mucosal

cyst of the maxillary sinus into the nose and extending to the choana. ACPs that are often unilateral arise from the maxillary sinus and account for only 5% of all NPs, with an increased incidence of 33% in children.[1]

GENETICS

In most survey studies, there is an association of a family history of NP (first-degree relative) with presence of NP in approximately 25% of patients and in AERD, up to 36% of patients have a first-degree relative with NP. There is no clear genetic linkage, and genetics in conjunction with environmental exposures are most likely required. In CF there are 1500 identified mutations of the autosomal recessive genes involved in the transmembrane conductance regulator (CFTR) gene, for which only 100 are routinely screened. Approximately 20% of CF patients have NP and NPs are most common in the patients carrying the most common mutation, delta F508. In a screening of 55 patients with NPs; however, the incidence of a CFTR gene mutations was no greater than that seen in the general population.[2]

PCD, also known as Kartagener syndrome, is associated with situs inversus in half of cases, rhinosinusitis, and recurrent pulmonary infections leading to bronchiectasis. Defects in the dynein arms as well as radial spoke and microtubule abnormalities may lead to problems in ciliary motion. Several inheritance patterns have been described including autosomal dominant, recessive, and X linked. Despite several reports of PCD's association with NP, the authors have never seen a patient with PCD and NP. In a study of 30 children with PCD in a tertiary care setting, not one case of NP was found.[3]

CLINICAL PRESENTATION

Patients with NP often present after a prolonged period of symptoms of nasal obstruction, rhinorrhea, and loss of smell. Facial pressure or pain can also be seen but is more common in patients without polyps and actually may be a negative predictor for sinus disease.[4,5] Olfactory dysfunction and associated taste problems are common in patients with polyposis due to inflammation and obstruction. Assessment of olfaction can be performed via subjective test methods including the University of Pennsylvania Smell Identification Test or Sniffin' Sticks. Objective measurement of smell is still being studied including the use of olfactory evoked potentials and functional MRI. Patients with sinonasal polyposis have significantly impaired quality of life especially due to impaired olfactory function.[6] Use of validated surveys is important to assess impact of treatment including medical and surgical therapy.

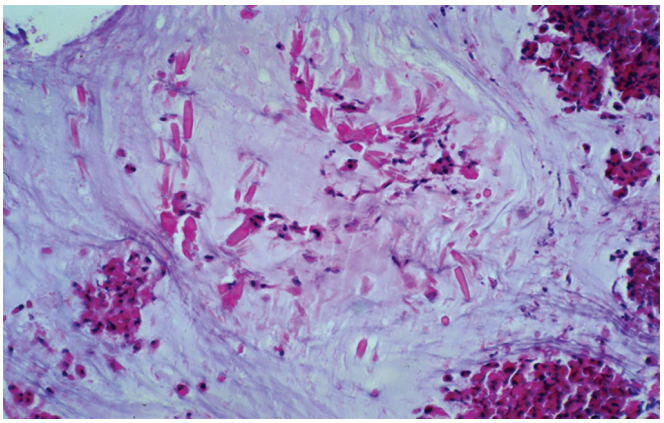


Fig. 29.1: Hematoxylin and eosin (H&E) of eosinophilic mucin with Charcot-Leyden crystals and necrotic eosinophils present. No hyphae are seen on fungal stains.

PATHOLOGY OF NASAL POLYPS

The majority of bilateral NP macroscopically are edematous, smooth sacs of translucent grape like material, except in long-standing NP, which may be more fibrous and vascular. Polyps are usually attached by a stalk to the underlying mucosa and commonly arise from the middle meatus. Microscopically, NPs have a ciliated pseudostratified epithelium, which is often abraded or ulcerated. The basement membrane is thickened and there is significant submucosal edema, admixed with a varying amount of inflammatory cells including lymphoid islands, plasma cells, eosinophils, and sometimes neutrophils. The predominant cellular infiltrate and histology have historically been used to classify polyps into eosinophilic, chronic inflammatory, and seromucinous types. The majority of NPs are eosinophilic with the neutrophilic predominance seen in patients with long-standing infectious component, such as the CF patient. Eosinophilic polyps are found in patients with AFRS, AERD, EMRS, and CSS. The mucin from patients with eosinophilic disease is thick, tenacious, and histologically characterized by clusters of eosinophils with their breakdown products, Charcot–Leyden crystals (Fig. 29.1). The diagnosis of AFRS requires that fungal elements be present in this mucin (Fig. 29.2). Chronic inflammatory polyps, also known as fibroinflammatory polyps, are less common and characterized by lymphoid predominance with germinal centers. Seromucinous-type polyps include the respiratory

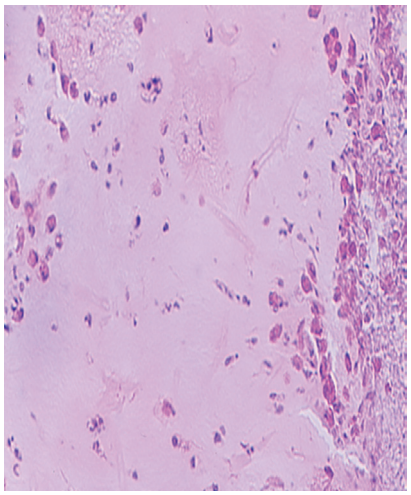


Fig. 29.2: Hematoxylin and eosin (H&E) with fungal hyphae discernible and characteristic eosinophilic mucin.

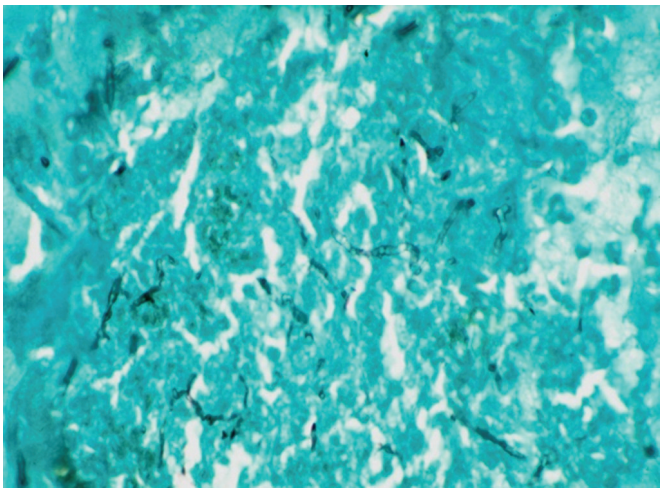


Fig. 29.3: GMS stain for fungi. Hyphae appear dark or black in this preparation.

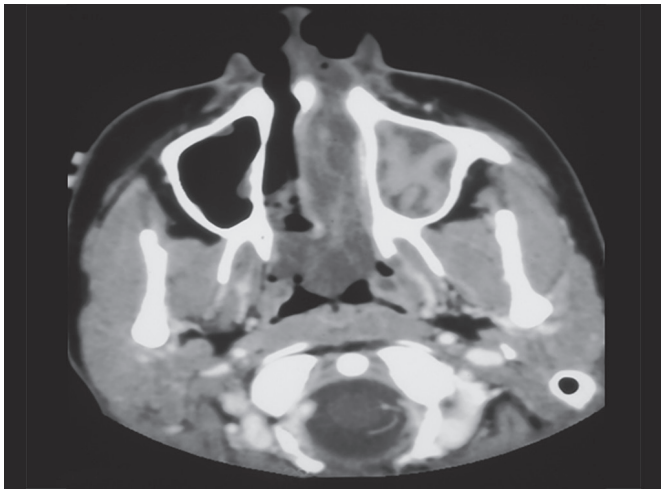


Fig. 29.4: Sinus CT of a patient with allergic fungal rhinosinusitis shows hyperdensities within the sinuses.

epithelial adenomatoid hamartoma. The ACP is unique in its absence of significant inflammatory infiltrate. Histologically, these polyps are also lined by respiratory epithelium with a thin basement membrane. Degenerative and angiomatous changes have also been described.

ETIOLOGY OF NASAL POLYPS

Eosinophilic Polyposis

Benign inflammatory NP account for 90% of NP and usually present in middle age. Colonization with *Staphylococcus aureus* occurs in up to 80% of patients with NP and may initiate the inflammatory response via nonspecific upregulation of T cells mediated through superantigen production. This topic is covered more fully in the chapter on superantigens. The most severely affected patients with CRS have NP and adult onset asthma. About 10% of patient in this latter category have AERD, sometimes referred to as aspirin triad, aspirin hypersensitivity, or Samter's triad. These are the most refractory of the patients with eosinophilic NP. Eosinophilic NPs account for the majority of patients with NPs, and while sometimes referred to as "allergic" pathologically, do not necessarily represent an allergic association or cause. A number of classifications follow under this umbrella and include AFRS, nonallergic fungal rhinosinusitis (NAFRS), and eosinophilic mucin rhinosinusitis (EMRS) (Table 29.1).

Allergic Fungal Rhinosinusitis

In AFRS growth of a variety of fungi in mucin is seen within the nose and the sinuses leading to a perpetuation of mucin production, fungal growth, and associated inflammation, which results in NP. Elevated IgE to the associated fungus is required for the diagnosis, although recent studies show a local immune response may also be present in patients without evidence of systemic IgE elevation.[7] This may be the case for patients without systemic evidence of IgE elevation to fungus, namely, nonallergic eosinophilic fungal rhinosinusitis (NAEFRS). Both AFRS and NAEFRS may ascribe to similar underlying mechanisms. Histopathologically AFRS is characterized by eosinophils in mucin, Charcot-Leyden crystals, and hyphal elements that can be comprised of a variety of fungal species depending on geographic location (Figs. 29.2 and 29.3). Erosions and hyperdensities are common on sinus CT secondary to inspissated mucous secretions (Fig. 29.4).

Table 29.1: Categorization and treatment of nasal polyposis

Category	*Saline lavage*	*Systemic steroids*	*Topical steroids*	*Systemic antifungals*	*Topical antifungals*	*Anti-biotics*	*Topical antibiotics*	*Zileuton*	*Omali-zumab*	*Immunotherapy*	*Aspirin desensiti-zation*	*Surgery*
AFRS	+++	+++	++	Mixed evidence ++	++	+ If bacte-ria also present	+ If bacteria present	–	++	++ Postoperatively	–	+++ Recurrence common
NAFRS	+++	+++	++	?	++	As above	As above	–	–	–	–	+++ Recurrence common
AERD	++	+++	++	-	-	As above	As above	++	–	–	++	+++ Recurrence common
EMRS	++	+++	++	-	-	As Above	As above	++	+ (super-antigen)	–	–	+++ Recurrence common
NP with-out E	++	++	-	-	-	?	?	–	–	–	–	+++ Recurrence less common
CF	Hyper-tonic	-	-	-	-	++	++	–	–	–	–	++ Repeated surgeries for biofilm removal common
Antral–choanal polyp	–	–	–	–	–	–	–	–	–		–	+++ Recurrence may occur unless total excision
REAH	++	++	++	–	–	–	–	–	–		–	+++

(AFRS: Allergic fungal rhinosinusitis; NAFRS: Nonallergic fungal rhinosinusitis; AERD: Aspirin-exacerbated respiratory disease; EMRS: Eosinophilic mucin rhinosinusitis; NP: Nasal polyps; CF: Cystic fibrosis).

AFRS Pathophysiology

The development of AFRS requires both geographic exposure to fungus and an immunologic predisposition to inflammation. Once a fungal spore is inhaled and lodges in the sinus, germination can increase the antigenicity of the fungus leading to the production of tenacious allergic mucin.[8] The inflammatory milieu that results can promote the growth of NPs via an eosinophilic Th2-mediated response including increased IgE and IgG to the specific fungus. Other proposed mechanisms include a nonallergic fungal immune response associated with increased CD8+ cells[9,10] and susceptibility to bacterial superantigen via specific class II major histocompatibility complex alleles (HLA-DR2 and HLA-DR5).[11,12]

AFRS Treatment

Treatment of AFRS includes surgical removal of polyps and eosinophilic mucin in conjunction with perioperative systemic steroid therapy. Endoscopic mucosal-sparing techniques can help preventing scarring and preserve mucociliary function. Several perioperative strategies have been utilized to help prevent recurrence including oral/topical steroids, oral/topical antifungal agents, and immunotherapy. A recent randomized placebo-controlled trial showed that oral steroid therapy with prednisolone 50 mg for 6 weeks and tapered for an additional 6 weeks was beneficial both in terms of symptom relief and polyp score.[13] Immunotherapy may also be indicated following surgical removal of all allergic mucin. Safety and efficacy of immunotherapy have been demonstrated in the first several years following surgery, but long-term improvement remains unclear.[14-16] Systemic or topical antifungals may have a role, but evidence is currently weak. In a study that randomized 50 patients with AFRS into one of five arms including oral and topical antifungal treatment or combination therapy, recurrence was the lowest in the group treated with topical fluconazole 10% in comparison to the other groups.[17]

Eosinophilic Mucin Rhinosinusitis

In some cases, the eosinophilic mucin and NPs are present without evidence of fungus on special fungal stains (Fig. 29.1) and these cases are disproportionately associated with bilateral NP, asthma, and aspirin hypersensitivity, namely EMRS.[18] Bacteria may also be found in the eosinophilic mucin and support the role of superantigen as does the occasional presence of lymphoid germinal centers in the NPs associated with fungal or bacterial presence. High levels of Th-2 biased cytokine expression are seen in eosinophilic NP including IL-4, IL-5, and IL-13.

EMRS Pathophysiology

Superantigen Theory

Bacteria may play a role in the development and persistence of inflammation in patients with CRSwNPs. *S. aureus* and its enterotoxin products [*S. aureus* enterotoxin (SAE)] can behave as superantigens activating T cells in a nonantigen-specific fashion resulting in chronic inflammation.[19] SAE can directly activate T cells by bridging the MHC class II molecule with the T-cell receptor, bypassing the particular antigen specificity of the APC. It has been hypothesized that the superantigen mechanism is involved in over half of all patients with CRS with polyps.[20] High total IgE, polyclonal IgE to multiple allergens, and IgE to SAE characterize the disease. This process may be involved in patients also with AERD. The hypothesis that SAEs cause CRS is suggested by the high rate of colonizing *Staphylococcus* in CRSwNP, and the observation that lymphocytes from CRSwNP patients demonstrate increased responsiveness to superantigens.[21] It has been proposed that patients with CRSwNP are susceptible to amplification and persistence of eosinophilic inflammation due to the effect of SAE.[22] SAE-specific IgE levels are associated with increased IL-5, eosinophilic cationic protein, and comorbid asthma but the relationship between *Staphylococcus* and NP still needs further clarification.

Biofilm: In patients with recalcitrant sinusitis, biofilm may play a role in perpetuating inflammation and epithelial dysfunction. Biofilms are organized communities of microorganisms encased in a polysaccharide matrix, allowing for increased resistance to host defenses and antimicrobial agents.[23] Increased disease severity and persistence of postoperative symptoms including infection and mucosal inflammation have been described in patients with CRS associated with biofilm.[24] Several biofilm-producing microbes have been detected in CRS including *S. aureus, Haemophilus influenzae, Pseudomonas aeruginosa,* and even fungus.[25] Bacterial biofilm has been recently described to provide the inflammatory conditions that can allow proliferation of fungal biofilm.[26] As described previously, *S. aureus* biofilms produce enterotoxins that can then behave as superantigens to escalate inflammation and also cause infection of sinonasal epithelial cells.[27] Pseudomonal biofilm has been associated with chronic respiratory

diseases including CF and can result in significant mucosal injury via secretion of enzymes and neutrophil degradation products. It is also plausible that a diminished innate immune response could predispose patients to biofilm formation. Decreased levels of the antimicrobial peptide lactoferrin as well as SPLUNC1 have been described in patients with biofilm-associated disease.[28,29]

Innate Immune Dysfunction: The sinonasal mucosal tract is lined by respiratory epithelium, which serves as a dynamic interface between the external environment and adaptive immune system. Mucociliary clearance is the primary mechanism of the innate immune system and is composed of a constantly moving mucous blanket. Sinonasal epithelial cells also play an active role by detecting potential pathogens at the surface via pattern-recognition receptors such as Toll-like receptors, and the secretion of antimicrobial molecules. Deficiencies in mucociliary clearance and innate immune function of the sinonasal mucosa can create a permissive environment for microbial colonization, infection, and chronic inflammation. Decreased expression of innate immune markers such as TLR-9, human beta-defensin 2, and surfactant protein[30] as well as diminished expression of the antimicrobial protein, lactoferrin, in the nasal mucosa, could result in increased predisposition to chronic inflammation and biofilm infection.[28] Epithelial dysfunction is characteristic of nasal polyposis and mechanisms in host defense, tissue repair, and regulation play important roles in maintaining homeostasis that may be deficient in these patients.

EMRS Treatment

Corticosteroids: Treatment of patient with polyposis includes topical and systemic corticosteroids and often surgery to allow for better access for topical therapy and irrigations. Sinus surgery and direct delivery to the sinuses with corticosteroids result in greater symptom improvement.[31] Mucosal edema, mucociliary function, and olfaction often improve with corticosteroid therapy. A recent systematic review of 46 studies, including randomized controlled trials, showed that topical corticosteroids improve symptom scores, decrease polyp size, and prevent polyp recurrence after surgery.[32] A greater reduction in polyps was also seen when topical steroid was administered after sinus surgery. Oral corticosteroids are often necessary for patients who have uncontrolled nasal polyposis and are helpful in the perioperative period. A randomized double-blind placebo-controlled trial demonstrated that prednisone 30 mg given for 5 days preoperatively and 9 days postoperatively reduced the technical difficulty of endoscopic sinus surgery and improved endoscopic assessment up to 6 months postoperative with the strongest effect seen at 2 weeks post-op.[33] Patients in this trial had failed medical therapy including 3 months of intranasal steroids, saline irrigations, and a 4–6-week course of culture-directed antibiotic therapy. Patients were also offered a tapering trial of systemic steroids and failure was defined as recurrence/persistence of symptoms and polyps within 2 months of taking steroids.

Antibiotics: The role of antibiotics and bacteria in nasal polyposis remains unclear. Although certain bacteria are commonly cultured from patients with CRSwNP such as *S. aureus* and *P. aeruginosa*, causation has not been shown. Short-term culture-directed antibiotic seems to be a reasonable strategy in patients with infectious exacerbations and topical antibiotics may be helpful in selected populations such as in CF. Only a few randomized trials have been conducted. Patients with recalcitrant CRS with and without polyps treated with a 12-week course of low-dose azithromycin showed no benefit over placebo.[20] Another study excluding patients with nasal polyposis, however, did show improvements particularly in the patients with low IgE suggesting that macrolides may have benefit in patients with neutrophilic inflammation.[34] Further rigorous studies are needed to define which populations of patients may benefit from antibiotic therapy.

Role of allergy: The correlation between allergy and CRS remains controversial and the data is mixed.[35] There has been increased interest in the use of anti-IgE therapy, omalizumab, for patients with CRSwNP and asthma. A recent study showed decrease in total nasal endoscopic polyp score and quality of life after 16 weeks of omalizumab therapy in comparison to control. Although it appears that IgE plays an important role in the pathophysiology of inflammation in CRSwNP patients regardless of atopic status, further research is needed in determining selection criteria for anti-IgE therapy.[36] Recently, food allergies have also been implicated as a possible cause of eosinophilic NPs. In 50 NP patients in Austria, 14% demonstrated in vitro evidence of dairy hypersensitivity compared with 0% of controls. Similarly 14% showed wheat sensitivity; however, controls had a similar rate of hypersensitivity. The definitive test of eliminating the food and determining whether NP regressed was not done.[37] In another study of patients with NPs, 81% of 80 NP patients had positive

intradermal food allergy testing compared with just 11% of controls. Elimination of the food and impact on NP and symptoms was not performed.[38] Anecdotally elimination of foods such as wheat or dairy in a small but still significant number of patients with NPs leads to improvement in congestion, drainage, and/or fatigue. Additional studies translating known hypersensitivities into observations on physical findings such as NPs or validated symptom scores are needed.

Aspirin-Exacerbated Respiratory Disease

Patients with AERD, also known as Samter's triad, have the most refractory sinus disease with the highest rate of revision surgeries and shortest interval time between surgeries. The aspirin triad is characterized by nasal polyposis, asthma, and sensitivity to aspirin. Other medications, such as NSAIDS, that inhibit the eicosanoid pathway, also cause symptoms in patients that can often be severe including bronchoalveolar constriction.

AERD Pathophysiology

The imbalance in production of inflammatory leukotrienes and prostaglandins are central to AERD pathophysiology. Overproduction of cysteinyl leukotrienes and prostaglandin D2 with reduction in prostaglandin E2 leads to airway inflammation.[39] Although the mechanism is still unclear, alterations in COX inhibition and kinetics of enzymes critical in the leukotriene pathway appear to be involved in resulting inflammation and nasal polyposis. Patients with AERD have elevated numbers of nasal inflammatory leukocytes expressing the CysLT1 receptor in comparison with patients without aspirin sensitivity.[40]

AERD Treatment

Medical therapy in conjunction with endoscopic sinus surgery to decrease polyp burden is often required. Leukotriene inhibitors such as montelukast, zafirlukast, and zileuton in conjunction with topical and/or systemic steroids can be helpful. Polyps in these patients have a high rate of recurrence and patients with a history of AERD especially in the setting of recalcitrant nasal polyposis should be considered for aspirin desensitization. Desensitization is usually performed postoperatively once the patient has healed from endoscopic sinus surgery. Patients need to be closely monitored and are therefore admitted to a pulmonary unit while aspirin is administered. Aspirin is given orally increasing to 100 mg on day one and up to 500 mg on day two. Patients can be maintained at 100 mg daily,[41] but the dosing needs to be individualized to the patient's symptoms. Most patients require 325 mg twice daily. A step-down approach has been proposed from 650 mg twice daily for 1 month, then to 650 mg in AM/325 mg in PM, then to 325 mg twice daily. Dosing is increased if symptoms such as nasal congestion return.[42] Desensitization may decrease recurrence of nasal polyposis and improve quality of life.

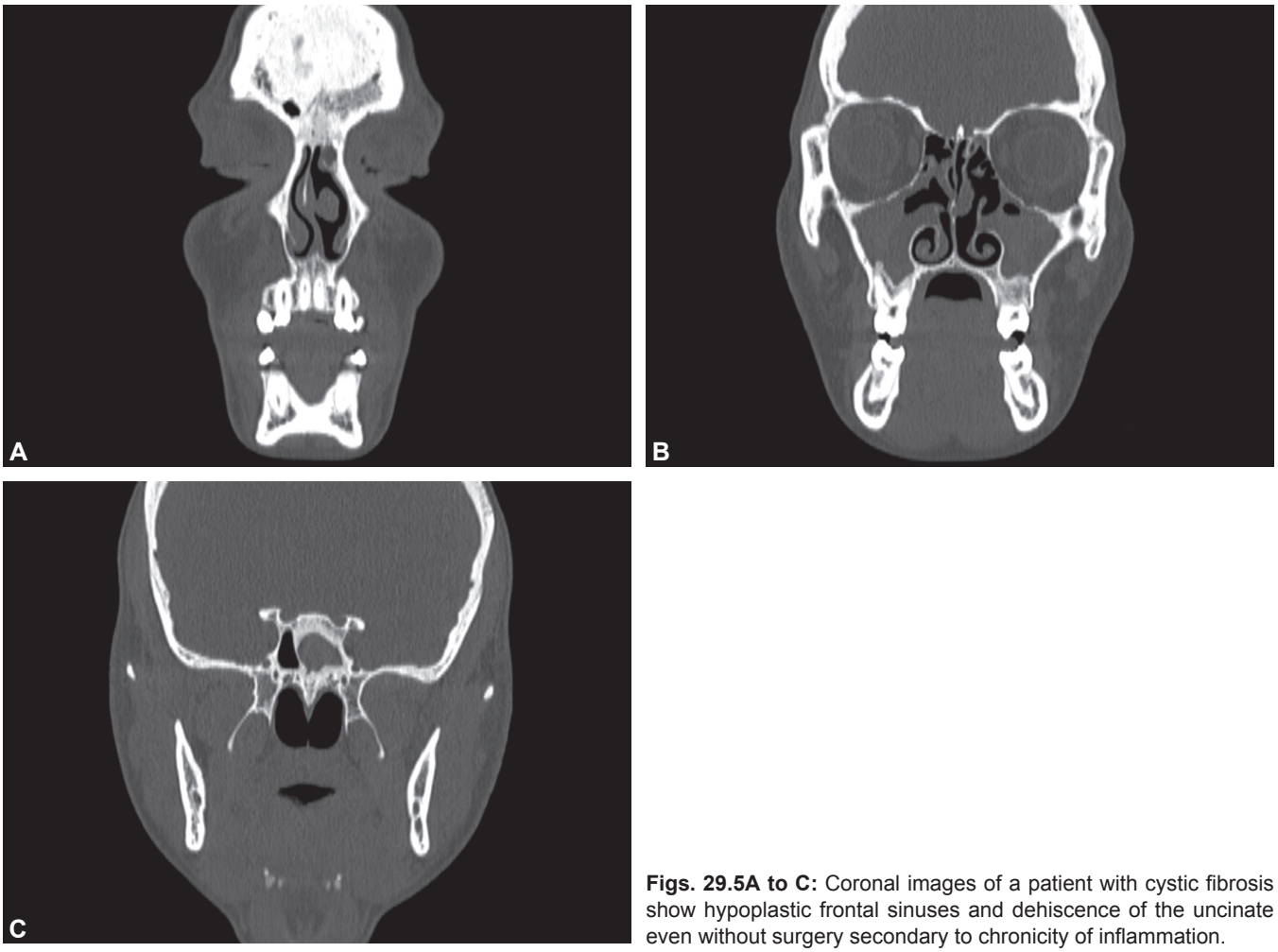
Cystic Fibrosis

Cystic Fibrosis Pathophysiology

Cystic fibrosis (CF) is an autosomal recessive disease characterized by mutations of the q31 region of chromosome 7 resulting in defective chlorine ion transport by the transmembrane conductance regulator protein (CFTR). Decreased chloride ion transport leads to increased absorption of water and sodium ion from the lumen of cells, increased viscosity of mucous, impaired mucociliary clearance, infection, and inflammation. A sweat chloride level >60 mEq/L is diagnostic for CF.

Patients with CF often have difficulty with chronic bacterial infections of their sinuses with *Pseudomonas* species. Steinke et al. recently showed that the long-standing notion that CF NPs were primarily neutrophilic was simplistic and that most have predominately an eosinophilic component with admixed neutrophils in 70% of the eosinophilic NPs. However, over 40% of the NP from CF patients had neither eosinophilic nor granulocytic infiltrate. Higher extracellular DNA concentrations were present in the mucus of CF patients than from non-CF sinus disease.[43] In CF NP, more so than any other NP classification, neutrophils predominate histologically, and are presumably present because of the associated biofilm infections (usually pseudomonas), so common in CF patients. Of all NP, the cytokine IL8, a neutrophil attractor, is dominant in the CF phenotype, compared with IL 5 dominance (eosinophil attractor) found in most other inflammatory NPs.

Mutations in the CFTR gene may account for NP in patients without clinical CF. In a recent large comparative study in Poland, 10% of adults with NP but without CF (negative sweat test) were heterozygotes for the ΔF508 CFTR mutation, compared with a baseline presence of the gene in the population of 1%.[44] Estimates of the frequency of NP in patients with CF vary from 6% to 60%, with differential expression of NP based on CFTR mutation.



Figs. 29.5A to C: Coronal images of a patient with cystic fibrosis show hypoplastic frontal sinuses and dehiscence of the uncinate even without surgery secondary to chronicity of inflammation.

In children with CF, NPs are usually noted sometime between the ages of 5 and 20, but can be appreciated in heterozygous mutations late into adult hood. Patients with CF usually have hypoplasia of the sinuses and dehiscence of the uncinate process even without surgery secondary to chronic inflammation (Figs. 29.5A to C).

Cystic Fibrosis Treatment

Medical therapy in the patient with CF includes nasal saline irrigations and appropriate antibiotic therapy. Hypertonic saline can be useful to clear thick mucous and biofilm. The addition of surfactant to irrigations can also help clear biofilm and 1% baby shampoo has been reported to inhibit Pseudomonal biofilm formation.[45] Other medications including intranasal steroids and cyclooxygenase inhibitors such as ibuprofen may be helpful. Intranasal corticosteroids have been reported to reduce inflammation by reducing the size of polyps. A recent review however could not find a demonstrable effect of topical nasal steroids on nasal symptom scores.[4] High-dose ibuprofen therapy has shown promise in slowing the progression of lung disease in CF patients and also in reducing polyp size in children with CF.[6] Further trials are needed to determine efficacy. *Pseudomonas* and *Staphylococcus* species are often cultured from the sinuses of CF patients with mucopurulence and culture-directed antibiotic therapy is important in managing infectious exacerbations. Often nebulized tobramycin is used to treat the pulmonary component and gentamicin irrigations can be helpful to treat the sinuses. The evidence for topical therapy, however, remains limited. Dornase alfa is a mucolytic agent that cleaves extracellular DNA and has the potential to reduce viscosity of secretions in patients with CF and improve symptom-specific quality of life.[46]

Endoscopic sinus surgery (ESS) is indicated for patients who continue to be symptomatic despite efforts to control their disease medically. Patients with exacerbations of pulmonary function due to repeated sinus infections, especially in patients who have undergone double-lung transplant are considered for sinus surgery. Whether surgery helps improve lung function, however, is unclear. Systematic reviews on the role of endoscopic sinus surgery in the management of CF indicate that surgery in patients with CF results in clinical improvement via symptom scores and endoscopic findings but do not consistently improve pulmonary function.[47,48] Meta-analysis of FEV1 scores following ESS did not reach statistical significance. The goal of surgery is to allow for improved access to the sinuses for irrigation, debridement, and topical therapy. The extent of surgery should be tailored to the patient's severity of disease seen on sinus CT. Careful perioperative management is crucial due to potential problems with bleeding and infection. Coordination with the patient's pulmonologist and anesthesiologist are necessary and optimization of coagulation status, antibiotic therapy, and meticulous technique are helpful to achieve the best surgical outcome. Despite the best of efforts, recurrence of polyps and persistent infection with *Pseudomonas* and *S. aureus* is common secondary to mucous stasis and inflammation. The median interval between surgeries has been reported to be approximately 4 years with a range from 18 months to > 6 years.[49]

Respiratory Epithelial Adenomatoid Hamartoma (REAH)

REAH are less common and often found coexisting with more common eosinophilic or chronic inflammatory NPs. Sporadic cases of hamartomas of the nasopharynx were reported prior to the definitive case series of 31 patients by Wenig and Heffner in 1995.[50] REAH can present uni- or bilaterally, with nonspecific symptoms indistinguishable from other inflammatory NP. The site of origin is usually high in the nasal cavity and olfactory cleft area, but REAH may also arise from the middle meatus, ethmoid, maxillary and frontal sinuses, inferior turbinates, and the nasopharynx. Conservative surgical resection is usually curative, with no recurrences reported in variable follow-up periods (from 4 months to 5 years).[51] Histologically, there is usually hyperplasia of the seromucinous glands within the polyp, lined by ciliated respiratory epithelium. On macroscopic examination they are slightly more rubbery and indurated than the usual benign inflammatory glistening NP. REAH NP usually arise unilaterally from the posterior superior septum and if occurring bilaterally, cause widening of the olfactory cleft.[51] Widening of the olfactory cleft is significantly greater in REAH than in benign NP.

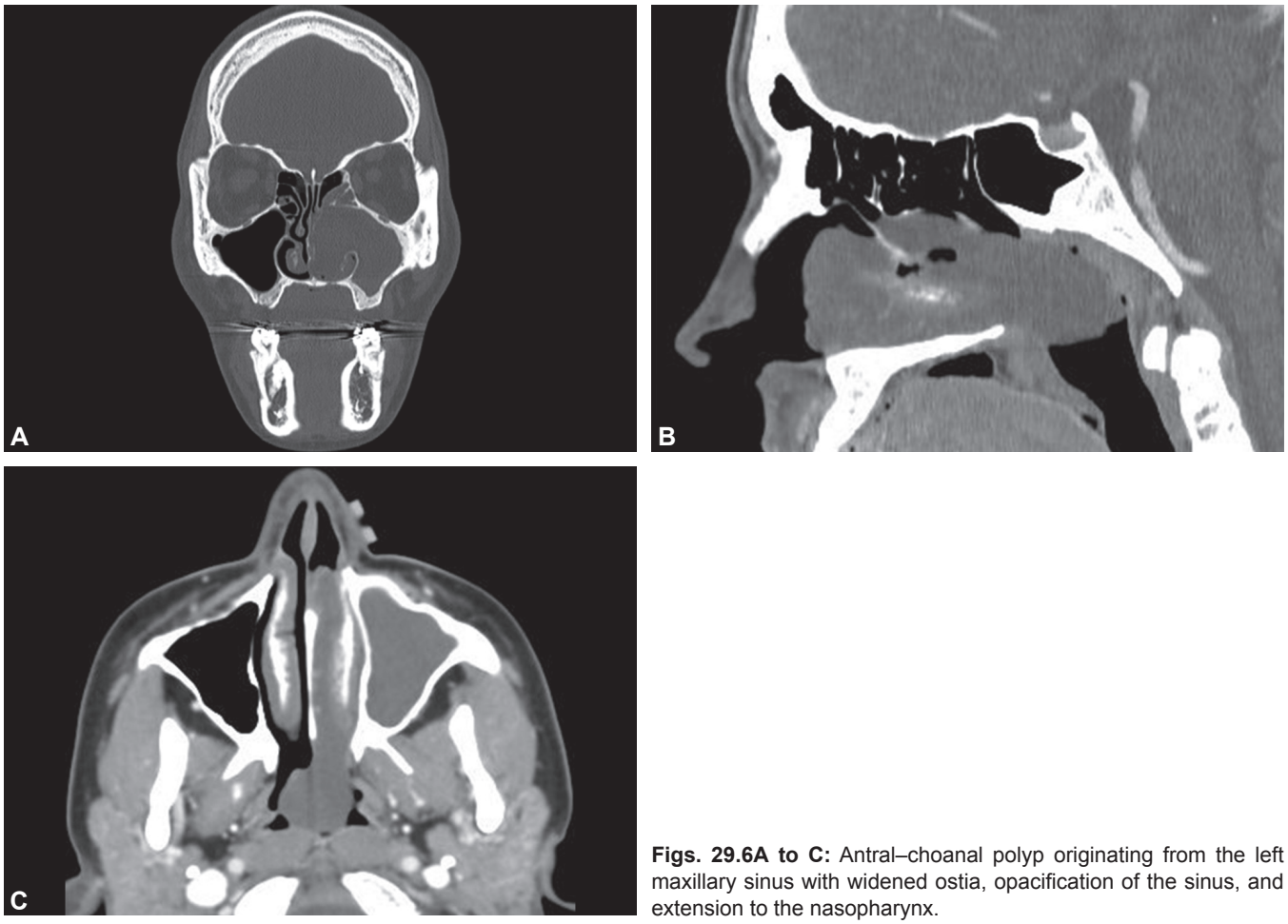
Antral–Choanal Polyps

ACPs are unilateral NP arising from maxillary sinus mucus cysts and consist of a homogeneous, hypocellular, noneosinophilic edematous stroma, covered by intact respiratory epithelium. The nasal portion of the ACP is often much more fibrous than the maxillary portion, possible due to long-standing presence in the nose associated with trauma from constant respiratory movement over months to years. This can then lead to scarring and associated inflammation.

ACPs usually arise on the posterior and medial wall of the maxillary sinus, enlarge an accessory ostia in 50–70% of cases, the natural ostia in 30–43% or both in 6%, as they continue to grow into the nose and posteriorly into the nasopharynx (Figs. 29.6A to C). The first report of an ACP is attributed to Palfyn in 1753, and was detailed by Killian in 1906 and are nonresponsive to steroids and occur in a younger demographic than patients with bilateral eosinophilic NP. CT imaging usually shows a mass filling the maxillary sinus with opacification of the middle meatus and extension into the nasopharynx. MRI is not required for diagnosis but if available will show a T1 hypodensity and enhanced brightness on T2. Treatment is removal, usually endoscopically. External approaches, such as via a mini Caldwell-Luc are rarely needed but may be helpful in revision cases. Endoscopic removal can be facilitated with a large middle meatal antrostomy and the use of curved grasping forceps to work via the antrostomy down to the maxillary sinus attachment, which is usually posteriorly based. A curved microdebrider is also helpful. Recurrence is common if the site of growth initiation within the maxillary sinus is not removed.

CONCLUSION

It is increasingly becoming clear that nasal polyposis is a final inflammatory manifestation of multiple possible pathways including dysfunctional epithelial and immune function. Although the etiology of nasal polyposis is still largely unknown, efforts to clarify the role of genetics, interaction with potential pathogens, allergy, and the innate and adaptive immune system continue to be



Figs. 29.6A to C: Antral–choanal polyp originating from the left maxillary sinus with widened ostia, opacification of the sinus, and extension to the nasopharynx.

pertinent. In the majority of cases, nasal polyposis is a benign disease that can significantly impair quality of life. Therefore, a targeted approach to the patient's symptoms, comprehensive medical management, meticulous surgical technique to preserve mucociliary function, and continued follow-up are important in the care of patient with polyps.

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CHAPTER

30

Fungus in Paranasal Sinus Disease

Kent Lam, Christopher Vanison, Robert C Kern

INTRODUCTION

Rhinosinusitis is a common inflammatory disorder of the nasal cavities and paranasal sinuses, affecting an estimated 5–15% of the population.[1] Although viruses and bacteria have traditionally been regarded as the prevalent causative organisms in both acute and chronic rhinosinusitis (CRS), fungal species have increasingly become implicated as an additional group of exogenous etiologic agents. Conceptualizations of the etiologic role that fungi play in rhinosinusitis have been based on evidence showing that fungi can cause disease through various mechanisms, including direct infectious invasion, surface colonization of sinonasal mucosa, and induction of allergic responses. Concepts of fungal rhinosinusitis, however, remain an evolving subject in the field of medicine as continued research aims not only to better elucidate the relationship between fungi and sinonasal diseases but also to develop effective therapeutic interventions.

A widely accepted classification system currently separates cases of fungal rhinosinusitis as either invasive or noninvasive. This distinction is determined by the histopathological presence or absence of sinonasal tissue invasion by fungal elements.[2-5] Additional features used to characterize different forms of fungal rhinosinusitis include immunologic status and duration of signs and symptoms.[6] Based on these factors, invasive fungal rhinosinusitis is subdivided into three distinct forms: acute invasive fungal rhinosinusitis (AIFRS), chronic invasive fungal rhinosinusitis (CIFRS), and granulomatous invasive fungal rhinosinusitis (GIFRS). Noninvasive types of fungal rhinosinusitis include allergic fungal rhinosinusitis (AFRS), saprophytic fungal colonization, and paranasal sinus fungus balls (FB). The features characterizing each of these subgroups are detailed in Table 30.1.

The classification system reflects the diverse manifestations of fungal rhinosinusitis, each of which is defined by distinct patterns of disease progression, associated prognosis, and therapeutic modalities. Distinguishing these varying features enables clinicians to adequately diagnose and initiate appropriate treatment strategies for sinonasal fungal infections. This chapter highlights these different classes of fungal rhinosinusitis and their inherent clinical, radiographic, and histopathologic characteristics.

BASIC MYCOLOGY IN FUNGAL RHINOSINUSITIS

Fungi constitute a kingdom of ubiquitous eukaryotic organisms that actively function in the decomposition and recycling of organic matter within the environment. The total number of fungal species ranges from 50,000 to as many as 5.1 million. Of these species, only about 400 are actual human pathogens, and approximately a dozen are responsible for 90% of the most commonly encountered fungal infections.[7-9] Pathologic fungi may be exogenous, primarily residing in the water, soil, and organic debris of the environment prior to their entry into the aerodigestive tracts of human hosts; or endogenous, contributing to the normal microbial flora of human surface tissues. In general, an intact immune system effectively prevents serious human infections attributed to fungal organisms. Human diseases of fungal etiology therefore tend to be opportunistic, resulting from the interactions between fungi and a host immune system that is absent, impaired, or dysfunctional.

Table 30.1: Spectrum of manifestations of fungal rhinosinusitis

Fungal manifestation	*Histopathology*	*Immunologic status*	*Chronicity*
Invasive			
• Acute invasive fungal rhinosinusitis	Invasion of fungal hyphae beyond mucosa with prominent angioinvasion, tissue necrosis, and scant inflammatory cellular infiltration. Primarily *Aspergillus* and *Zygomycetes* organisms	Immunocompromised	Less than 4 weeks duration
• Chronic invasive fungal rhinosinusitis	Invasion of fungal hyphae beyond mucosa with modest inflammatory cellular infiltration and an appearance of a sinus fungal ball. Primarily *Aspergillus flavus* and dematiaceous molds	Mildly impaired immune function from diabetes mellitus or chronic steroid use	At least 12 weeks duration
• Granulomatous invasive fungal rhinosinusitis	Invasion of fungal hyphae beyond mucosa but contained within multinucleated giant cells producing a noncaseating granuloma. Primarily *Aspergillus flavus*	Immunocompetent	At least 12 weeks duration
Noninvasive			
• Allergic fungal rhinosinusitis	Noninvasive fungal hyphae contained within sheets of eosinophils and Charcot–Leyden crystals producing an allergic mucin and chronic inflammation along the mucosa. Primarily *Aspergillus* species and dematiaceous molds	Atopy	At least 12 weeks duration
• Saprophytic fungal colonization	Fungal elements isolated from nasal secretions and crusting	Immunocompetent	Nonspecific
• Paranasal sinus fungus ball	Accumulation of fungal hyphae without tissue invasion but with predominance of eosinophils, granulomas, or allergic mucin. Primarily *Aspergillus* species	Immunocompetent	Nonspecific

Fungal organisms are heterogeneous in morphology, existing in both mold and yeast forms. Molds are multicellular and produce hyphae, which are branching tubular extensions that may coalesce to form a mycelium. Yeasts, in contrast, are unicellular and reproduce asexually by budding into separate cellular components. Yeasts may form pseudohyphae if the asexual reproductive process results in the incomplete separation of budding cells. Both molds and yeasts have the capacity to produce spores, which are reproductive units that enable fungi to remain latent and widely disperse over long distances during times of adverse conditions. Fungal spores resume their germinative potential when more favorable conditions are encountered. Introduction of fungi into the sinonasal cavities routinely occurs though the inhalation of spores from the environment.[10,11]

Common fungal species responsible for both the invasive and noninvasive forms of fungal rhinosinusitis vary geographically, but the most frequently encountered microorganisms in fungal rhinosinusitis are the *Aspergillus* species, the species that belong to the class of Zygomycetes, and the dematiaceous molds. All three groups may be differentiated by their structural characteristics on histopathologic sections. The rate of growth, texture, and pigmentation are other features used to distinguish these molds when they are inoculated under standard growth conditions in the laboratory.[8]

In particular, the *Aspergillus* species exhibit narrow hyphae with regular septations and 45-degree branches, as depicted in Figure 30.1. In contrast, the Zygomycetes organisms, including *Mucor*, *Rhizopus*, and *Rhizomucor*, are broad, irregular ribbon-like structures without septations. Third, the defining feature of the dematiaceous molds is a melanized cell wall, which not only imparts a brown or black pigment to the appearance of the fungal organisms but also contributes to their virulence. Dematiaceous molds, which include *Alternaria, Bipolaris,* and *Cladosporium*, demonstrate septated hyphae with irregular branching patterns.[8]

INVASIVE FUNGAL RHINOSINUSITIS

Defined by the histopathological presence of tissue necrosis due to infiltration by fungal elements, invasive fungal

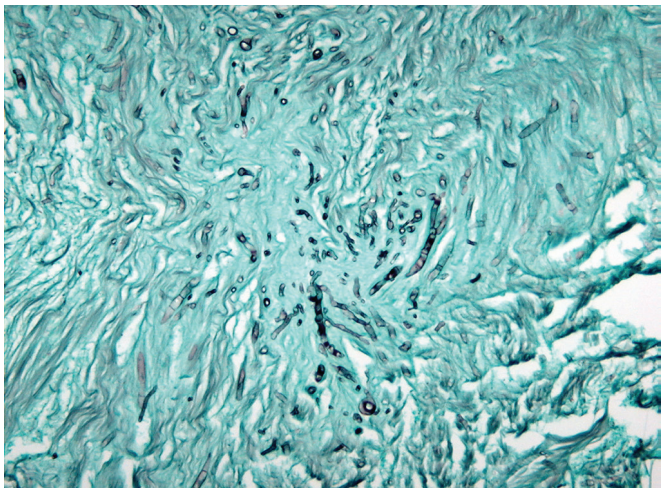


Fig. 30.1: Fungal hyphae of *Aspergillus* species on Grocott's methenamine silver stain (x20). The characteristic hyphal morphology of *Aspergillus* species is by regular septations and 45-degree branches.
Courtesy: Rakesh Chandra, MD, Department of Otolaryngology—Head & Neck Surgery, Northwestern University , Chicago, IL, USA.

rhinosinusitis is characterized by three distinct forms: AIFRS, CIFRS, and GIFRS.[3,4,12] AIFRS is the most serious of the three invasive manifestations, typically occurring in patients with significant immunologic compromise and portends a rapid progression of infection. Current medical advancements have prolonged the life expectancy of patients with various immunocompromised states, but the increased survival has also resulted in a larger population that is at risk of development of AIFRS.[13] CIFRS is also associated with an immunocompromised state, although the degree of impaired immune function is milder than that in AIFRS, whereas patients who develop GIFRS are usually immunocompetent.

AIFRS is additionally distinguished from CIFRS and GIFRS by the propagation of tissue invasion over a time course of less than 4 weeks.[3,6] CIFRS and GIFRS, however, are more characteristically indolent in the onset and progression of disease. Duration of at least 3 months with locally invasive fungal invasion is necessary to define CIFRS and GIFRS.[14]

ACUTE INVASIVE FUNGAL RHINOSINUSITIS

Overview

AIFRS provides the most dangerous and challenging manifestation of all forms of fungal rhinosinusitis with rapid progression of disease, significant morbidity, and high risk of mortality. The primary risk factor for the development of AIFRS is an altered host defense mechanism with an impaired neutrophilic response. Neutropenia is most traditionally correlated with absolute neutrophil counts below 500 cells/μL, but functional neutropenia, as relevant in patients with poorly controlled diabetes mellitus, has also been strongly linked to the development of AIFRS.[10,11,13,15] Impairment of the immune system results from a variety of medical disorders, including diabetes mellitus, acquired immunodeficiency syndrome, hemochromatosis, aplastic anemia, organ transplantation, and hematologic malignancies. Iatrogenic immunosuppression with use of chemotherapeutic agents and chronic systemic corticosteroids also predisposes individuals to AIFRS. Nonetheless, rare cases of AIFRS in individuals with an otherwise healthy immune system have been reported in the literature.[16,17]

The histopathology for AIFRS characteristically consists of direct fungal invasion of sinonasal tissue, specifically hyphal forms extending into the mucosa, submucosa, blood vessels, or bone of the nasal cavity and paranasal sinuses.[4] The affected tissue specimens demonstrate extensive areas of coagulative necrosis in a background of scant host inflammatory reactions.[18] Because the fungi implicated in AIFRS have a propensity to invade the surrounding blood vessels, the resulting angioinvasion is ultimately accompanied by vasculitis with thrombosis, which ultimately results in hemorrhaging and tissue infarction on histopathology.[13,19]

While AIFRS typically originates in the nasal cavities and paranasal sinuses, the aggressive fungal infection can rapidly extend into adjacent structures, including the orbit and intracranial cavity, within a period of hours or days.[20,21] Disease limited to the nasal cavity alone represents an early stage of the pathogenesis with improved likelihood of survival following initiation of treatment. In the absence or delay of diagnosis and treatment, however, the disease rapidly invades the anatomic structures beyond the sinonasal cavities. Turner et al. performed a systematic review with a total of 807 patients who were diagnosed with AIFRS and reported that disease extension beyond the sinonasal cavities occurred in over a majority of the patients. The most frequent sites of progression in this review included the orbit (49.6% of cases), intracranial compartment (21.2%), hard palate (20.8%), and cavernous sinus (8.6%).[22]

Cases of AIFRS that are caused by the Zygomycetes organisms are commonly designated as mucormycosis or zygomycosis. The occurrence of mucormycosis and zygomycosis is closely associated with diabetes mellitus, which

Turner et al. identified as the most common predisposing condition in patients with AIFRS (47.8%).[22] About half of these diabetic patients, furthermore, present in a state of diabetic ketoacidosis. The increased susceptibility to Zygomycetes organisms is based on an altered iron-binding capacity of transferrin proteins in the acidotic serum of diabetic patients when compared with that in patients without diabetes mellitus. The resulting alteration in iron metabolism is understood to provide a more favorable environment for the growth of the Zygomycetes organisms. Given the high virulence of Zygomycetes organisms in general, mucormycosis and zygomycosis are regarded as the most acutely aggressive fungal infections with significant potential for tissue necrosis and infectious propagation via vascular invasion.[11,23]

Besides the Zygomycetes organisms, the *Aspergillus* species form a second common fungal group that is routinely implicated as a causative agent in AIFRS. The *Aspergillus* species differ from the Zygomycetes organisms in their predilection for patients with hematologic malignancies, use of systemic chemotherapy, and use of chronic steroids.[7] Although *Aspergillus* species are also considered angioinvasive, their potency for obliterative invasion occurs at a lesser degree when compared with that of the Zygomycetes organisms.[24] *Aspergillus fumigatus* is the most common species that is responsible for AIFRS in the United States.

Clinical Presentation and Diagnosis

The presentation of AIFRS is nonspecific and variable, but this aggressive form of fungal rhinosinusitis should be suspected in immunocompromised hosts who develop fevers and acute onset of rapidly progressive localized sinonasal symptoms. Turner et al. reported facial swelling (64.5% of cases), fever (62.9%), and nasal congestion (52.2%) as the most common presenting symptoms in their review of 807 patients with AIFRS.[22] Rhinorrhea, epistaxis, periorbital swelling, headaches, facial pain, and anesthesia of the nasal mucosa and facial soft tissues are other symptoms suggestive of AIFRS in patients with immunologic compromise. Orbital and intracranial extension is highly suspicious in at-risk patients with accompanying signs and symptoms of diplopia, changes in visual acuity, mental status changes, and seizures. The presence of fever of unknown origin in the appropriate patient population, especially after 48 hours of appropriate broad-spectrum intravenous antibiotics, also raises concern for AIFRS.[12]

Similar to the subjective symptoms, the physical findings concerning for AIFRS are often subtle, making direct visualization of the nasal cavity a mandatory step in the evaluation of individuals with suspected AIFRS. Nasal endoscopy is essential for the examination, because anterior rhinoscopy often does not afford a full view of the nasal cavity. The most consistent physical finding for AIFRS is an alteration in the color and appearance of the nasal mucosa. White and black discoloration of the mucosa is indicative of various stages of AIFRS, representing tissue ischemia secondary to ongoing angiocentric invasion during the early stages of the disease course and tissue necrosis during the late stages, respectively.[13] The lower left quadrant of Figure 30.2 demonstrates the black discoloration of the middle turbinate in a patent with AIFRS. Crusting, ulcerations, decreased bleeding, and hypoesthesia of the intranasal mucosa are all complementary findings.

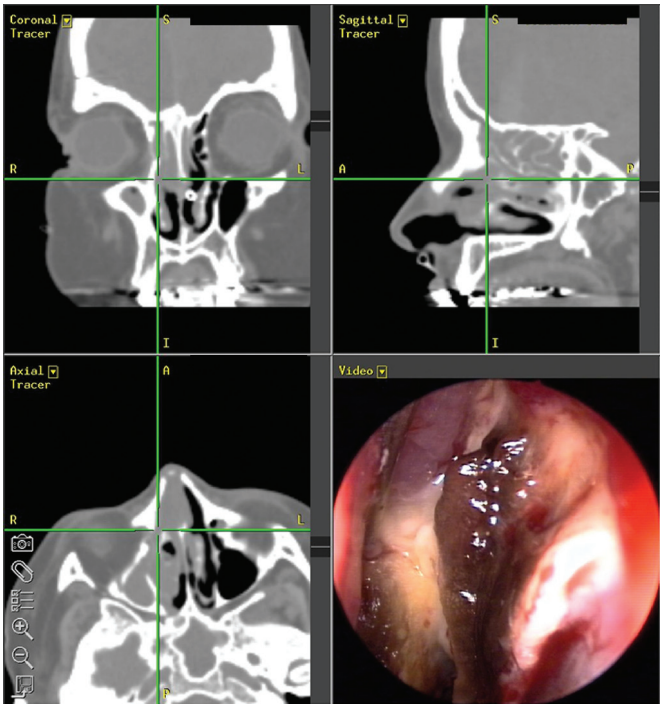


Fig. 30.2: Acute invasive fungal rhinosinusitis as seen on nasal endoscopy and diagnostic imaging. The endoscopic view of the right nasal cavity reveals a middle turbinate with significant black mucosal discoloration, suggestive of tissue necrosis from thrombosis-induced ischemia. The coronal, axial, and sagittal views of the computed tomography scan from the patient demonstrate predominantly unilateral soft tissue thickening and opacification of the right nasal cavity, specifically the ethmoid and sphenoid sinuses.
Courtesy: Rakesh Chandra, MD, Department of Otolaryngology—Head & Neck Surgery, Northwestern University , Chicago, IL, USA.

These mucosal abnormalities are most commonly found on the middle turbinate (67% of patients in a patient series with 25 patients with AIFRS), followed by the septum (24%), palate (19%), and then inferior turbinate (10%).[19]

In addition to a thorough evaluation of the nasal cavity, a complete physical examination of the head and neck provides other clinical clues that may suggest a highly aggressive infectious process with potential for extension beyond the sinonasal cavities. Palpation of the face in patients with AIFRS tends to elicit significant maxillary and nasal pain. Performing an examination of the oral cavity allows for inspection of the hard palate for diminished sensation, ulcerations, and mucosal necrosis, all of which may represent invasion through the inferior partitions of the maxillary sinuses. Immunocompromised patients with evidence of periorbital edema and erythema, ophthalmoplegia, proptosis, chemosis, or visual loss indicate likely orbital extension of the sinonasal infection, whereas an altered sensorium, neck tenderness, photophobia, and cranial nerve dysfunction are suggestive of intracranial involvement of any potential sinonasal fungal infection.

Diagnostic imaging for AIFRS primarily utilizes computed tomography (CT) and magnetic resonance imaging (MRI) to characterize the location and extent of infectious involvement of a fungal sinonasal infection. Diagnostic imaging additionally provides vital information regarding the sinonasal anatomy that aids in planning for potential surgical intervention. Sinus CT imaging generally serves as the initial imaging modality of choice, because it provides critical information regarding the anatomy and pathology of the sinuses, orbit, retro-orbital tissues, and intracranial structures. Severe soft-tissue thickening of the nasal cavity mucosa and unilateral sinus opacification, with a tendency to involve the ethmoid and sphenoid sinuses, have been shown to the most consistent findings for underlying AIFRS. In advanced disease, evidence of bony erosion or soft tissue invasion is further evident on CT imaging.[7,25] The representative cross-sections of a CT scan for a patient with AIFRS are included in Figure 30.2.

For patients with potential orbital or intracranial extension of AIFRS, MRI is superior to CT in delineating the extent of the disease. On MRI, inflammatory changes in the orbital fat and extraocular muscles denote intraorbital invasion by sinonasal fungal infections. Infiltration and obliteration of the periantral fat planes on MRIs have been found to represent the earliest imaging evidence of AIFRS.[26] For intracranial extension, leptomeningeal enhancements may be evident as early diagnostic clues on MRIs, while overt evidence of cerebritis, granulomas, and cerebral abscess formation may indicate advanced infections.

Establishing a diagnosis of AIFRS ultimately requires adequate biopsy specimens of diseased and healthy sinus mucosa for pathology and cultures. In order to expedite the initiation of a therapy regimen for AIFRS, tissue biopsies are usually sent for microscopic examination using both frozen and permanent sections. For frozen sections, the use of potassium hydroxide and calcofluor white in the laboratory provides a highly sensitive and efficient technique to quickly evaluate for fungal elements invading into the sinonasal mucosa and to also determine the fungal morphology. Potassium hydroxide serves to dissolve human material that could otherwise be mistaken as fungus, while calcofluor white is an optic brightener that binds to the cell walls of fungal hyphae. Specialized microscopes can thereafter be used to detect the fluorescent cell walls of fungi included in the clinical specimens.[12]

Following initial evaluation with the potassium hydroxide-calcofluor white method, permanent histopathologic sections must be completed to confirm the diagnosis of AIFRS. Permanent histopathologic evaluation of the suspicious biopsy specimens is primarily performed with Grocott's methenamine silver (GMS), which is regarded as the most sensitive of the commonly used histologic stains to detect the presence of fungal cell walls. Fungal cultures are additionally taken from biopsy specimens, although results may take days to weeks to grow and should not delay the treatment of AIFRS. Cultures nonetheless provide important details regarding antifungal susceptibility and help direct medical therapy.[5]

Treatment and Prognosis

Therapy for AIFRS incorporates a multimodality approach, which includes primary reversal of the underlying predisposing condition, medical treatment with both systemic and topical antifungal drugs, and surgical debridement of all tissue with evidence of fungal invasion. Of these three modalities, treatment of the predisposing condition is the most important, because survival is highly dependent on the ability to reverse the afflicted patients' neutropenia. Thus, for diabetic patients, efforts should be made to correct their diabetic ketoacidosis, treat the underlying dehydration, and maintain strict glycemic control. For patients with organ transplantations or hematologic

malignancies, white blood cell transfusions and administration of granulocyte colony stimulating factor to increase an absolute neutrophil count to above 1000 cells/μL have been shown to improve survival.[12,27]

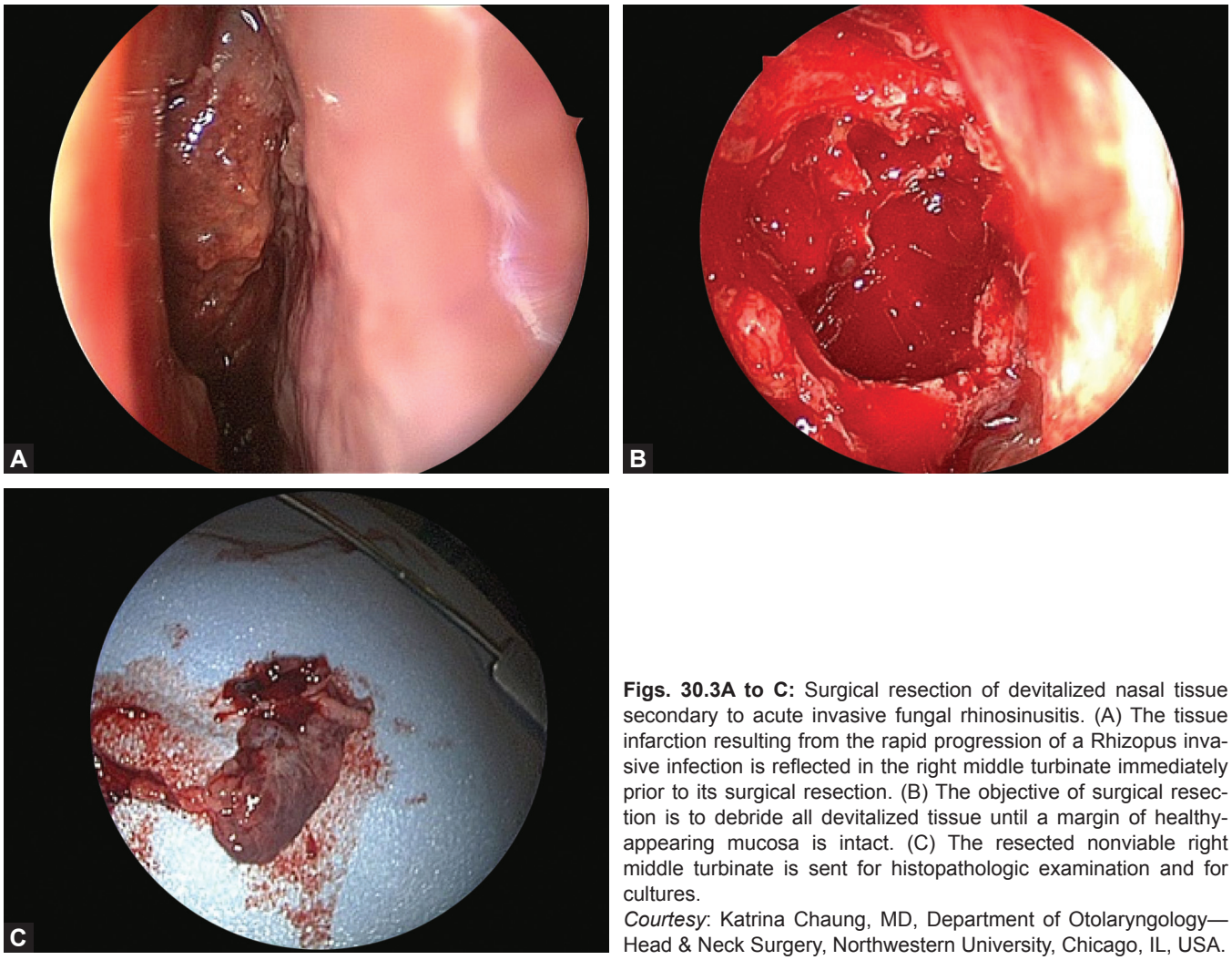
Medical therapy for most patients who have AIFRS consists of both systemic and topical antifungal therapies. Deoxycholate amphotericin B, with its fungicidal activity against a wide range of pathogenic microorganisms, serves as the drug of choice for systemic antifungal therapy at intravenous doses of 0.6–1.2 mg/kg/day up to a total dose of 2–4 g/day. The use of deoxycholate amphotericin B, however, may be limited in critically ill patients by the drug's side effects. Nephrotoxicity is the most established side effect, occurring in approximately 80% of patients treated with deoxycholate amphotericin B, but other adverse symptoms associated with its use include fevers, chills, nausea, hyperkalemia, and hypotension. These toxicities can be reduced or eliminated, while delivering a high concentration of the antifungal agent, with the use of lipid-based formulations of amphotericin B at a concentration of 3–5 mg/kg/day. The higher drug expenses of liposomal amphotericin B, however, have limited the routine use of this formulation in all AIFRS cases.

In addition to amphotericin B, intravenous voriconazole has increasingly become an important drug for medical treatment of AIFRS that is attributable to an *Aspergillus* species as the etiologic pathogen. The advantage of voriconazole over amphotericin B is a much favorable side effect profile, although use of voriconazole as monotherapy in cases of mucormycosis and zygomycosis is limited by the resistance that Zygomycetes organisms have developed to the drug. Voriconazole can thus be used in place of amphotericin B only when Zygomycetes organisms are ruled out as the etiologic agents.[12,28] With either amphotericin B or voriconazole, nonetheless, systemic administration of antifungal therapies can be further supplemented with intranasal application of these drugs through nasal irrigations and nebulizer treatments. The potential benefits of such topical therapies outweigh the minimal risks of these adjunctive measures.

Operative intervention serves as the third modality in treatment of AIFRS, with aims to slow the progression of the disease, reduce the fungal load, improve penetration of antimicrobial agents, and provide a specimen for culture and histopathologic diagnosis. The goal of surgical intervention in cases of AIFRS is to debride all devitalized tissue until clear bleeding margins remain. An endoscopic approach to debridement has largely replaced external surgical approaches, as depicted in Figures 30.3A to C, although external approaches may still be the most appropriate approach for removal of disease outside the sinonasal cavity. Radical resections, including radical maxillectomy, craniofacial resection, and orbital exenteration, rarely achieve negative margins or improve long-term survival, however. A highly individualized approach is indicated and these procedures may be more appropriate if negative margins are anticipated and the underlying etiology of neutropenia has been reversed. Thus, patients with orbital or intracranial spread of disease should be appropriately counseled when a radical surgical procedure is considered. A second-look procedure should be scheduled within 48–72 hours if residual disease in the sinonasal cavity is suspected. Follow-up consists of weekly rigid nasal endoscopy until reversal of neutropenia, and should be once a month for 6 months thereafter.[12]

The mortality associated with the aggressive infection has traditionally been regarded as high at 50–80%, with fatality almost certain in patients with symptomatic intracranial involvement.[13,19] Recent case series, however, have reported mortality rates that have improved from prior figures, likely due to increased understanding of the disease and early initiation of treatment. Turner et al. established an overall survival rate of 49.7% in a systematic review with 807 patients.[22] Parikh et al. even noted an overall mortality rate of 18% in a group of 45 cases of AIFRS.[21] Significant negative prognostic factors associated with increased mortality from AIFRS include advanced age of afflicted patients, preexisting renal and liver failure, altered mental status, and intracranial extension of the infectious process. Aggressive surgical resection of devitalized tissue and initiation of liposomal amphotericin B are regarded as positive prognostic predictors.[22]

Conflicting results, however, exist regarding the use of diabetes mellitus as a positive or negative prognostic predictor for AIFRS. Smaller case studies have previously reported that mortality from AIFRS is significantly higher with diabetes mellitus as the predisposing conditions than with other causes of immunosuppression.[21] In these case studies, the mortality in diabetic patients is attributed to the highly aggressive nature of Zygomycetes organisms and the delayed diagnosis of AIFRS in this patient group. More recent reports, however, have noted that diabetic mellitus is actually a positive prognostic predictor, citing



Figs. 30.3A to C: Surgical resection of devitalized nasal tissue secondary to acute invasive fungal rhinosinusitis. (A) The tissue infarction resulting from the rapid progression of a Rhizopus invasive infection is reflected in the right middle turbinate immediately prior to its surgical resection. (B) The objective of surgical resection is to debride all devitalized tissue until a margin of healthy-appearing mucosa is intact. (C) The resected nonviable right middle turbinate is sent for histopathologic examination and for cultures.
Courtesy: Katrina Chaung, MD, Department of Otolaryngology—Head & Neck Surgery, Northwestern University, Chicago, IL, USA.

the ability to promptly reverse diabetic ketoacidosis and to control hyperglycemia as a possible reason for the improved survival in this patient subgroup.[22]

CHRONIC INVASIVE FUNGAL RHINOSINUSITIS

CIFRS is a rare form of invasive fungal sinusitis that most frequently occurs in patients with mild immune dysfunction from diabetes mellitus, chronic low-dose corticosteroid use, or other ongoing immunosuppression. *Aspergillus flavus* and the dematiaceous molds, including *Bipolaris, Curvularis, and Alternia*, are the most frequently responsible organisms associated with CIFRS.[14] Compared with the rapidly fatal course of AIFRS, CIFRS is characterized by an indolent progression of symptoms, with manifestation occurring over a course of 12 weeks or longer. Early symptoms corresponding with CIFRS include nasal congestion, facial pain, and headaches. Because of the nonspecific nature of the symptomatology, the disease may be advanced at the time of diagnosis with resulting proptosis, decreased visual acuity, and abnormalities in ocular mobility following extension of the indolent fungal infection into the orbital compartment.[29]

The diagnostic workup of immuncompromised patients with suspected of CIFRS requires a similar head and neck examination that is essential for evaluation of AIFRS. Nasal endoscopy of patients with suspected CIFRS allows for biopsies to be collected for histopathologic confirmation of direct fungal invasion of nasal tissue in CIFRS. As opposed to the highly necrotic and angiotrophic process seen in AIFRS, CIFRS is characterized by modest sinonasal

inflammation with a low-grade mixed cellular infiltrate of the affected tissues.[18] Histopathology for CIFRS oftentimes demonstrates dense accumulation of invasive fungal hyphae resembling a mycetoma.[2] There is no pathognomic imaging finding for CIFRS, but CT imaging of the sinuses reveals severe soft tissue thickening and bony erosion or expansion.

Treatment of CIFRS involves a combination of reversal of predisposing conditions, surgery, and antifungal therapy. Surgical debridement is performed with removal of all tissue with evidence of fungal invasion until there is a residual margin of healthy bleeding tissue. As in the case of AIFRS, systemic antifungal therapy is centered on the use of amphotericin B, although voriconazole is used in cases that are caused by an *Aspergillus* species.

GRANULOMATOUS INVASIVE FUNGAL RHINOSINUSITIS

Described as "primary paranasal granuloma" and "indolent fungal sinusitis", GIFRS is an aptly named form of invasive fungal rhinosinusitis given the histologic picture of a noncaseating granuloma in which multinucleated giant cells contain the profuse fungal hyphae that are responsible for infection. The formation of a noncaseating granuloma in GIFRS is evident in Figure 30.4. Cases are reported mostly from the Sudan, India, and Pakistan, where afflicted patients are typically immunocompetent. *Aspergillus flavus* is the fungal species isolated in almost all cases of granulomatous fungal sinusitis in the Sudan.[14]

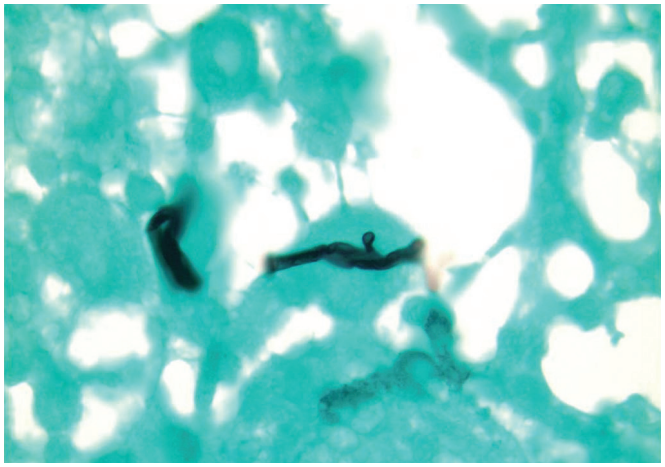


Fig. 30.4: Fungal hyphae contained within a granuloma on Grocott's methenamine silver stain (x1000). The presence of invasive fungal hyphae within a noncaseating granuloma is characteristic of granulomatous invasive fungal rhinosinusitis.
Courtesy: Rakesh Chandra, MD, Department of Otolaryngology—Head & Neck Surgery, Northwestern University, Chicago, IL, USA.

The clinical presentation and physical examination are similar to those of CIFRS, but proptosis resulting from an enlarging mass within the orbit, nose, or paranasal sinuses is a well-established presentation in the few case reports available.[14,29] Findings on diagnostic imaging are similar to those of CIFRS. From a histopathologic standpoint, GIFRS is defined by mucosal inflammation with fungal hyphae seen within multinucleated giant cell granulomas. The surrounding tissue consists of dense fibrosis and mild inflammatory infiltrates composed of eosinophils and lymphocytes.[18]

Treatment of GIFRS consists of surgical debridement of all tissue with signs of invasive infection and initiation of antifungal treatment to decrease the relapse rate. Voriconazole is the drug of choice for infections caused by an *Aspergillus* species, but for all non-*Aspergillus* molds, empiric amphotericin B is recommended.[2]

NONINVASIVE FUNGAL RHINOSINUSITIS

Allergic Fungal Rhinosinusitis

Overview

Allergic fungal rhinosinusitis is a form of polypoid CRS first described by Millar[30] and Katzenstein[31] in the 1980s. This disease was characterized by paranasal sinuses filled with dark, tenacious mucus resembling bronchial secretions found in allergic bronchopulmonary aspergillosis. This material has been termed "eosinophilic mucin". Histologically, it consists of a mucinous background with an onion-skin pattern of degranulating eosinophils, Charcot-Leyden crystals (products of eosinophil breakdown), and sparse fungal hyphae. Occasionally, patients who otherwise appear to have AFRS have no detectable fungi in their eosinophilic mucin. It has been proposed that these individuals suffer from a similar yet distinct clinical entity known as eosinophilic mucin chronic rhinosinusitis (EMCRS).[32] Such observations have generated controversy regarding the underlying pathophysiology of AFRS, leading some to question the roles of both allergy and fungus.

Pathophysiology

Current theories suggest that the pathogenesis of AFRS begins with an underlying hypersensitivity to fungus.[33] Susceptible individuals nasally inhale fungal spores, some of which are able to evade mucociliary clearance. These spores can then germinate, which enhances their antigenicity and incites a local inflammatory response.[34] This

appears to be a T_H2-mediated process with locally elevated levels of IL-4, IL-5, and IL-10 after fungal antigen exposure.[35] The resulting inflammatory cascade leads to the formation of polyps and eosinophilic mucin, further impeding mucociliary clearance. Fungal germination continues, leading to an ongoing inflammatory response.

Type I hypersensitivity is hypothesized to play a central role in AFRS pathogenesis, and there is evidence both for and against this theory. Evidence of fungal allergy can be seen both systemically and locally. AFRS patients have significantly higher levels of circulating fungal-specific and total IgE compared with those with nonfungal polyp disease.[36] Greater production of fungal- and nonfungal-specific IgE is found in sinonasal tissue in AFRS compared with CRS and normal control patients.[37] Eosinophilic mucin samples from AFRS patients are significantly more likely to demonstrate fungal-specific IgE compared with samples from EMCRS patients.[38] Even so, fungal-specific IgE can be detected in mucin of some patients who lack evidence of systemic fungal allergy or hyphae in their eosinophilic mucin. Species responsible for fungal allergy are not always the same as those isolated from the eosinophilic mucin. While certain groups have found strong correlations between nasal fungal culture and species-specific fungal allergy,[38,39] some suggest that this correlation might actually be as low as 42%.[40] Specific IgE levels may be higher in AFRS compared with CRS, but they do not differ significantly from levels in patients with both fungal allergic rhinitis, a disease state that is phenotypically quite different.[41] Nasal polyp tissue from EMCRS patients appears to have higher eosinophil counts compared with polyp tissue from CRS patients.[42] However, the presence or lack of fungal allergy does not seem to alter these counts. Thus, controversy still exists regarding the importance of fungal allergy in the development of AFRS.

There has been further investigation of the humoral immune response in AFRS. In addition to IgE, fungal-specific IgG is also elevated in AFRS and EMCRS.[40] In particular, IgG3 is elevated in these two populations compared with both normal control patients and patients with fungal allergic rhinitis. EMCRS patients also demonstrate increased proliferation of fungal-specific lymphocytes.[42] This population seems to be skewed toward CD8+ cells, whereas there is a predominance of CD4+ cells in CRS. The presence or lack of fungal allergy does not seem to influence this finding, again questioning the importance of type I hypersensitivity in AFRS.

A possible genetic susceptibility to AFRS has been investigated. Individuals with the HLA-DQB1*03 genotype (a class II gene of the major histocompatibility complex) appear to be at increased risk of developing AFRS and CRS.[43] This association seems to be the strongest in the AFRS cohort. A recent microarray study demonstrated that certain genes mediating lysosomal activity are elevated in AFRS and EMCRS compared with normal control patients.[44] The clinical and pathophysiologic relevance of these findings is not yet understood.

Epidemiology

Patients suffering from AFRS are typically younger than those with CRS, with an average age of 21.9 years at time of diagnosis.[45] Children may be affected as well, with the typical pediatric patient presenting at around age 13. Overall, there is an approximately equal distribution among genders. Among pediatric patients, there is a 2.1:1, male:female predominance. AFRS accounts for 7–12% of CRS patients taken to the operating room for sinus surgery in the United States.[33] Compared with other types of chronic sinusitis, African Americans are disproportionately affected compared with Caucasian patients.[45,46] AFRS patients more commonly reside in counties with high poverty rates, have lower median incomes, and are more likely to be uninsured or have Medicaid compared with CRS patients.

AFRS has a worldwide distribution; however, most cases occur in warmer, humid regions. In the United States, the disease is most common in the South and along the Mississippi basin, with the highest reported incidence occurring in Memphis, Tennessee.[47] AFRS is much less common in the northern parts of the country. In the United States, dematiaceous species are found in about 87% of cultures, with *Aspergillus* species being the next most common.[39] Common dematiaceous species include *Curvularia, Bipolaris, Alternaria,* and *Fusarium.*[45] In India, where AFRS is also prevalent, *Aspergillus flavus* appears to be the most common organism.[48]

Clinical Presentation

Patients with AFRS are immunocompetent and initially have symptoms similar to those of CRS. These individuals present with long-standing, slowly progressive nasal congestion that may lead to complete obstruction. Symptoms are frequently unilateral and almost always asymmetric. Patients often report thick, dark-colored nasal debris and discharge. Unlike in CRS, pain is not a typical symptom. Olfactory disturbances are common, and approximately 86% of patients will present with some degree of clinical

hyposmia.[49] Late symptoms include visual changes and distortion of facial appearance, including proptosis and telecanthus. Bony remodeling of the paranasal sinuses, orbits, and skull base is frequently encountered, but frank erosion can also be found in up to 56%.[50] A preceding history of allergic rhinitis and asthma is reported in 66% and 50% of patients, respectively.[39] On average, patients are treated for CRS symptoms for about 11 months and undergo 2.4 surgeries before the actual diagnosis of AFRS is made.[45] On nasal endoscopy, severe nasal polyposis is seen and is often asymmetrically distributed. Eosinophilic mucin fills the sinuses and is thick and sticky, resembling the consistency of axel grease or peanut butter, and is often brown or amber in color, as shown in Figure 30.5.

Although the pathophysiologic distinction between AFRS and EMCRS is still unclear, there seems to be clinical differences between the two states. AFRS patients are significantly more likely to have allergic rhinitis and are less likely to have asthma, aspirin intolerance, and bilateral disease.[32] Bony erosion appears to be more common in AFRS as well.[48]

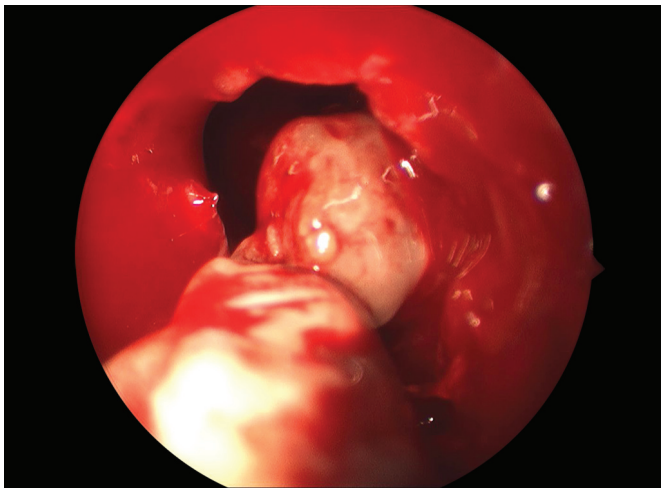


Fig. 30.5: Intraoperative image of allergic mucin. The allergic mucin is characterized by its thick, tenacious consistency.
Courtesy: Rakesh Chandra, MD, Department of Otolaryngology—Head & Neck Surgery, Northwestern University, Chicago, IL, USA.

Diagnosis

The diagnostic criteria first described by Bent and Kuhn in 1994[51] continue to be the most widely accepted. These diagnostic criteria, as highlighted in Table 30.2, include the following: type I hypersensitivity to fungus, nasal polyposis, characteristic CT findings, eosinophilic mucus, and positive fungal staining of sinonasal contents removed during surgery. There is no currently accepted schematic that defines the number of criteria that must be met for formal diagnosis. Minor diagnostic criteria have also been designated and consist of the following: history of asthma, identification of Charcot-Leyden crystals, eosinophilia, unilateral disease, osseous erosion, and positive fungal culture from the nasal cavity.[45] In order to meet diagnostic criteria for AFRS, a patient must undergo both medical and radiographic evaluation in addition to sinus surgery.

Type I hypersensitivity should be documented either by positive skin prick, intradermal, or serologic testing. Patients with AFRS typically demonstrate hypersensitivity to multiple fungal and nonfungal antigens. Eosinophilic mucin should contain degranulating eosinophils, Charcot-Leyden crystals, and fungal hyphae. The detection of fungal elements within mucin often proves to be difficult and may be missed in up to 39.4% of initial histopathologic evaluations.[18] The sparse distribution of fungal elements contributes to this difficulty, even when traditional periodic acid-Schiff (PAS) and GMS preparations are utilized. The use of newer techniques such as trypsin digestion and chitinase fluorescence labeling may help to greatly increase the sensitivity of fungal detection.[52] By definition, absence of sinonasal mucosal invasion by fungus should be noted.

Table 30.2: Major criteria[51] and minor criteria[45] for diagnosis of AFRS

Major criteria	*Minor criteria*
Type 1 hypersensitivity to fungus	Asthma
Nasal polyposis	Histopathologic identification of Charcot-Leyden crystals
Characteristic CT scan findings	Eosinophilia
Eosinophilic mucin	Unilateral disease
Positive fungal staining of sinus contents removed during surgery	Osseous erosion
	Positive fungal culture from the nasal cavity

(AFRS: Allergic fungal rhinosinusitis; CT: Computed tomography).

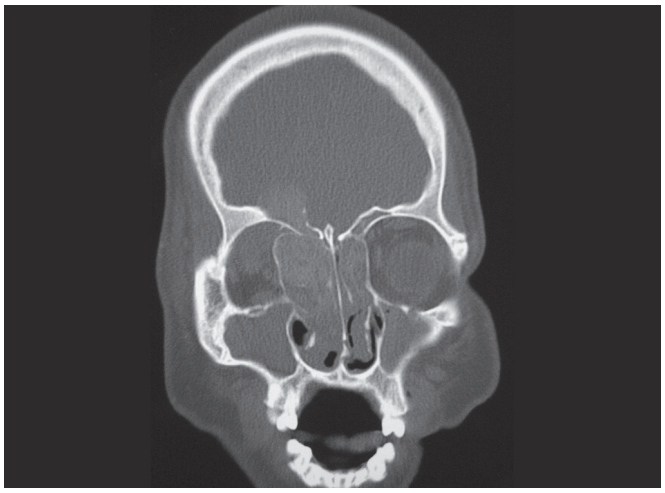


Fig. 30.6: Coronal image from a computed tomography scan of a patient with allergic fungal rhinosinusitis. The imaging demonstrates extensive heterogeneous opacification of multiple sinuses and significant remodeling of the right lamina papyracea with resulting mass effect on the right orbital contents.
Courtesy: Rakesh Chandra, MD, Department of Otolaryngology—Head & Neck Surgery, Northwestern University, Chicago, IL, USA.

Radiographic assessment is important both diagnostically and for surgical planning, and is often the first distinguishing characteristic of AFRS in patients previously assumed to have CRS. CT scanning is the preferred initial radiologic modality. Heterogeneous opacification is noted in multiple sinuses with areas of central hypoattenuation[53] Figure 30.6 provides a characteristic CT scan of AFRS. Mucocele formation is a common finding.[33] Bony remodeling and erosion are important findings on CT when planning surgical intervention. When bony erosion occurs in AFRS, the burden of disease remains within the sinuses. This can be distinguished from invasive fungal disease, which tends to spread outside of the sinuses. MRI is less useful, but may help to delineate the extent of intracranial or intraorbital extension in cases of severe disease. A characteristic MRI finding is central areas of low or no signal within the sinuses on T1- and T2-weighted images.[33] These areas represent collections of eosinophilic mucin.

Surgical Treatment

Virtually all patients with AFRS will require surgical treatment. As with surgery for CRS, approaches should focus on maintaining functionality and minimizing mucosal loss. Mucocele formation is common in AFRS and should be treated during surgery. The use of image guidance is critical, as important landmarks, such as the lamina papyracea and skull base, are often obscured by extensive polyp burden and chronic remodeling. Recurrence is common and has been noted to occur in 10–79% of patients.[54] A common cause of surgical failure is inadequate removal of eosinophilic mucin. Epidemiologic studies demonstrate that female and African American patients tend to have greater improvements in symptoms and endoscopic examination after surgery.[55] Surgical therapy alone is unlikely to result in long-term disease and symptom control without concomitant medical therapy.

Medical Treatment

Medical therapy is used to treat exacerbations and to maintain long-term disease and symptom control. Systemic corticosteroids are frequently used both pre- and postoperatively. When given for a short duration before sinus surgery, steroids may reduce nasal polyp burden, facilitating surgical exposure.[56,57] A short corticosteroid taper administered in the immediate postoperative period and sporadically in long-term follow-up may be helpful in preventing recurrences.[33] Because of the risks of long-term systemic corticosteroid use, topical intranasal steroids are frequently used for maintenance treatment. Currently, there are no randomized control trials comparing the efficacy of nasally inhaled and systemic steroids.

Nonsteroidal medications have also been used, although there are little data to advocate their regular use in treating AFRS. Immunotherapy (IT) has been shown to be safe in AFRS patients.[58] In smaller cohorts, IT has been shown to improve endoscopic appearance, improve patient symptom scores, and reduce the need for systemic and nasal corticosteroids.[59] After longer periods of follow-up, however, there does not appear to be a difference in disease remission rates whether or not IT is used.[60] Currently there are no large, randomized controlled trials that have examined the use of IT in AFRS.

Systemic antifungal therapy is not commonly used to treat AFRS. These agents are typically expensive, must be used for longer periods of time, and have significant side effects including renal and hepatic toxicity. Itraconazole has been studied, and there is evidence that it may result in improvement of symptoms and reduce the need for revision sinus surgery in a small subset of AFRS patients when used as an adjunctive treatment.[61,62] Nevertheless, antifungal medications are not regularly used in AFRS treatment protocols at this time.

Follow-Up

Given the propensity for AFRS to recur after initially successful treatment, patients should be followed closely over time. With adequate surgical and medical treatment,

it is possible for patients to achieve a quiescent disease state lasting for several years.[60] Even so, it is anticipated that a large proportion of patients will eventually need further surgery. Return of polyps and eosinophilic mucin may indicate that maintenance therapy has become ineffective and that revision surgery is needed. Therefore, nasal endoscopy should be done during regular follow-up visits.

SAPROPHYTIC FUNGAL COLONIZATION

Saprophytic fungi utilize dead and decaying matter as a source of nutrition. Colonization of the nasal cavity with these organisms can be asymptomatic or, in the setting of immunocompromise, can result in AIFRS.[63] Saprophytic colonization can be a transient phenomenon in the postoperative period following endoscopic sinus surgery. In immunocompetent individuals this is likely of no significant consequences. This condition more commonly occurs in individuals suffering from atrophic rhinitis. Fungal elements may be isolated from crusts and secretions in up to 93% of patients with atrophic rhinitis.[64] It is proposed that impairment of mucociliary clearance and underlying pyogenic osteomyelitis create an environment that favors colonization by fungi, which are able to persist. Colonization by these saprophytic organisms contributes to the foul odor of the crusts found in the nasal cavities of these patients. Treatment consists of nasal irrigations and debridements as needed.

PARANASAL SINUS FUNGUS BALL

Overview and Pathophysiology

Paranasal sinus FB is characterized by a discrete accumulation of fungal elements within a sinus cavity. This is a noninvasive entity, and fungal elements are found extramucosally. Although not required by definition, FB most often occurs in immunocompetent patients. The disease is often noted incidentally during medical imaging of the sinuses or brain. FB is commonly misclassified as a mycetoma or "aspergilloma", both of which are misnomers. In rare cases, if patients become immunocompromised, preexisting FBs can become invasive.[6]

FB is almost exclusively a disease of adults. The average age at time of presentation is 55–64 years.[65,66] For unknown reasons, a female predominance of 2:1 has been traditionally cited.[14] Patients with FB are no more likely than unaffected individuals to have allergic rhinitis. Similarly, intranasal anatomic variations such as septal deviations or paradoxical middle turbinates are not predisposing factors. A recent small study demonstrated that the incidence of FB may be increased in immunocompromised individuals.[67] In the vast majority of cases with positive fungal cultures, *Aspergillus fumigatus* appears to be the causative organism.[14,65,68]

The underlying pathophysiology of FB is still poorly understood; currently there are two competing theories. The aerogenic hypothesis posits that a large burden of inhaled fungus enters a sinus cavity through a natural ostium. Once inside the sinus, fungal elements are able to evade mucociliary clearance. Poor ventilation of the sinus creates a relatively anaerobic environment that may enhance fungal pathogenicity. A second theory suggests that FB may be an iatrogenic consequence of endodontic procedures.[65] In particular, it has been suggested that overfilling of dental sealants into the maxillary sinus can promote FB formation. Zinc oxide, a main ingredient in many sealants, may promote metabolic activity in *Aspergillus* species.[65] It is hypothesized that overtime the zinc diffuses throughout the sinus cavity, promoting fungal growth. While history of prior dental procedure has been noted in 56[69]–84%[65] of patients with FB, some studies report this incidence to be as low as 10.4%.[68] Furthermore, this theory does not explain why isolated FB may develop in locations other than the maxillary sinus. Development of FB does not seem to be a consequence of defects in humoral immunity as IgG levels in affected patients are similar to those in normal control patients.[70] Elevated levels of mucosal IgA have been noted in surgical specimens from FB patients; however, it is uncertain how this contributes to the underlying disease pathophysiology.[71]

Clinical Presentation and Diagnosis

It is estimated that 13–20% of patients with FB may be asymptomatic.[65] When present, symptoms are often longstanding and are similar to those experienced by patients with CRS. The most common symptoms include recurrent bacterial sinusitis, headache, facial pain, postnasal drip, cough, and cacosmia. Individuals with isolated sphenoid sinus FB commonly complain of retro-orbital headache.[72] Uncommon symptoms include epistaxis, visual changes, and proptosis. Approximately 97% of patients will have disease in a single sinus, although multiple sinus and pan-sinus disease is possible. The maxillary sinus is most commonly affected and is involved in 70–94% of cases.[65,66,73] Isolated sphenoid sinus disease is the next

most common presentation and is noted in approximately 4–8% of patients.[65] Less commonly, FB occurs in ethmoid and frontal sinuses and it has even been reported to occur within a concha bullosa.[74]

Radiographic assessment can often help distinguish FB from other pathologies. On CT imaging complete or near-complete opacification of a sinus is noted. In 90% of cases, this opacification is heterogeneous.[65] Hyperattenuation of the FB is a common finding and the use of contrast enhancement may help to distinguish fungus from inflamed mucosa, often denoted by a rim of relative hypoattenuation. Dense microcalcifications can be seen in up to 67% of CT scans.[75] Even in the absence of mucosal invasion, bony erosion may be noted, and its presence, along with calcifications, may help distinguish FB from isolated CRS.[76] Bony sclerosis, as seen in Figure 30.7, is another common finding and is noted in about 60% of cases.[65] MRI is less frequently employed. On T1-weighted imaging, the FB is iso- or hypointense.[75] On T2-weighted imaging the FB is markedly hypointense and the adjacent inflamed mucosa is hyperintense.

Preoperative nasal endoscopic examination is normal in about 52% of patients.[69] A common yet nonspecific finding on endoscopy is purulent discharge from a sinus cavity. Surgical specimens may appear grossly as a friable, cheesy masses ranging from yellow to brown or black in color. The gross appearance is reportedly 100% sensitive and 99% specific for FB.[65] Histologically the FB is characterized by densely packed hyphae that may be surrounded by a neutrophilic exudate. Despite the dense accumulation of fungal elements, culture is positive in only 23–51% of specimens.[6,66] Staining with PAS or GMS may increase the chance of positive culture. Bacterial coinfection is noted in approximately 68–74% of specimens.[77,78] The most commonly isolated organisms appear to be coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and *Enterobacter aerogenes*.[78]

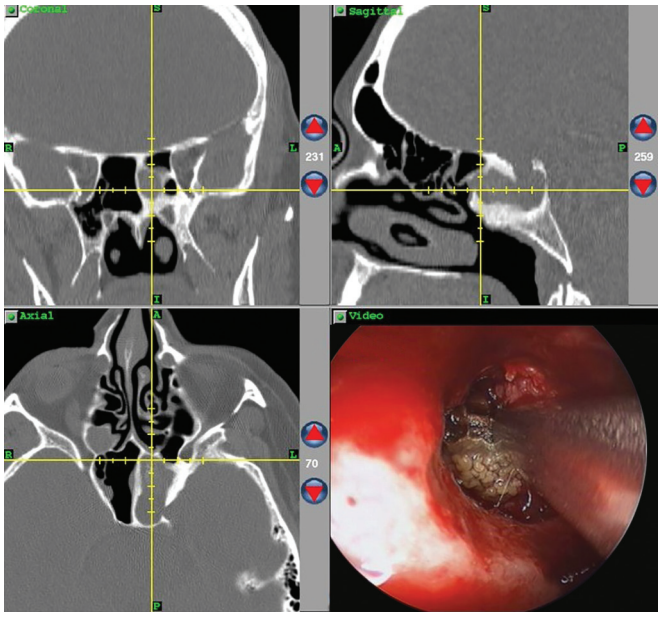


Fig. 30.7: Image-guidance computed tomography scan and associated intraoperative image of an isolated left sphenoid sinus fungus ball. Boney sclerosis of the affected sinus is evident. The friable, dark appearance of the surgical specimen is typical of fungus balls.
Courtesy: Rakesh Chandra, MD, Department of Otolaryngology – Head & Neck Surgery, Northwestern University, Chicago, IL, USA.

Treatment

Patients with FB who are symptomatic should be treated surgically. Most clinicians agree that asymptomatic patients should be treated surgical as well, in order to rule out more sinister pathology. Endoscopic sinus surgery has become the method of choice.[79] The surgeon must take care to widen the sinus opening enough so that the FB can be removed and so that the sinus can be thoroughly inspected for any residual fungal material. Angled telescopes and instruments must often be used, particularly with maxillary sinus disease. Rarely adjunctive approaches, such as Caldwell-Luc, must be used to extirpate disease from the anterior portion of the maxillary sinus. The so-called gauze-assisted technique has been used to push fungal debris out of this portion of the sinus during endoscopy.[80] The use of such techniques may help surgeons avoid the need for open approaches. Surgical therapy is curative in most cases and recurrence is thought to be exceedingly rare. Significant improvements in SNOT-20 scores have been reported after surgical therapy in patients with FB.[73] There is currently no definitive role for medical therapy. Some otolaryngologists may opt to treat patients postoperatively with a short course of steroids as well as sinus rinses or irrigations. Systemic antifungal therapy is not indicated in the treatment of FB. Treatment of bacterial coinfection may be considered in instances of positive culture or in a symptomatic patient. Given the excellent cure rate of FB after surgical intervention, long-term follow-up is likely unnecessary.

FUNGUS AND CHRONIC RHINOSINUSITIS

Although CRS is a prevalent condition, an understanding of its underlying etiology and pathogenesis remains

incomplete. A role for fungi in this process has been suggested, and this has become a source of great controversy. In 1999, Ponikau et al. at the Mayo Clinic used a novel culture technique to demonstrate that fungus was present in nasal secretions from 202/210 (96%) CRS patients.[81] This technique utilized the application of a mucolytic agent to secretions prior to inoculation onto culture media. In addition to the high rate of positive fungal culture, 96% of the 101 CRS patients taken to the operating room also had eosinophilic mucin. While these patients appeared to meet criteria for diagnosis of AFRS, only a small percentage had evidence of increased levels of fungus-specific IgE. Thus, the authors proposed a change in nomenclature from AFRS to "eosinophilic fungal rhinosinusitis".[81] Subsequent studies utilizing similar culture techniques have found positive fungal cultures in 91.3%[82] and 92%[83] of CRS patients. Critics of this work point out that all of the control patients in Ponikau's study also had positive fungal cultures with no significant difference in speciation between the two groups. Non-IgE-mediated mechanisms have been proposed for the pathophysiologic role of fungi in CRS. Hyperactivity of the host immune system to fungal antigens in CRS patients but not normal control patients has been noted by some investigators.[84] Peripheral blood mononuclear cells (PBMC) isolated from CRS patients have been shown to generate a mixed T_H1/T_H2 cytokine profile when exposed to high doses of *Alternaria* antigen. Increased cytokines include IL-13 and IL-5 that are implicated in the migration, activation, and survival of eosinophils. *Alternaria*-specific IgE levels were increased in only a small subset of these patients and did not correlate with IL-5 levels, leading authors to suggest an IgE-independent mechanism. Critics of this study note that a large proportion of patients had concurrent asthma that may have also caused PBMC activation.[85] A more recent study using similar methods found that exposure of PBMC to *Alternaria* could in fact cause release of IL-5 and IL-13 in control patients.[86] In contrast with the previously mentioned study, these cytokine levels did not differ between control and CRS groups.

Fungi contain intrinsic proteases that have been shown to activate protease-activated receptors (PAR) on sinonasal epithelial cells, and certain PARs have been shown to be upregulated in CRS.[87,88] Evidence suggests that activation of PAR-2 in particular causes epithelial desquamation, changes in cell morphology, and release of inflammatory factors.[89] Furthermore, *Alternaria alternata* appears to have the capability to cause eosinophil degranulation through a similar protease-dependent mechanism.[90] These findings suggest that *Alternaria* may cause intraluminal epithelial cell targeting and eosinophil-mediated damage through nonspecific protease-dependent mechanisms rather than by antigen-specific mechanisms. This theory does not provide a mechanism for eosinophil chemotaxis, however, as the activation of PAR-2 does not appear to cause release of chemokines such as eotaxin or RANTES from sinonasal epithelium.[91]

Antifungal therapies, both systemic and local, have been studied in CRS patients. Initial pilot studies showed promising results with the use of amphotericin B nasal irrigations in CRS patients.[92,93] These studies noted significant post-treatment improvements in symptoms, endoscopic examination, and CT findings. Subsequent studies have failed to yield similar results however. Multiple studies have found that, compared with placebo saline irrigations, amphotericin B irrigations do not result in significant improvements in symptoms, endoscopy, imaging findings, or quality of life in CRS patients.[94-96] Furthermore, use of topical amphotericin B does not appear to decrease levels of inflammatory cytokines and growth factors associated with CRS.[97,98] A study examining the efficacy of oral terbinafine in CRS patients demonstrated no improvement in symptoms or radiographic appearance compared with placebo treatment. A recent pooled meta-analysis determined that topical and systemic antifungal agents had worse side effect profiles and no treatment benefit compared with placebo.[99] Some authors have pointed out that certain fungal species cultured from CRS patients may be more amenable to treatment with agents not often used in clinical trials.[100,101] Nevertheless, the preponderance of evidence thus far fails to indicate a benefit from the use of antifungals in CRS.

Currently the potential role of fungus in CRS remains hypothetical and controversial. While several in vitro studies seem to support the proposed non-IgE-mediated pathogenic mechanisms, conflicting data exist as well. The overall failure of antifungal agents casts doubt over the hypothesis that fungi play a central role in either the etiology or the pathogenesis of CRS. Fungi may play a significant role in subsets of CRS however, but this issue is complicated by a lack of standardization of fungal culture techniques and a disagreement over the definition of entities such as AFRS and EMCRS. Until a better consensus is reached on these issues, it will likely remain unclear whether fungus plays an inciting, contributory, or no role at all in the pathophysiology of CRS.

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CHAPTER

31

Osteitis

Adam S DeConde, Alexander G Chiu, Jeffrey D Suh

INTRODUCTION

Chronic rhinosinusitis (CRS) affects 12% of the population of the United States.[1] Endoscopic sinus surgery (ESS) is an effective intervention that manages to control 82% of patients after a single surgery.[2] There remains, however, a subset of patients who, despite multiple surgeries and maximum medical management, suffer from persistent CRS. Historically, CRS was thought to be exclusively a disease of the sinonasal mucosa. Messerklinger's theory that narrowed outflow pathways enlarged by surgery with additional medical therapies for diseased mucosa would successfully treat all patients with CRS is not universally applicable. Therefore, there has been further investigation into the role of subepithelial disease, specifically diseased bone, as a driving force of recalcitrant CRS.

Bone serving as a reservoir for chronic sinus infection and inflammation is extrapolated from the pathophysiology of osteomyelitis of the long bones.[3] Osteomyelitis is thought to begin with an acute bacterial infection. The local inflammatory reaction to the bacteria triggers a cascade of events by increasing tissue pressure, with subsequent lowering of pH and oxygen tension leading to microthrombi ultimately creating bony necrosis. Necrotic bone provides a reservoir without vascularity and subsequent antibiotic penetration, thus perpetuating the infection.[4] Bony remodeling further occurs through stimulation of osteoclasts via inflammatory mediators as well as osteoblasts bolstering newly weakened bone,[5] grossly leading to both bony resorption and bony sclerosis.

Osteomyelitis is an imperfect pathophysiologic analogy for sinonasal osteitis. Controversy remains over the role of bacteria in CRS as either a primary factor or merely the consequences of dysfunctional mucociliary clearance exacerbating underlying chronic inflammation.[6] Intraosseous bacteria have only recently been identified within sinonasal bone, yet there is no correlation between intraosseus bacteria and osteitic bone.[7] Additionally, the haversian canal systems of ethmoid bone have been found to have inflammatory infiltrates with the surrounding bone harboring increased inflammatory cytokines compared to controls.[8] These inflammatory changes may represent some of the mechanisms by which osteitis can lead to spread[9] and persistence of sinus disease.[10] Similarly, infectious processes of dental origin are effective at promoting overlying mucosal disease with resolution of sinus inflammation with treatment of the underlying dental disease.[11] Bony remodeling has similarly been observed around dental infections, particularly at sites of oroantral fistula closure failure.[12] However, discriminating the causality vs. correlation of osteitis and CRS remains an area of active research.

The term "osteomyelitis" refers to bony infection within the marrow space. The bony framework of the sinuses is composed of flat bones. Therefore, inflammation of these bones is referred to as "osteitis". Throughout the literature, a range of terms has been used, including "osteitis", "osteomyelitis", "hyperostosis", "bone hyperplasia", "bone remodeling", and "neo-osteogenesis". "Osteitis" by far predominates in the literature and the diversity of terms used reflects some of the controversy of the pathophysiology and tend to reflect the authors' underlying beliefs of the etiology of the involvement of the underlying bone. "Osteitis" and "osteomyelitis" denote an inflammatory

and infectious etiology, respectively, whereas the terms "neo-osteogenesis", "hyperostosis", and bone hyperplasia imply a more reactive bony process. This chapter seeks to review the evidence underpinning the pathophysiology and clinical implications of this process. The process by which periosteal thickening and immature woven bone formation occurs in the presence of CRS, will be referred to as "osteitis". This term is chosen solely because it is the most ubiquitous term, not because there is any attempt to imply an underlying pathophysiology.

PATHOPHYSIOLOGY

Histopathology

Recognition that CRS changes might extend beyond the epithelium was first recognized in the animal model. Westrin et al.[13] demonstrated that rabbit sinuses obstructed and then infected with *B. fragilis* leads to epithelial desquamation, edema, goblet cell hyperplasia, fibrosis, including bony changes such as periosteal reaction, bone resorption, and neo-osteogenesis.[13,14] Rabbit sinuses infected and obstructed with *B. fragilis* results in chronic inflammation that lasts at least 12 weeks with a thickening of the entire mucosal layer with regions of both bony thickening and resorption.[13,15] Similarly, rabbit maxillary sinusitis induced with *Pseudomonas aeruginosa* demonstrates boney remodeling and fibroplasia.[16] The bony reaction and chronic inflammatory response of animal sinuses to *B. fragilis* and *P. aeruginosa* is in contrast to the self-limiting infection seen in rabbit sinuses inoculated with *Streptococcus pneumonia*.[15]

These studies in animals triggered further investigation into similar changes recognized in humans with CRS. Biedlingmaier et al.[17] noted that bony thickening of the middle turbinate on computed tomography (CT) correlated with histopathologic thickening of the middle turbinate in patients with CRS. Kennedy et al.[3] further investigated the histologic changes of ethmoid bone in patients undergoing ESS and compared these findings to ethmoid bone in noninflammatory conditions (e.g. CSF leak repair and orbital decompression). Patients with CRS had increased osteoblastic and bony resorption compared to controls. Thirty-eight percent of patients with CRS showed marked activity compared to 6% of controls. The majority of controls demonstrated quiescent bone (69%) in contrast to only 30% of patients with CRS. All of the patients with CRS demonstrated a mild-to-marked degree of chronic inflammation including increased fibrosis, neo-osteogenesis, presence of woven bone, and bone resorption (Table 31.1).

Normal ethmoid bone is composed predominantly of collagen and hydroxyapatite that organizes into lamellar bone.[18] Lamellar bone is marked by highly organized parallel layers, lamellae, of mineral crystals and collagen fibers that are slowly formed. In contrast, woven bone consists of randomly arranged collagen fibers and course mineral and is produced rapidly. The parallel fibers of lamellar bone interact uniquely with polarized light, allowing for semi-quantitative analysis of the degree of lamellar bone formation.[18] Biedlingmaier et al.[17] originated a scale defined from zero to four, ranging from normal bone (0), to presence of periosteal thickening (1), evidence of bone resorption and/or remodeling (2), presence of widened

Table 31.1: Histopathologic findings of osteitis

Study	*Inflammatory bony infiltrate*	*Woven bone*	*Bone resorption*	*Periosteal thickening*	*Fibrosis*
Humans					
Lee et al.[31]	NA	+	+	+	NA
Cho[57]	NA	+	+	+	NA
Giacchi et al.[18]	NA	+	+	+	+
Kennedy[3]	NA	+	+	NA	+
Biedlingmaier et al.[17]	NA	+	+	+	NA
Animals					
Antunes[58]	+	+	+	+	NA
Khalid[59]	+	+	+	NA	+
Perloff et al.[9]	+	NA	+	NA	+
Norlander et al.[14]	NA	+	+	+	NA
Westrin et al.[13]	NA	+	+	+	+

osteoid seams (3), and frank osteomyelitis with leukocytes and boney destruction (4). Patients with CRS again demonstrated significantly increased woven bone formation in the ethmoid bones compared to normal (e.g. CSF leakrepair ethmoid bone) controls.[18] This pattern of bone formation was also shown to correlate with thickening ethmoid bony lamella on computed tomography.[18]

Molecular Mechanisms

Bone is a dynamic tissue that remodels in response to both biochemical and mechanical stimuli.[18–20] In CRS, obstructed drainage pathways may lead to increased intraluminal pressures with subsequent stress force on bony walls. There is no evidence to support this mechanism, and clinical experience teaches that at times extreme bony remodeling can occur without thickening of the bone in the presence of significant nasal polyposis and tissue eosinophilia.[21] A more likely etiology lies in the complex milieu of enzymes, growth factors, and cytokines present at sites of chronic inflammation.

Spread and persistence of sinus disease by the underlying bone may similarly act via inflammatory cytokines. Osteitic bone stripped of its mucosa carries higher levels of the inflammatory cytokines IL-6, IL-11, and TNF-α compared to controls with CRS but no evidence of osteitis.[8] Haversian canals demonstrated lymphocytic infiltrate, and these systems have been implicated in spread of disease as well. Rabbits with experimentally induced maxillary sinusitis demonstrate inflammatory changes around the haversian canals in the uninfected contralateral maxillary sinus.[9] Perhaps these inflammatory changes are merely artifacts of the surgical approach, and certainly more study is warranted, but spread of inflammation through the haversian canal system serves as a plausible mechanism by which bone propagates sinusitis.

Once the inflammation is established, it ultimately results in a common final pathway of tissue remodeling that is broadly mediated by matrix metalloproteinases (MMPs), fibroblast growth factors (FGFs), and bone morphogenetic factors (BMPs). A mouse model of allergic fungal sinusitis demonstrates significant upregulation of MMP1a, MMP7, MMP8, and MMP12 3 months after inoculation. Similarly, BMP9 shows a 14-fold upregulation after 3 months of inflammation, along with upregulation of FGF3, FGF5, FGF6, and FGF8.[19] Further work in humans has identified that MMP9 is also upregulated in patients with recalcitrant CRS with moderate to severe radiographic evidence of osteitis.[22] These shifts in protein profiles play important roles in the tissue remodeling seen in sinonasal osteitis.

Eosinophilic Remodeling

The lack of correlation between osteitic bone and bacterial bony invasion[7] has prompted a search for an inflammatory-based mechanism.[23] Eosinophilic CRS is a subtype of recalcitrant CRS defined by ≥10 eosinophils per high-power field in the surgical specimen and is associated with poorer treatment outcomes than noneosinophilic CRS.[24] Eosinophils are also associated with potent exuberant bony responses to surgical trauma. Endoscopic modified Lothrop procedures in patients with eosinophilic CRS are predisposed to restenosis compared to noneosinophilic disease.[24] Similarly, there is an increased incidence of radiographic evidence of osteitis in eosinophilic disease.[25] The observation that patients with elevated serum and sputum eosinophilia but normal serum IGE levels correlate with radiographic osteitic rates suggests that an osteitic response may in part be mediated by eosinophils at a local level.[26]

The strong association of eosinophils with osteitic bone and recalcitrant disease offers a compelling explanation for sinonasal osteitis. Although eosinophils are best known for their potent ability to stoke mucosal disease, they are also equipped with growth factors that directly impact osteogenic cells. Eosinophils produce transforming growth factor β (TGF-β), which directly affects osteoblasts.[27] Patients with asthma, a common comorbid condition of eosinophilic CRS, demonstrate elevated levels of TGF-β.[28] Similarly, eosinophilic chemotactic factor L has also demonstrated influence over osteoclastogenesis.[29] Additionally, although initial animal studies of osteitis were performed using a bacterial obstruction model in rabbit maxillary sinuses, the best elucidation of the molecular changes responsible for tissue remodeling was performed in an allergic fungal murine model.[19,20]

Traumatic Remodeling

Surgical intervention is a source of trauma that is known to predispose to osteitis. Anecdotal observations of postoperative exposed bone with associated mucosal inflammation on nasal endoscopy spurred some of the initial investigations into the role of osteitis in CRS.[3] A strong association exists of osteitis with a history of prior surgical interventions. [10,25,30,31] With an increasing number of interventions there is also a direct increase in the severity of osteitic bone on radiography.[30] The correlation between number of prior surgeries and extent of osteitic findings on computed tomography was strong, with patients with one prior surgery having less osteitic bone than patients with two prior surgeries, than patients with three prior surgeries, than patients with greater than six prior surgeries.[30]

This study also controlled for duration of sinus disease and found that the degree of osteitis was still impacted by number of interventions. Additionally, the sites of osteitis correlated with the sites of prior surgical intervention. This strong correlation between prior surgery and osteitic bone may simply be correlation of secondary endpoints for primary recalcitrant disease. However, two plausible mechanistic explanations exist. Surgery can increase the risk of exposed bone with subsequent bacterial colonization and increased bone inflammation, as well as direct trauma to the underlying bone.

It is known from long-bone wound healing that trauma is a strong stimulus of osteogenic activity. The boney wound healing process begins when destruction of bony tissue and vessels leads to a release of chemotactic cytokines. Mesenchymal stem cells localize to the site of injury and are stimulated to divide and differentiate toward chondrogenic or osteogenic lines. These cells coordinate formation of woven bone and eventually evolve into a bony callous that over time remodels refining strength.[32] The endoscopic modified Lothrop procedure is a unique example of widely traumatized and exposed bone that even in patients with relatively mild disease demonstrates significant bony sclerosis and narrowing of the common outflow tract.[21] Although further study is required, investigation and manipulation of bony repair may further elucidated the role of boney wound healing on osteitis.

Bacteriology

The recalcitrant inflammation associated with osteitic bone has yet to be associated with intraosseus bacteria.[7] Similarly, intraosseus bacteria have been identified in normal sphenoid bone,[7] highlighting that direct bacterial invasion of the underlying bone is unlikely an underlying mechanism of osteitis. However, it has been postulated that perhaps certain bacteria may predispose to recalcitrant infection.[33] There is some evidence that *Staphylococcus aureus* can exist intracellularly, thereby escaping beta-lactam therapy, acting as a reservoir to trigger multiple infections. Interestingly, in the rabbit animal model, *S. pneumoniae* infection of obstructed maxillary sinuses appears to be self-limited,[15] whereas gram-negative inoculation (*Pseudomonas, Bacteroides*) triggers chronic infections that demonstrate histologic evidence of bony osteitis.[13,16] There is no direct study examining the bacteriology as related to radiographic or histologic evidence of osteitic bone, and further study may help elucidate the role ofdifferent bacteria in osteitis.

IMAGING

Radiography

The initial radiographic criteria describing osteitis of the sinonasal bones was first described by Biedlingmaier in 1996.[17] This study was investigating the role of partial resection of the middle turbinate, and the role of osteitis in perpetuating disease in the osteomeatal complex. Osteitis was defined as rarefaction and/or demineralization, loss of trabeculae, cortical destruction, focal sclerosis, loss of expected structures, or landmarks. Although the grading scale was only applied to the middle turbinate bone, and had limited ability to predict histologic findings of osteitis, it was the first step in connecting the histologic appearance of osteitic bone to the radiographic appearance of osteitic bone.

Lee et al.[31] sought to define a more clinically relevant grading scheme that included more of the sinonasal bony framework, and has since been referred to as the Kennedy Osteitis Score (KOS)[25] (Table 31.2). Examination of the CT findings of 37 patients with CRS was compared to postoperative histologic specimens. The ethmoid bony partitions and borders along with sphenoid and maxillary sinus borders were measured on CT scan and graded as mild (3 mm), moderate (4–5 mm), or severe (>5 mm) osteitis (Fig. 31.1). The frontal sinus was not included because of the innate thickness of the frontal beak. The results of radiographic grading were then compared to histologic presence of bony osteitis, specifically the presence of bony remodeling and immature woven bone. A total of 36% of the patients in the cohort demonstrated CT evidence of osteitis. Of these, 73% demonstrated mild thickening (2 mm), 45% with moderate thickening (4–5 mm), and 18% with severe thickening (>5 mm). Presence of osteitis also correlated with higher Lund–MacKay scores compared to patients in this cohort without evidence of osteitis. All cases

Table 31.2: CT grading scales of osteitis

Sinus score	*Kennedy osteitis scale*	*Global osteitis scale*
0	<3 mm	<3 mm, and <50% of sinus
1	3–5 mm	3–5 mm and <50% of sinus
2	>5 mm	>5 mm and <50% of sinus OR <3 mm and >50% of sinus
3	–	3–5 mm and >50% of sinus
4	–	>5 mm and >50% of sinus
Total range	0–20	0–40

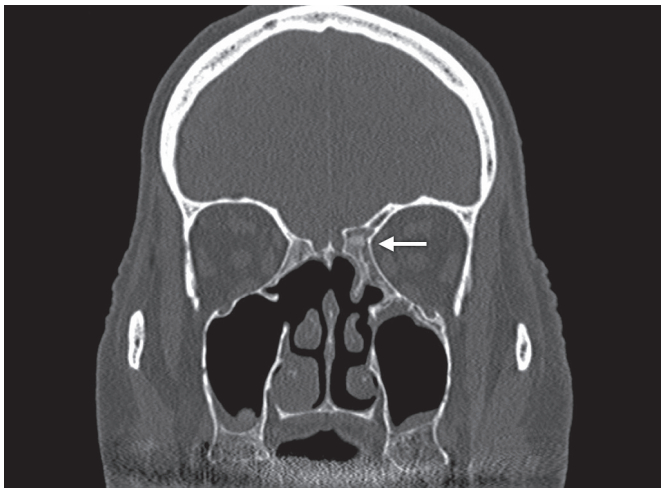

Fig. 31.1: Coronal CT in the bone window demonstrating osteitis of the posterior ethmoids (arrow).

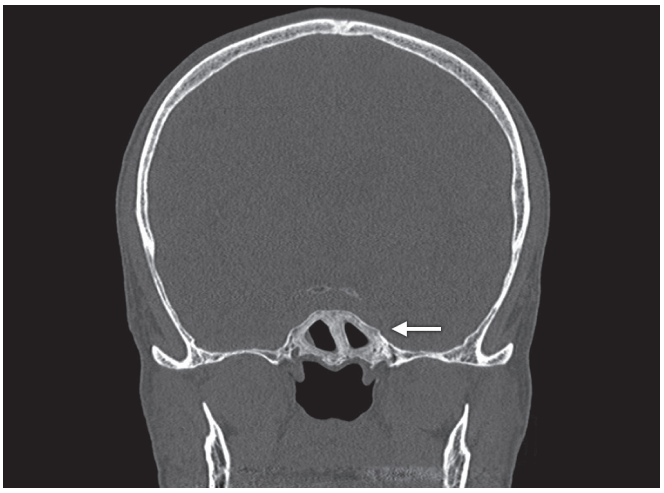

Fig. 31.2: Coronal CT in the bone window demonstrating osteitis involving >50% of the sphenoid sinus walls (arrow).

of radiographic evidence of bony thickening demonstrated histologic evidence of bony osteitis, specifically, periosteal thickening, osteoblastic–osteoclastic activity with bony resorption and/or remodeling on postoperative evaluation.This effectively links the histologic changes of osteitis to the radiographic findings of thickened, irregular, heterogeneous localized, or global bony thickening.

There has since been an effort to provide a more refined radiographic assessment with the Global Osteitis Scale (GOS) has been proposed.[30] By design the GOS is modeled after the Lund–Mackay mucosal grading scale, and is intended to be its boney analog. In contrast to the KOS, this grading system does not address explicitly how under-pneumatized frontal sinuses are scored or how frontal sinuses with innately (>3 mm) thick walls are counted toward determining the extent of osteitis, but it does score the frontal sinus. The concern of the KOS is that localized thickening of a sinus would receive the same score of a globally thickened sinus (Fig. 31.2). The GOS incorporates not only the thickness of bone but also the extent of the sinus walls involved (Table 31.2).

A modified version of the KOS to include grading of the frontal sinus has been compared to the GOS.[25] Frontal sinus grading was achieved by gleaning evidence of immature woven bone through rarefaction and irregularity of the peripheral sinus wall. The intraosseous septum was also used as a marker as it tends to be thinner than the frontal table when involved. Both the KOS and GOS were effective at differentiating between subgroups, both showing statistically significantly higher scores for patients with a history of prior surgery and eosinophilia (>10/HPF). Additionally, there is a strong correlation between the two grading systems ($R = 0.93$, $p < 0.001$).[25] The complexity and refinement of the GOS scale has yet to translate into any additional prognostic value beyond the KOS. Future trials will be needed to better establish the role of the KOS vs. the GOS.

NUCLEAR MEDICINE

Single-photon emission computerized tomography (SPECT) measures the metabolic activity of bone. It has been used in other regions of the head and neck for detection of early tumor invasion of bone, follow-up of free bone flaps, and for osteomyelitis by enabling recognition of localized early bone disease with higher sensitivity than radiological scans.[34] SPECT imaging may serve as a noninvasive early indicator of subradiographic osteitis.

In order to explore this hypothesis, Catalano et al.[35] performed preoperative SPECT analysis on 36 preoperative patients with CRS. SPECT positivity of the ethmoid bone was observed 89% (32/36) of the patients. Histologic evaluation demonstrated presence of osteitis in 94% (31/33) of ethmoid bone. Of the four patients with SPECT negativity, two had histologic evidence of osteitis. With the histologic gold standard, the sensitivity of SPECT imaging was 93.9% and specificity of SPECT was 66.7%. The small number of patients and the lack of a negative control group make it hard to draw conclusions about the true specificity of SPECT. A lack of specificity may be a fundamental flaw of SPECT, and further study is required, but the fact that none of the patients included in the study demonstrated

radiographic evidence of osteitis on preoperative CT imaging does support SPECT as a noninvasive means of early detection of osteitis.

Early detection of osteitis by SPECT may facilitate early identification of recalcitrant cases of CRS. A prospective trial of 24 patients undergoing medical management of CRS were evaluated with pretreatment SPECT.[34] The medical management consisted of oral antibiotics for 3 weeks and topical nasal steroids for 4 weeks. Treatment success was based on subjective improvement of symptoms. Patients with SPECT-positive scans had a limited response to medical management with only 5%, demonstrating a response to treatment. All patients with a SPECT-negative scan responded to medical therapy. This is in contrast to an assessment of the sinusitis by CT. Patients with "extensive" disease on CT showed improvement in 45% of the cases. The patients with "limited" disease on CT scan, but with SPECT positivity is a group that may benefit from earlier and more aggressive management. SPECT's ability to identify osteitis, prior to radiography, without surgical intervention, may serve as a means to stratify patients. Additionally, SPECT has the potential to differentiate between actively osteitic bone and quiescent remodeled bone. Validation of these hypotheses along with cost analysis is required prior to wide adoption.

CLINICAL SIGNIFICANCE

Baseline Characteristics

Many of the characteristics that have come to be hallmarks of recalcitrant sinus disease correlate with osteitis. The association of osteitis with prior surgery is one of the earliest recognized associations,[3] and the association is dramatic. There is a direct relationship between the number of prior surgeries, the location of the prior surgery, and the degree and extent of osteitis.[30] Lee et al.[31] reported that 41% of patients undergoing revision surgery had presence of osteitic bone vs. only 5% of patients undergoing primary surgery. However, even patients with no prior history of surgery also demonstrate evidence of osteitis.

The mechanisms underlying osteitis are multifactorial (see above), and patients undergoing primary ESS with osteitis are more likely to have eosinophilic-mediated CRS (ECRS). Multiple studies have demonstrated the association of osteitis with nasal polyps,[10,25,30] asthma,[10] and eosinophilia (>10/HPF).[25] These patient characteristics are also classically affiliated with tissue[10,30] and serum eosinophilia.[25,26] The eosinophilia is independent of atopic status, with no studies identifying allergy as a risk factor for osteitis.[10,25,30] Since recalcitrant disease is associated with ECRS, it is difficult to separate the influence of ECRS from prior surgery. However, in patients undergoing primary surgery, the only risk factor for osteitis was tissue eosinophilia.[25] Future studies may benefit from stratification by tissue eosinophilia, as tissue eosinophilia is present in 19% of patients without nasal polyposis.[36]

Baseline symptomatology is consistent with prior data demonstrating disconnect between objective and subjective findings of CRS.[37] To date, only three studies have investigated osteitis with validated quality of life measures (Table 31.3). The sinonasal outcome test 22 (SNOT-22),[25] rhinosinusitis outcome measure (RSOM),[30] rhinosinusitis disability index (RSDI), and chronic sinusitis survey (CSS)[10] at baseline are equivalent in patients with and without osteitis.

Although osteitis is not associated with subjective measures of more severe disease, all levels of objective measure of mucosal disease are increased. Nasal endoscopy scores are worse at baseline.[10,25] Similarly, average Lund–MacKay scores are 6–15 points higher in patients with radiographic evidence of osteitis.[10,31,38] Finally, patients with osteitis also have higher degrees of mucosal inflammation at the histologic level.[39]

Table 31.3: Quality of life and osteitis

Study	*Number of patients with osteitis*	*Number of patients without osteitis*	*Outcome measure*	*Baseline symptoms*	*Post-ESS improvement*
Georgalas et al.[30]	34	43	RSOM	No difference	Not evaluated
Bhandarkar et al.[10]	79	111	RSDI, CSS	No difference	OR 0.44, p = 0.028*
Snidvongs et al.[12]	43	45	SNOT-22	No difference	Not evaluated

*Odds ratio (OR) on RSDI physical subscale of patients with osteitis vs. without osteitis. Patients without osteitis were 3.85 times more likely to improve after ESS.

(ESS: Endoscopic sinus surgery; RSOM: Rhinosinusitis outcome measure; RSDI: Rhinosinusitis disability index; CSS: Chronic sinusitis survey; SNOT-22: Sinonasal outcome test).

Outcomes

The role of ESS in treatment of osteitis is paradoxical. There is a strong association between prior surgery and osteitis, but it has also been shown to improve symptoms and endoscopic examination. Post-ESS patients with osteitis demonstrated improvement across all elements of the RSDI, the CSS, olfactory scores, and nasal endoscopy scores.[10] However, this improvement comes with the caveat that patients with osteitis have less improvement than post-ESS patients without osteitis. This finding held true even in a multivariate model controlling for age, nasal polyposis, history of prior surgery, and baseline quality of life scores. Although tissue eosinophilia was not examined, nasal polyps are associated with tissue eosinophilia, and controlling for nasal polyposis is the closest surrogate available and offers some control of underlying inflammatory severity, an important factor in post-ESS success.[24] As Bhandarkar et al.[10] nicely summarize, the odds of improvement in patients without osteitis were 3.85 times that of patients with osteitis. Remarkably, the endoscopic appearance improves more in osteitic patients than it does in nonosteitic patients, but remains higher than nonosteitic patients.[10] Only two other studies have formally examined outcomes post-ESS related to presence of osteitis. Both studies are limited by soft endpoints and a lack of accounting for confounding variables (endoscopic appearance), but both demonstrated worse outcomes in patients with presence of osteitis.[40,41] Currently, the surgical treatment of osteitis is based on expert opinion (*see* below), and future outcome studies will need to help clarify the impact of removal of osteitic bone, and better control for factors typically associated with severe inflammatory disease.

Management

Surgical

No study to date exists that examines the removal of osteitic bone in CRS, and current surgical management is dictated by expert opinion.[42] In general, endoscopic surgical management of CRS ranges from minimal interventions targeted at relieving sinus outflow paths with subsequent normalization of upstream sinus mucosa[43] to radical surgery aimed at marsupializing all of the sinuses into a common cavity.[44] When CRS involves osteitis, a more aggressive surgical approach is advocated.[42] This conclusion is drawn from the following inferences: (1) evidence of inflammatory cells[9] and cytokines[8] in underlying osteitis serve as an inflammatory reservoir that could persist and propagate overlying mucosal disease, (2) the strong association of osteitis with more severe inflammatory mucosal disease[25] benefits from more aggressive topical therapies that depend upon prodigious openings,[45] and (3) aggressive mucosal disease is predisposed to exuberant cicatricial scarring, and wider openings allow for some anticipated scarring while still maintaining patency.[21]

These guiding tenants therefore dictate the surgical philosophy for each of the sinuses involved with osteitis. Ethmoid partitions are the most commonly involved sinus with osteitis[31] and ostial areas of ethmoid bone are completely removed through skeletonization of the lamina papyracea and the skull base. The middle turbinate can also be involved with osteitis, and partial middle turbinate resection has been advocated in the context of osteitis.[17]

The maxillary sinus can show thickening throughout all walls, but only the ostial wall can be easily addressed. Large maxillary antrostomies demonstrate better topical access (at least 4 mm) and endoscopic medial maxillectomies provide even greater access[45] while simultaneously removing potentially more osteitic bone. There is little clinical data on the impact of medial maxillectomy, but aggressive surgery is advocated for recalcitrant disease.[44]

The frontal recess poses a surgical challenge in osteitic disease. The narrow anatomic limits and proximity to the orbit and skull base can make the frontal recess treacherous. Osteitic bone can completely occlude the frontal recess requiring a Draf 3 drillout procedure for ventilation. Eosinophilic disease is associated with exuberant cicatricial scarring[21] and maximally sized neo-ostium is advocated in anticipation of exuberant scarring. In the case of a frontal recesses with osteitic bone that can be safely removed without a Draf 3, a more conservative approach is reasonable. However, other markers of severe disease (specifically, asthma, aspirin intolerance, nasal polyposis) have lower revision rates after Draf 3.[46] Future studies examining the impact of the presence of osteitis in the frontal sinus are warranted to clarify the ideal surgical intervention.

Osteitic involvement of the sphenoid sinus has been observed to predispose to scarring of the sphenoid sinusotomy.[47] A variety of surgical interventions have been described to maintain patency ranging from a complete sphenoid drill-out[48,49] to a more conservative mininasoseptal flap.[47] Again, the extent of sphenoid sinusotomy in the context of sphenoid osteitis has not been well

defined, but a variety of experts advocate a more aggressive intervention in the context of highly inflammatory disease and osteitis to prevent cicatricial stenosis.

Medical

There is a similar dearth of evidence underpinning medical treatment of osteitis. Expert opinion recommends aggressive medical management of the underlying inflammatory process,[42] yet no studies have specifically examined the impact of medical management on osteitis in a controlled fashion. Just as the pathophysiology of long bone osteomyelitis has been projected onto sinonasal osteitis, so has the medical management. Long-term intravenous antibiotic treatment of long bone osteomyelitis is based in part on the presence of bacteria in acute bacterial osteomyelitis. It is also a challenge to achieve high concentrations of antibiotics within the bone.[50] In the case of sinonasal osteitis there is little evidence to support intraosseus bacteria as the underlying mechanism. One study has identified microcolonies of bacteria within sphenoid bone, but there was no correlation between presence of intraosseus bacteria, degree of sinusitis, and osteitis.[7] There is a conceptual gap between the current understanding of osteitis as either an inflammatory reaction or association with mucosal disease and long courses of intravenous antibiotics. The two studies that have pursued the use of intravenous antibiotics for osteitis suffer from small numbers.[51,52] There is not sufficient evidence of biologic mechanism to support the use of parenteral antibiotics as a treatment of CRS associated with osteitis.

Prolonged courses of oral macrolide therapy in CRS have been advocated in part for their anti-inflammatory properties.[53,54] This is an appealing possible therapy by which to mitigate inflammatory disease and osteitis. Interestingly, macrolide therapy has been shown to decrease MMP-9 in nasal secretions,[55] which is the same enzyme recently found to be upregulated in the presence of osteitis.[22] The use of macrolides has yet to be explicitly studied in patients with evidence of osteitis. Recent data showed no difference between 3 months of macrolide therapy in patients with recalcitrant disease and placebo.[54] The findings of decreased MMP-9 raise the possibility that patients with CRS with osteitis represents a subset of CRS patients that may benefit from macrolide therapy. Regardless, expert opinion recommends antibiotic treatment of the overlying mucosal disease through use of culture-directed antibiotics.[42] However, further evidence is required to establish the role and length of treatment with oral antibiotics in osteitis.

Use of steroids to mitigate the inflammation of CRS is effective in the short term, but carries serious consequences with extended use. Topical steroid therapies are an area of intense research, and may provide a relatively low-risk means of combating significant inflammation within the sinuses.[56] No study has yet examined the role of topical steroids in CRS associated with osteitis. There is evidence that the bony remodeling may be independent of steroids, as one of the enzymes associated with osteitis is independent of systemic steroid administration.[22] However, there exists good evidence for the use of meter-dosed nasal steroid sprays in the context of CRS and off-label topical irrigation continues to be a closely studied therapy for recalcitrant CRS.[56]

CONCLUSION

Osteitis can be associated with severe inflammation and revision surgery, but its role in the pathogenesis remains unclear. From the first observations of bony inflammation in the bone of animal studies, bone turnover in the presence of CRS has been well established in humans. Despite the strong association with recalcitrant disease and prior surgery, it is not yet possible to attribute causality. Current treatment is guided by expert opinion extrapolating from the hypothesis that osteitic bone can propagate mucosal disease. Future studies investigating the underlying mechanisms of bony remodeling in CRS will help elucidate if osteitic bone indeed propagates mucosal disease, and further clinical study will be required to clarify what unique treatments, if any, are indicated in CRS with osteitis.

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CHAPTER

32

Odontogenic Sinusitis

Adam S DeConde, Alexander G Chiu, Jeffrey D Suh

Messerklinger's description of the pathophysiology of chronic rhinosinusitis (CRS) has focused surgical treatment on the ostiomeatal complex and ascending disease;[1] however, odontogenic disease is an important etiology of CRS that results when underlying boney pathology triggers mucosal inflammation that can persist independent of an unobstructed maxillary sinus.[2] Once thought to represent only a small percentage of patients with chronic maxillary sinusitis, recent publications are revealing dental disease to be a common and often unrecognized source of mucosal disease.[3] Remarkably, in a review of all sinusitis guidelines from 1998 to 2010, only 13% of guidelines actually mention an odontogenic source of maxillary sinusitis.[3] This apparent disinterest in odontogenic maxillary sinusitis (OMS) by the guidelines is likely a symptom of the dearth of studies investigating the diagnosis and treatment of the disease. The otolaryngologist plays an important and unique role in diagnosis and treatment of OMS, and therefore what data is available is elevated in importance.

INCIDENCE

The incidence of OMS historically has been quoted on the order of 10% of maxillary sinusitis cases.[3] This incidence has been propagated through the literature since the 1950s, but more recent data suggest a higher prevalence ranging from 12% to 40%.[4,5] Some of the reviews predate modern definitions of CRS, but upon review of 198 patients with 3 months of nasal symptoms and objective findings of sinus disease of the maxillary sinus, 40.6% were found to be of dental origin.[5] Data from the modern era of CRS diagnosis[6] also suggest a higher prevalence than previously thought. Of 515 patients operated on for maxillary CRS without nasal polyps, 104 patients (20%) were related to odontogenic disease or an oroantral fistula.[4] It has been suggested that there is indeed an increasing incidence of odontogenic sinusitis in recent years. A review of a single institution from the United Kingdom suggests that there is an increasing incidence from 2004 to 2009.[7] It was postulated that this was related to a decreased access to dental care. The wide range of incidences of OMS is in part due to the small nature of these reported case series. The disparate geographic locations, and inherent biases of a single institution review, make it impossible to generalize to the population, but they are currently the only data available. Certainly, wider-scale reviews would help establish the true prevalence of the disease. This is important information, because the diagnosis is often overlooked and a correct diagnosis and intervention would be improved by heightened vigilance.

PATHOPHYSIOLOGY

Development of the maxillary sinus only begins prenatally but continues to pneumatize into adulthood. The sinus begins as an ectodermal invagination in the middle meatal groove and measures only 7 × 4 × 4 mm at birth. Children have considerable distance between dental roots and the maxillary sinus floor, but rapid pneumatization occurs between the ages of 12–14 lowering the sinus floor to the level of the nasal floor.[8] This rapid pneumatization parallels the eruption of permanent teeth as well as establishing the adult relationship between the nasal floor and dental roots.[9] The degree of pneumatization is variable, but can extend in all directions to involve the zygomatic bone, the palatine bone, and the dentoalveolar portion of

the maxilla.[10] Inferior pneumatization into the dental alveolus can extend around the roots of teeth. In edentulous patients, further lowering of the maxillary sinus floor can leave roots protruding into the maxillary sinus (Fig. 32.1).[10] Dental roots can therefore become intimately associated with the overlying mucoperiosteum even absent of any disease.

The maxillary sinus does not extend anteriorly beyond the first premolar.[9] The canine and central incisor roots are not as predisposed to be involved with OMS. Cadaveric and computed tomography (CT) evaluation of the relationship of roots to the maxillary sinus floor identified the average distance between the apex of the mesiobuccal root of the second molar from the sinus floor to be 1.97 mm. The apex of the buccal root of the first premolar was the farthest from the maxillary sinus floor at 7.05 mm.[11] The reported relative proximity of dental roots to the maxillary sinus floor from closest to farthest is the second molar, first molar, third molar, second premolar, first premolar, and finally the canine.[12] The thin bone separating the maxillary sinus from these teeth roots is not necessarily mirrored on the buccal side of the roots. The relationship is inverted, with the second molar with the farthest distance from the bony buccal surface (mean 4.45 mm) and the first premolar with only 1.63 mm to the lateral bony surface.[11] In effect, these measurements are highlighting the fact that the molars tend to be seated closer to the maxillary sinus than the lateral buccal surface of the maxillary sinus in contrast to the premolars and canines. This anatomic relationship theoretically predisposes dental disease of the molars to extend medial into the sinus as opposed into the soft tissue overlying the maxilla, which can be seen as a canine fossa abscess off of canine apical disease. Interestingly, the incidence of the source of OMS does not quite mirror the anatomic measurements.[13] A review of 770 published cases of OMS found that the first molar was the most frequently reported (22.5%), followed by the third molar (17.2%), then the second molar (4.0%). The premolars represented the source for OMS in only 6.0% of cases and only 0.7% cases were from the canine.[13] Despite the relatively narrow distances separating tooth root and sinus, maxillary sinusitis as a fraction of all dental disease is relatively low and highlights how effective dense cortical bone is as a barrier to spread of infection.[10]

Disruption of the maxillary sinus bony wall can result from dental infection or iatrogenic destruction. Dental infections begin as caries that progress to a pulpitis and subsequent periapical abscess.[10] Bacterial release of lysosomes and collagenase enzymes along with neutrophilic degranulation can lead to destruction of surrounding bone and rupture into the maxillary sinus. Similarly, iatrogenic dental causes can induce periapical inflammation during endodontic therapy. Instrumentation can inadvertently seed bacteria into the sinus cavity, and material used in obturation can extrude into the sinus as well. Dental implants often require augmentation of the maxillary sinus floor, which can both lead to maxillary sinusitis (Fig. 32.2). Roots fractured on extraction can require removal of alveolar bone surrounding them as well, exposing the maxillary mucosa.[10] An osteomucosal communication between the oral cavity and the maxillary sinus, an oroantral fistula, can result from these interventions. A persistent oroantral

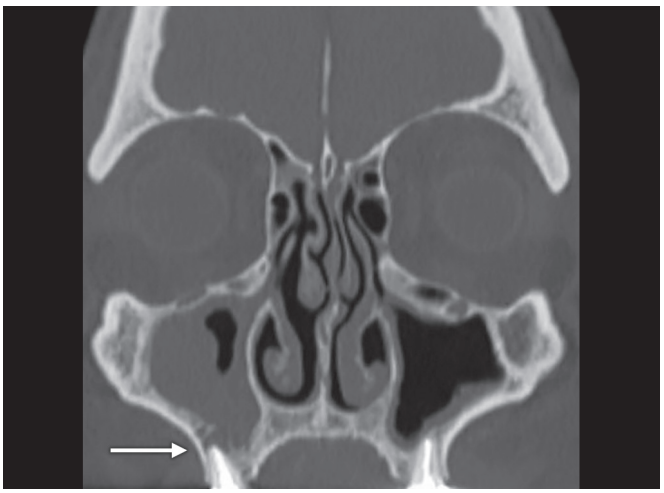

Fig. 32.1: Coronal computed tomography in the bone window demonstrating odontogenic maxillary sinusitis. The diseased tooth root protrudes within the maxillary sinus (arrow).

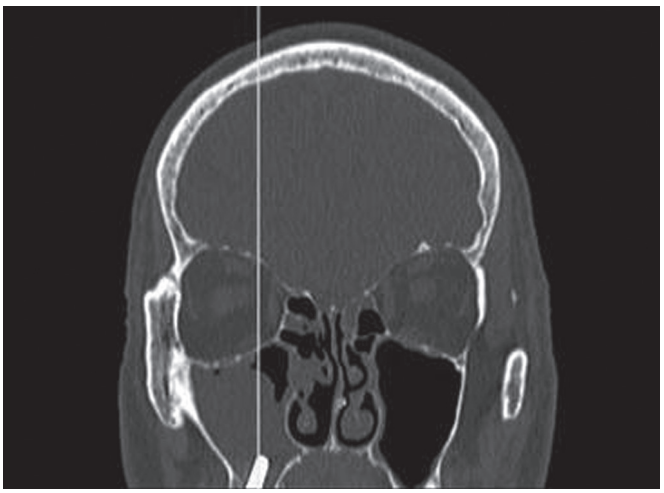

Fig. 32.2: An infected dental implant protruding into the maxillary sinus causing maxillary sinusitis, as seen on a coronal computed tomography in the bone.

fistula, a known side effect of tooth extraction, can also propagate maxillary sinusitis. Similarly, forces on the roots can displace the root into the maxillary sinus resulting in persistent maxillary disease as well.[10] With this long list of iatrogenia, it is no wonder that the leading cause of OMS is iatrogenic.[13] Other common causes included periodontal disease (40.4%) and odontogenic cysts (6.7%). Of the iatrogenic cases, the most common cause was postextraction oroantral fistulas and remnant roots (47.6%).[13]

MICROBIOLOGY

Odontogenic infections of the maxillary sinus shift the microbiology of sinusitis. Nonodontogenic acute sinusitis is associated with *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*.[14] Chronic sinusitis demonstrates a higher prevalence of anaerobes in as many as 67% of chronic maxillary sinusitis cases.[15] A small subset (5–10%) of patients with acute sinusitis do have presence of anaerobic bacteria, and these patients are associated with an odontogenic source.[16] In a review of 48 patients with OMS, only two had the presence of the traditional aerobic bacteria associated with acute sinusitis.[16] The anaerobic bacteria commonly isolated tend to be polymicrobial and biased toward oral flora with the most common anaerobes isolated, *Peptostreptococcus* spp., *Fusobacterium* spp., pigmented *Prevotella*, and *Porphyromonas* spp., all being present in oral flora.[16] Similarly, the microbiology of the periapical abscess reflects a heterogeneous group of anaerobic bacteria with the most common bacteria including *Peptostreptococcus, Bacteroides, Prevotella, Porphyromonas* spp., and aerobic streptococci.[17] Aspirates of periapical abscesses associated with OMS indeed show concordant microbiology.[18]

CLINICAL PRESENTATION

Diagnosis of OMS is a challenging. The underlying pathophysiology straddles professional territory and often it is the sinonasal symptoms that are predominate in the clinical presentation. The mean age of patients reported in the literature is between 16 years and 80 years and the disease most commonly presents in the fourth decade of life.[13] Women are more commonly affected than men at a ratio of 1:1.33.[13] Patients with OMS may present with CRS. Historically, OMS was thought to be restricted to acute rhinosinusitis (ARS). A review of 11 guidelines found that 4 of the 11 restricted the diagnosis to ARS, but 90% of patients with OMS have symptoms more than 8 weeks, averaging 2.6 years.[3]

A prospective review of patients undergoing treatment for treatment of chronic OMS at a single institution[3] highlights some of the challenges in diagnosing OMS. Only a minority (29%) of patients reports a history of dental pain, and this is not necessarily specific to OMS.[19] The more commonly anaerobic profile of OMS is also thought to lead to cacosmia, but only 48% of patients experience a rotten smell or bad taste. Cacosmia, however, is not specific for OMS as anaerobic microbiology can predominate in rhinogenic CRS. Additionally, only one of the patients who presented with dental X-rays demonstrated dental caries. In other words, 86% of the dental X-rays failed to identify the odontogenic source. A prior series reporting on 99 cases of OMS, similarly found that evaluation by a dentist identified a dental source in 56% of cases.[5] A negative dental evaluation does not exclude OMS. Regardless, an oral exam may raise suspicion of an odontogenic source, with 14.8% of patients presenting with gingival swelling in one series.[20] The most common symptom found by Longhini et al.[3] was nasal obstruction, which is frustratingly nonspecific and is often the most bothersome symptom in a wide variety of pathologies affecting the nose. Despite the nonspecific clinical symptoms of OMS, unilaterality should raise suspicion of OMS as this is a very common findings of OMS and atypical of rhinogenic CRS.[20] Clinical symptoms of OMS overlap rhinogenic CRS, and a high level of suspicion is required when evaluating patients with OMS, particularly when symptoms areunilateral.

IMAGING

A lack of specificity of signs and symptoms raises the importance of the radiography to identify the underlying odontogenic source. Unfortunately, dental plain films have only a 60% sensitivity in identifying dental caries and an 85% sensitivity to identify periodontal disease.[21] Coupled with nonspecific clinical signs and symptoms, it is no wonder that most patients presenting with OMS arrive to the otolaryngologist after a dental evaluation with no identified odontogenic source.[5] Similarly, remarkably, in one series, 66% of patients with OMS had prior sinus CT scans with overlooked dental sources by the radiologist.[3] It therefore not infrequently falls to the otolaryngologist to establish the odontogenic source through CT imaging of the sinuses. Computed tomography scan findings can be subtle, and if not looking beyond the osteomeatal complex, odontogenic sources are easily overlooked.

Particularly in cases of unilateral maxillary sinusitis, active evaluation of dental findings is critical to identify the source of pathology. In a review of over 100 patients undergoing scans of the maxillary sinus with the presence of maxillary sinus mucosal thickening, 26% of sinuses were associated with active dental disease and 36% demonstrated presence of periodontal disease.[22] Presence of oroantral fistula (defined as absence of bone of the maxillary sinus floor), apical abscess, periodontal disease, and a projecting tooth root were all associated with maxillary sinus fluid. Oroantral fistulas were found to be independent predictors of maxillary sinus fluid. Examination of the extent of sinus disease is important to identify as well. Extension of maxillary sinusitis to involve the osteomeatal complex can lead to upstream sinusitis. Presence of ethmoid and frontal opacification was present in 71% and 48%, respectively.[3] When ipsilateral dental and periodontal disease is identified in the presence of unilateral maxillary sinusitis, causality should be inferred and treatment for OMS initiated.

MANAGEMENT

Treatment of OMS is currently guided by expert opinion and small case series. A range of recommendations exist, but there is consensus that treatment of at least the underlying dental disease is required, with controversy regarding the extent and means of further intervention of the sinuses. At a minimum, addressing the underlying odontogenic pathology is required[3] via dental extraction or closure of a fistula. Secondarily, retrieval for foreign materials, retained tooth roots, unroofing of odontogenic cysts can be simultaneously accomplished through approaches to the maxillary sinuses. The maxillary sinus can be approached via an endoscopic transnasal approach or an open Caldwell-Luc approach. Debate over the ideal technique remains in the context of OMS. Transnasal endoscopic approaches offer comfortable access to the osteomeatal complex, easy surveillance, postoperative irrigations, and no risk to the infraorbital nerve.[23] In contrast, a Caldwell-Luc approach allows easier access to the anterior wall of the sinus, provides a broader view of the sinus, and can be performed under local anesthesia.[4] The endoscopic approach offers the additional advantage of surgical intervention at an obstructed osteomeatal complex. There is concern that failure to address the sinus outflow tract may predispose to increased sinus pressures, particularly causing problems in patients undergoing oroantral fistula repair.[24] However, recent evidence has cast doubts on this theoretical concern.

Longhini et al.[3] demonstrated that dental therapy alone can resolve sinusitis in 95% of the patients they encountered. Similarly, isolated treatment of the sinuses occurred in six patients prior to recognition of the underlying odontogenic source. Despite 15 sinus surgeries performed in these six patients, there was no resolution of symptoms prior to the treatment of the underlying dental source. The 95% resolution rate of patients treated with isolated dental interventions is remarkable considering that sinusitis extended to the ethmoids in 71% of patients and as far as the frontal sinuses in 48% of the patients in the series. This data raises questions about the natural history of even relatively extensive odontogenic sinusitis after treatment of the underlying dental disease.

Albu et al.[4] sought to investigate the role of the ostiomeatal complex in OMS by randomizing patients with OMS to simultaneous treatment of dental disease with an adjuvant approach consisting of an endoscopic endonasal approach or a Caldwell-Luc approach. The endoscopic endonasal approach allowed for direct intervention of the osteomeatal complex. This group underwent maxillary antrostomy, uncinectomy, and anterior ethmoidectomy along withremoval of retained debris, unroofing of cysts, and debridement of irreversibly diseased mucosa with angled scopes, instruments, and debriders via the maxillary antrostomy. In contrast, patients randomized to a Caldwell-Luc approach underwent no intervention of the osteomeatal complex. Again, foreign debris, cysts, and diseased mucosa were removed, but no intervention in the sinus outflow tract was undertaken. Patients were assessed with a validated symptom score at 3-month intervals, with a mean follow-up of 18.5 months. No difference in nasal obstruction, facial pressure, nasal discharge, postnasal drip, or dental pain was identified between the two groups. Similarly, in the patient subgroup that underwent oroantral fistula closure there was no difference in closure failure rates. It should be noted that 25% of the patients who underwent a Caldwell-Luc approach reported cheek paresthesias, which at 3 months postoperatively were still present in 3.5% of patients. Given that both approaches result in similarclinical outcomes, either approach is a valid therapy for OMS. Further study is required to better identify which patients require no intervention of the sinuses.

Medical management is an important component of OMS as well. As previously discussed, the antimicrobial profile of OMS skews toward anaerobic involvement, and addition of a medication active against oral anaerobes is recommended.[10] Treatment regimens for chronic sinusitis are recommended for at least 3 weeks and 21–28 days.[10] Beta-lactamase activity has also been identified in

increasing quantities and therefore penicillin is considered inadequate. Odontogenic maxillary sinusitis should, therefore, be treated with a penicillin combined with a beta-lactamase inhibitor (e.g. amoxicillin and clavulanate) in addition to an antimicrobial with good anaerobic coverage (e.g. metronidazole).[10]

CONCLUSION

Odontogenic maxillary sinusitis is likely a more common source of inflammation than previously recognized. A high level of suspicion on the part of the otolaryngologist is critical to clinically identify patients with OMS. Although no standardized guidelines exist establishing the diagnostic guidelines, objective evidence of dental disease in association with a diseased sinus is the basis of the diagnosis of OMS. Management is both medical and surgical. The high prevalence of anaerobic bacteria in even acute OMS highlights the need to provide adequate anaerobic antimicrobials. Surgical intervention first and foremost must address the underlying dental pathology. The extent of sinus surgical intervention requires further study, but open and endoscopic approaches to the maxillary sinuses provide equivalent clinical outcomes and recurrence rates.

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CHAPTER

33

Reflux and Sinusitis

Adrienne M Laury, John M DelGaudio

INTRODUCTION

Chronic rhinosinusitis (CRS) is a significant health problem affecting almost 30 million Americans each year and costing upward of $6 billion.[1,2] It is a complex medical condition that is currently managed with a variety of medical and surgical treatments. This management is often dictated by the underlying disease process causing the CRS. For example, the current treatment regimen for a patient with nasal polyposis secondary to cystic fibrosis significantly differs from that of a patient with allergic fungal sinusitis. Therefore, as we develop in our understanding of CRS, it appears that consideration of the underlying cause is a significant factor when developing a treatment algorithm.

Laryngopharyngeal reflux (LPR) is one of the most common diseases seen in the otolaryngologist's office. While it is a distinct entity from gastroesophageal reflux (GER), occurring concurrently in only 20–40% of patients, its unique manifestations in the head and neck make it extremely prevalent in our patient population.[3] For decades, LPR has been implicated as a contributing factor in numerous disease processes including dysphonia, benign vocal fold lesions, laryngospasm, and subglottic stenosis.[4] Yet, it has only been over the past 15–20 years that LPR has been suggested as a potential contributing factor in both pediatric and adult refractory rhinosinusitis.

PATHOPHYSIOLOGY

CRS is defined as the prolonged inflammation of the mucosa of the paranasal sinuses and the nasal cavity. Various etiologies of sinusitis have been identified, including environmental (i.e. viral URIs), anatomic, systemic (i.e. HIV), and genetically mediated (i.e. cystic fibrosis). Regardless of the inciting event, the mucosal inflammation leads to obstruction of the paranasal sinus ostia, stasis of secretions, and often superimposed bacterial infections. The treatment of this disease is, therefore, often dependent on the underlying cause. For example, bacterial chronic sinusitis may resolve with a course of nasal saline irrigations, intranasal steroid spray, and antibiotics, while a patient with a concha bullosa obstructing the entire osteomeatal complex will likely require surgical intervention to resolve their symptoms.

LPR is defined as the entry of gastric acid into the larynx, hypopharynx, oropharynx, and even nasopharynx. The physiologic mechanism of LPR can be attributed to a breakdown in one or more of the four barriers to reflux: the upper esophageal sphincter (UES), lower esophageal sphincter, esophageal acid clearance, and epithelial resistance.[3] In LPR, a weakening in the normal pressures maintained by the UES is one of the two most significant contributing factors. This can be due to a physiologic mechanism or a variety of environmental influences including general anesthesia, sleep, cigarettes, and dietary factors. Additionally, a breakdown in epithelial resistance also plays a substantial role in LPR. While esophageal epithelium has both a mucous and aqueous layer to prevent penetration of gastric enzymes and acid, the squamous epithelium of the larynx, hypopharynx, and nasopharynx does not possess such protective mechanisms, and therefore, is subject to even more injury with relatively less acid exposure.

Based on this physiology, it is not surprising that LPR has been repeatedly implicated as a significant contributing factor in refractory CRS. While the exact mechanism is still unclear, three hypotheses have been proposed:

- Nasopharyngeal reflux (NPR)—acid from the stomach along with gastric enzymes reflux into the nasopharynx causing significant mucosal inflammation and impaired mucociliary clearance. This has been shown to be true in both children and adults. In children, NPR has been shown to play a significant role in choanal atresia, serous otitis media, as well as CRS.[5-7]
- Vagus nerve reflex—refluxed acid can directly stimulate receptors at the level of the larynx, oropharynx, and nasopharynx. This has been described more frequently in the larynx with the propagation of laryngospasm or reflexive vocal fold adduction after significant exposure of laryngeal receptors to acid.
- *Helicobacter pylori*—*Helicobacter* was found in a small number of patient's undergoing endoscopic sinus surgery, specifically in diseased polypoid tissue, and therefore may play a contributing role in CRS.[8]

Whether one or more of these truly does mediate the disease process in CRS is yet to be fully understood. However, several studies have sought to examine this relationship further.

CURRENT EVIDENCE

Over the past several years, multiple studies have sought to define the relationship between LPR and sinusitis (Table 33.1). Some of the earliest studies focus on this relationship in the pediatric population. In 1991, Contencin and Narcy evaluated 31 children for the presence of NPR by performing 24-hour nasopharyngeal pH studies.[9] Of these, 13 had recurrent or chronic rhinitis while the control group of 18 children had no nasopharyngeal disease based on symptoms or physical exam. Following the pH studies, they found the CRS group, when compared with the controls, had significantly lower pH drops, more frequent drops, and overall longer study time spent below the study cutoff pH of 6.0. Unfortunately, the study was limited by the fact that they only used a nasopharyngeal sensor without an esophageal sensor, therefore preventing confirmation that a drop in esophageal pH preceded the nasopharyngeal pH drops. Also, their study hypothesized that a pH drop below 6.0 in the nasopharynx is equivalent to a pH drop below 4.0 in the esophagus, which was not supported by any previous work or their current study findings.

However, in order to further examine this proposed relationship, in 2000 Phipps et al. examined a cohort of patients with CRS refractory to medical therapy including at least a 3-week trial of broad-spectrum antibiotics.[10] The purpose was to determine the prevalence of gastroesophageal reflux disease (GERD) in these patients using a dual-sensor pH probe. In this cohort, 63% of patients were diagnosed with GERD, and of those 32% were identified with NPR. Subsequently, in those with GERD, various antireflux mediations and dietary changes were initiated, resulting in a 79% improvement in parental evaluation of sinusitis symptoms. Further support for the use of antireflux medical therapy as a potential treatment of refractory CRS was proposed by Bothwell et al.[11] In this study of 30 children with CRS for whom functional endoscopic sinus surgery (FESS) was recommended, all were instead placed on aggressive antireflux medications and dietary changes. At a 24-month review, it was found that 89% of children avoided surgery based on clinical improvement from parental review. Additionally, they found that positive pH probe results and day care attendance were two independent predictive factors in determining which children were more likely to symptomatically improve with reflux treatment.

Extrapolating from pediatric studies, investigators have more recently sought to draw a relationship between LPR and refractory CRS in the adult patient population. One of the first to examine this relationship was Chambers et al. who, in 1997, retrospectively reviewed 182 patients who had undergone FESS to determine which prognostic factors predispose to a poor outcome. They found that a history of GERD was the only historic factor that was predictive of poor outcomes after FESS. A history of GERD was determined based on a report of heartburn or regurgitation that required medication on review of the patient's medical records. However, because this was a retrospective study, no pH probes were utilized for diagnostic confirmation of reflux disease.[12] Subsequently, DiBaise et al. retrospectively reported on 18 patients with refractory CRS of which 78% were found to have GERD based on pH probe testing.[13] In turn, all 18 patients had their reflux medically or surgically treated, resulting in a 67% improvement in their sinus symptoms over an almost 6-month follow-up. Dramatic improvement was confined to patients with documented abnormal pH probe results. Unfortunately, no control group was used in this study.

More recently, DelGaudio examined a cohort of 38 patients with a history of CRS who had failed surgical

Table 33.1: Evidence-based studies on reflux and sinonasal disease

Authors	*Year*	*Type*	*Size*	*Measurement*	*Result*	*EBM Level*
Contencin et al.[5]	1991	Prospective case-control	31	Presence of NPR in patients with sinonasal disease vs control	Significantly more time with pH spent below threshold in NPR patients	2b
Phipps et al.[10]	2000	Prospective cohort	30	Percentage of CRS patients with GERD	63% of patients with CRS had GERD by dual-channel pH probe	4
Bothwell et al.[11]	1999	Retrospective cohort	28	Avoidance of surgery if treated for GERD	83% of patients avoided surgery	4
Chambers et al.[12]	1997	Retrospective cohort	182	Historical factors that affect success of FESS	GERD was the only historic predictor of poor outcome following FESS	4
DiBaise et al.[13]	1998	Retrospective cohort	18	Incidence of GERD in patients with refractory CRS s/p FESS	78% incidence of GERD with 67% improvement in sinus symptoms with PPI	4
DelGaudio[14]	2005	Case-control	68	Presence of NPR, reflux at UES, or GERD by 3-channel probe	Significantly more reflux at the nasopharynx, UES, and esophagus in the CRS group compared with 2 control groups	2b
Ozmen et al.[15]	2008	Case-control	52	Presence of LPR by dual-channel pH probe and presence of pepsin in sinonasal tissue	More pharyngeal acid reflux events in CRS group; more pepsin found in patients with reflux	2b
Wise et al.[16]	2006	Cohort	68	Association between PND and NPR and LPR by 3-channel pH probe	Significantly more PND symptoms in patients with NPR and LPR	2b
Vaezi et al.[17]	2010	Randomized controlled trial	75	Improvement in PND with PPI	Significantly greater improvement with PPI over placebo	1b
Pincus et al.	2006	Cohort	15	Response to daily PPI in patients with CRS	Modest symptom improvement	4

(NPR: Nasopharyngeal reflux; CRS: Chronic rhinosinusitis; GERD: Gastroesophageal reflux disease; FESS: Functional endoscopic sinus surgery; PND: Postnasal drip; laryngopharyngeal reflux; UES: Upper esophageal sphincter; PPI: Proton pump inhibitor).

therapy by both symptomatic and endoscopic evaluation and compared them with two groups—one who had undergone FESS and were now symptom free, and one control group with no history of CRS or sinus surgery.[14] All were then evaluated for 24 hours using a 3-channel pH probe—with sensors at the nasopharynx, hypopharynx, and distal esophagus. He found that the refractory CRS group had significantly more NPR events at a pH less than 4 compared with the other two groups combined (39% vs 7%) as well as at a pH less than 5 (76% vs 24%). Additionally, the refractory CRS patients also had statistically significantly more reflux above the UES as well as at the distal esophagus in comparison with the pooled control group. These findings were then further supported in 2008, by Ozmen et al. who conducted a prospective case-control study on 33 patients who had been recruited for FESS for medically refractory CRS and 20 patients who had been recruited for FESS for some other sinonasal anatomic variation (i.e. concha bullosa).[15] Prior to surgery, all patients underwent dual-channel pH probe and sinonasal tissue evaluation for the presence of pepsin. They found that there was a significantly higher incidence of pharyngeal acid reflux events in patients with CRS (88%) compared with controls (55%). Additionally, they established that the presence of pepsin in sinonasal tissues was 100% sensitive and 92.5% specific for the

Table 33.2: Reflux symptom inventory

Hoarseness or a problem with your voice?	0	1	2	3	4	5
Clearing your throat?						
Excess throat mucus or postnasal drip?						
Difficulty swallowing food, liquids, or pills?						
Coughing after you ate or lie down?						
Breathing difficulties or choking episodes?						
Troublesome or annoying cough?						
Sensation of something sticking in your throat or a lump in your throat?						
Heartburn, chest pain, indigestion, or stomach acid coming up?						

0 = no problem.
5 = severe problem.

diagnosis of LPR based on pH probe results. Therefore, these investigators suggested that not only is there an association between CRS and LPR, but that pepsin assays may provide a noninvasive and feasible method for LPR screening.

Finally, the relationship between LPR and other extrinsic sinonasal complaints has also been examined in several studies. Specifically, the association between postnasal drip (PND) and LPR was recently observed by Wise et al.[16] They surveyed 68 patients with PND using the SNOT-20 questionnaire and modified Reflux Symptoms Index (RSI), who then underwent 24-hour 3-channel pH testing. Of the patients with NPR events with a pH less than 5, there were significantly more PND symptoms reported on the SNOT-20 and modified RSI survey compared with patients without reflux in the nasopharynx. Vaezi et al. further supported this relationship in their double-blinded, placebo controlled study.[17] They took 75 patients with PND and no signs of chronic sinusitis or allergy and randomized them to twice daily proton pump inhibitor (PPI) or placebo. At 16 weeks, the median improvement in the PPI arm was 50% compared with only 5% in the placebo arm. In addition, there were also significant improvements in several validated quality of life outcome measures in the group using the PPI; therefore, supporting the link between reflux and extrinsic sinonasal complaints.

CLINICAL FINDINGS

The diagnosis of LPR as a contributing factor in CRS is often a difficult conclusion to make. These patients will frequently present with the typical course of CRS refractory to multiple medical therapies. Additionally, these patients often present having already undergone outside surgical intervention with subsequent return of CRS symptoms and clinical findings. This clinical picture of failures at both the medical and surgical management levels forces the otolaryngologist to evaluate other possible causes of this persistent disease state. While other underlying factors such as allergies, immune deficiency, or genetic abnormality (i.e. cystic fibrosis) must all be considered, the authors suggest that reflux disease must also be proposed as a possible pathophysiologic contributor to refractory CRS. One relatively simple tool that can be utilized to help define the potential role of LPR is the administration of the Reflux Symptoms Inventory (RSI) (Table 33.2).[27] However, if this fails to raise any significant findings, further exploration can be accomplished through two possible means—testing (i.e. pH probe) or treatment (i.e. empiric PPI therapy).

TESTING

Multiple modalities have been utilized to definitively diagnose LPR over the past several decades. Barium esophagram is an inexpensive, noninvasive, and readily available test to identify any structural or functional abnormalities of the esophagus. However, it has a relatively poor sensitivity of detecting GERD at only 20–60% and specificity of 64–90%.[3] Flexible endoscopic evaluation of swallowing, or FEES, is another test utilized in the diagnosis of LPR. This allows for actual visualization of reflux into the nasopharynx, hypopharynx, or larynx following swallowing. However, this evaluation often only lasts for a few minutes and therefore events can frequently be missed.

Currently, the pH probe is the gold standard for the diagnosis of LPR and NPR with a sensitivity and specificity as high as 92%.[18] Often multiple probes can be placed depending on the location the clinician desires to analyze (i.e. nasopharynx for CRS). Unfortunately, the pitfalls of the test include its invasiveness and subjectivity of the results based on technique and documentation of patient position. The cutoff for what is considered an abnormal pH is also debated. While a pH of < 4 at the level of the distal probe (5 cm above the lower esophageal sphincter) is almost unanimously considered abnormal, the pH that is considered abnormal at the nasopharynx is controversial. This relates to the fact that pepsin, which has been implicated as a major factor in tissue damage and whose presence has been confirmed in the nasopharynx, is active at a pH of up to 5. Therefore, some clinicians consider findings of pH< 5 in the nasopharynx to be diagnostic of NPR.[19]

Additionally, newer technology has advanced the capabilities as well as lessened the discomfort of traditional pH probes. A wireless capsule-sized telemetry device now exists that can monitor distal esophageal pH for 48 hours with less discomfort (Bravo device). However, when examining for LPR or NPR, this device proves less applicable secondary to its restrictions in placement—above the UES risks the complication of dislodgement or aspiration, while immediately below the UES, often causes significant globus sensation and is not well tolerated. Alternatively, multichannel intraluminal impedance (MII) is designed to detect movement of bolus secretions. When combined with pH monitoring, it has the advantage of defining LPR.[20] The benefits of this dual modality technique are the ability to detect reflux of gas, liquid, or both, as well as defining if it is acidic or not. This in turn, affords detection of patients with acid reflux (25% of those patients despite acid suppression) as well as those who have nonacidic reflux (up to half of patients with continued symptoms despite PPI therapy).[21]

Finally, one of the more recent technologic advances, the Restech device, is specifically designed for detecting reflux into the oropharynx, or LPR. This minimally invasive oropharyngeal probe measures both the pH of aerosolized, humidified refluxate, and traditional liquid events. Its advantage over the pH probe alone is that it does not require immersion in liquid for accurate readings and the device can be easily inserted transnasally in the clinic. Additionally, when examining LPR events, it has been shown to provide reliable results when compared with the standard dual-channel pH probe (especially when sleep and meals are accounted for) and is better tolerated then a pH probe.[22] However, with regard to NPR, there is no published data to determine its efficacy.

Therefore, currently, the dual-channel pH monitoring system, with at least one channel in the nasopharynx, along with MII capability, provides the most reliable clinical data regarding the presence of LPR/NPR in a patient with refractory chronic sinusitis. While the use of a pH probe is not essential for diagnosis of LPR as the underlying cause of CRS, especially if symptoms or clinical findings are highly suspicious, it is strongly recommended as an important tool in further understanding this complex disease process.

MEDICAL MANAGEMENT

Medical management of CRS related to LPR is relatively straightforward. It involves specific treatment of both the sinuses and the reflux. Currently, there are multiple components to antireflux management in terms of both behavioral modifications and medical or even surgical interventions. In terms of behavioral modifications, nocturnal reflux precautions alone have been shown to provide 50% improvement in symptoms.[23] These include not eating or drinking 3 hours prior to sleep, avoiding tobacco, alcohol, fatty foods, caffeine, spicy foods, chocolate, and elevation of the head of the bed. However, compliance with these challenging modifications is obviously highly variable. PPIs are considered the gold standard in the treatment of GERD, LPR, and NPR. They work primarily in the parietal cell by blocking the final step in acid production. As mentioned above, treatment with PPIs in patients with refractory CRS has been shown in multiple studies (Table 33.1) to decrease sinonasal symptoms and even prevent surgical intervention. In another study by Pincus et al., 30 patients with medically and surgically refractory CRS were evaluated by pH study, followed by treatment with PPIs. Twenty five of the thirty patients were found to have reflux. Fourteen of fifteen patients who completed a 1 month course of once-a-day PPI had improvement in their symptoms, with 7/15 having a complete or near complete resolution.

Therefore, the authors recommend that patients with refractory CRS, who have had a negative workup for allergic, immune or genetic causes, be treated with dietary modifications as well as a daily PPI for approximately 8 weeks, along with their sinonasal regimen. After 8 weeks, reassessment of patient symptoms should occur, and if

no significant improvement, the PPI dose can be increased to a bid dosing, similar to the treatment of refractory LPR.[24]

The authors further advocate that this treatment may be initiated without prior pH probe testing, instead utilizing PPI therapy as both a diagnostic and therapeutic modality for refractory CRS. This empiric treatment is possible secondary to the relatively minimal side effects inherent in PPI therapy, especially when it is utilized as part of a finite treatment regimen. However, each physician must be aware, and appropriately counsel their patients regarding the modestly increased risk of nontraumatic fracture while on a PPI.[25] This effect is thought to be secondary to inhibition of osteoclastic proton pumps that may reduce bone resorption, and profound acid suppression could also potentially hamper intestinal calcium absorption.[26] While it appears that postmenopausal women are most significantly at risk, the authors still recommend that all patients over the age of 50 and undergoing a prolonged course of proton pump therapy should also be started on supplemental calcium with vitamin D. Furthermore, we recommend the use of pH probe testing for patients with failure to respond to maximal PPI therapy and dietary management.

CONCLUSION

Overall, the role of LPR/NPR in CRS is a well-studied and verified phenomenon that should be considered in all medically and surgically refractory cases. While there are many theories regarding its pathophysiology, the most compelling describes significant NPR that, in turn, causes chronic inflammation and impaired mucociliary clearance in the nasal cavity. Numerous prospective studies have supported this association as well as the possibility of CRS symptomatic improvement with reflux treatment. Additionally, the use of a pH probe makes the confirmatory diagnosis relatively easy. Finally, the typical treatment regimen of PPI therapy, while not completely without side effects, is well-tolerated with minimal side effects, especially if utilized for a short duration. Overall, we suggest that LPR/NPR should be an important consideration for every otolaryngologist in their evaluation of a patient with refractory CRS.

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CHAPTER

34

Complications of Rhinologic Disorders

Philip G Chen, Peter-John Wormald

INTRODUCTION

Sinusitis is a term that denotes presence of inflammation of the paranasal sinus mucosa. While the etiology of sinusitis is likely to be multifactorial, millions of people around the world suffer with varying forms of sinusitis comprising of symptoms such as nasal obstruction, facial pressure, and nasal drainage. While the exact cause(s) is yet to be elucidated, evidence supports that microbial pathogens play a prominent role in the inflammatory process. Historically, sinusitis was categorized based on duration of symptoms. Symptoms of acute sinusitis lasted fewer than 4 weeks, subacute disease lasted between 4 and 12 weeks, and disease was classified as chronic when lasting >12 weeks.

Therapies treating sinusitis aim to decrease the inflammation with topical and oral steroids, nasal irrigations, and antibiotics. The mucosal inflammation compromises ciliary movement and clearance of pathogens. As a result, bacteria and fungus become trapped within the sinuses resulting in an infection that can subsequently spread to adjacent structures. Given the importance of the surrounding structures, extension of disease beyond the confines of the paranasal sinuses can be catastrophic. Extracranially, pathogens affect the orbit via direct extension through the lamina papyracea or by traveling hematogenously through valveless veins. The effects range from preseptal cellulitis that can be controlled with oral antibiotics to orbital abscesses requiring antibiotics and urgent surgical intervention. Access of pathogens into the intracranial vault can culminate in life-threatening conditions such as meningitis and intracranial abscess.

EVALUATION

History and Physical Examination

Whenever there is concern for complications arising from sinusitis, it is crucial to obtain a detailed history and perform a comprehensive physical examination with emphasis on neurological manifestations. The duration of symptoms provides information about the chronicity of sinusitis. Subjective vision changes (diplopia, blurry, vision loss) suggest involvement of the postseptal orbit or cavernous sinus (CS). Facial numbness indicates involvement of the fifth cranial nerve. Headaches, vertigo, nausea, vomiting, and meningismus imply intracranial involvement. Patients should be questioned regarding recent trauma, insect bites, dental work, and caries, as these can all be the initial nidus of infection.

The patient's medical history of sinusitis and treatments provide insight into potential causes for the infection. Patients in an immunosuppressed state are at higher risk for developing complications from seemingly typical sinusitis especially when fungus is involved. These include patients with diabetes, HIV/AIDS, and malignancy, or those taking chronic steroids or immune modulators. Knowledge of tobacco use is important since it compromises ciliary function.

Many of these patients present in toxic states, thereby limiting the utility of history. Vital signs should be recorded as well as neurologic status, Glasgow coma score, and cranial nerve function including corneal reflex. An ophthalmology consult is important to determine visual fields and acuity. The ophthalmologist should also assess the

pupil for an afferent pupillary defect and papilledema as well as proptosis of the globe. The skin is evaluated for insect bites, lacerations, and traumatic breaks. Dentition and mucosal surfaces of the oral cavity and oropharynx are examined. Purulent otorrhea or otitis media should be sought. If sinusitis is suspected, nasal endoscopy provides the most thorough examination and purulence is cultured. Necrotic tissue or black eschar may indicate invasive fungal sinusitis and must be biopsied emergently.

Laboratory Studies

Serologic testing includes complete blood count with cell differential (CBC), glucose, erythrocyte sedimentation rate, C-reactive protein, and blood culture. If possible, cultures should be obtained prior to implementation of antibiotics. If an immune deficiency is suspected, immunoglobulin levels, HIV, and hemoglobin A1c can be helpful. Lumbar puncture (LP) should never be performed prior to radiographic imaging to determine whether a high pressure system exists. In these situations, an LP can result in a potentially fatal cerebellar tonsillar herniation. Evaluation of cerebral spinal fluid (CSF) is most useful if meningitis is suspected; however, its utility is limited in diagnosing other intracranial infections.

Radiographic Imaging

The utility of sinus X-rays is limited since they exhibit both poor sensitivity and specificity. Computed tomography (CT) scans with intravenous contrast allow accurate evaluation of the orbit, sinus, and brain when complications of sinus disease are suspected. If no complication is anticipated, it is prudent to delay CT scanning until the acute exacerbation is controlled, especially in children when efforts are made to limit radiation exposure. CT scans are ideal for imaging bony anatomy and defects. As a result, sinus disease, expansion or erosion of lamina and skull base, and chronic osteomyelitis are well visualized with CT. Soft tissue is not detailed well; however, extraocular muscle edema, globe proptosis, and cerebral edema can all be appreciated. With the addition of intravenous contrast, the CS, superior ophthalmic vein, and the presence of abscesses are able to be detected.

Magnetic resonance imaging (MRI) is superior to CT for evaluation of the soft tissue and provides better detail regarding intracranial and skull base structures. Therefore, MRI is useful in imaging empyema and meningeal inflammation. MRI is also superior to CT in evaluating tissue within the orbit as well as the CS. Diffusion-weighted imaging protocols are helpful to delineate intracranial extension or cavernous sinus thrombosis (CST), and MR venography can be helpful if venous thrombosis is suspected.

ORBITAL COMPLICATIONS

The proximity of the orbits to the sinuses makes them susceptible to spread of infection. The orbit shares its floor with the roof of the maxillary sinus, while the medial orbital wall is the lateral extent of the frontal, ethmoid, and sphenoid sinuses. Not only is the medial orbital wall especially thin but numerous defects (Zuckerkandl dehiscences) and valveless blood vessels also provide an easy conduit for pathogens to cross from the sinuses into the orbit. Further, the periorbita is rather loosely adherent to the bone of the medial orbital wall, thus allowing movement of bacteria within the subperiosteal space. The venous drainage from the paranasal sinuses is primarily through the valveless orbital veins. As a result of these anatomic characteristics, the orbit is by far the most common location for complications from the sinuses. Similarly, the sinuses are the most common etiological factor of orbital cellulitis and infections. Bacteria are the primary offenders although fungal disease is also possible. *Staphylococcus aureus* and streptococci species are most common and anaerobic bacteria are often present as well.[1,2] *Haemophilus influenza* type B was once a common pathogen, but the incidence has decreased with widespread immunization. In fact, within the pediatric population the overall rate of orbital infections has decreased after advent of *H. influenza* type B immunization.[3]

The most well-known and historic categorization of orbital infections was described by Chandler and colleagues.[4] This was more recently modified by Mortimore and Wormald based on the increasing availability of CT scanners.[5] This classification divides infection into pre- and postseptal compartments with and without abscess, and further considers CST as an intracranial complication. This modified classification is presented below (Table 34.1).

Preseptal Cellulitis (Mortimore and Wormald IA)

The orbital septum (palpebral ligament) serves as the boundary between the eyelid and orbital contents. It represents the anterior boundary of the orbit and extends from the orbital rims to the eyelid margins. The septum consists

Table 34.1: Chandler classification of orbital complications of sinusitis and Mortimore and Wormald's modification

Group	*Chandler classification*[4]	*Mortimore and Wormald*[5]
I	Preseptal cellulitis	Preseptal A. Cellulitis B. Abscess
II	Orbital cellulitis	Postseptal (subperiosteal) A. Phlegmon/cellulitis B. Abscess
III	Subperiosteal abscess	Postseptal (intraconal) A. Cellulitis I. Localized II. Diffuse
IV	Orbital abscess	B. Abscess
V	Cavernous sinus thrombosis	–

primarily of eyelid skin and preseptal orbicularis oculi muscle fibers and serves as the only soft tissue barrier between the outside environment and orbit. Infections within the sinuses can spread directly across the lamina papyracea, venous channels, foramina, and natural dehiscences to affect the orbit and eyes. Spread also occurs via thrombophlebitis of the ethmoid veins.

Preseptal cellulitis is categorized as Mortimore and Wormald group IA. Infection is limited in this circumstance to the preseptal tissue and manifests with significant eyelid edema and erythema. This condition tends to affect younger children (<5 years) more frequently with an increased incidence in the winter paralleling that of sinusitis.[3] While the ethmoid sinus is the nidus of infection in approximately 80–90% of cases,[5,6] other etiologies are possible including facial skin trauma such as lacerations or insect bites as well as periocular pathology such as dacrocystitis.

Patients present with unilateral edema, erythema, and tenderness of the eyelid. Conjunctival chemosis is usually limited when present. Further, proptosis, impaired vision, and compromised eye movement are absent since the orbital contents are unaffected. Presence of fever is not uncommon in children, though it is usually mild. Purulent nasal discharge, skin trauma, or dental caries may be present. Lymphadenopathy may or may not be present.

An ophthalmology consult is warranted for a complete ocular examination to ensure normality of vision and eye movement. The nidus of infection should be sought by examining the nose, mouth, neck, and skin.

Laboratory studies tend to be of limited use in diagnosis, though following serial CBC along with physical examination is helpful in assessing the clinical course. Culture of nasal or ocular discharge guides targeted antibacterial therapy. CT scan of the sinuses is not necessary when preseptal cellulitis is diagnosed but can be of value to determine the extent of edema, presence of a forming abscess, and the extent of sinus disease.

Aerobic nonspore forming bacteria are most common including streptococci species and *S. aureus*. Unfortunately, antibiotic resistance is climbing and over half of *S. pneumoniae* strains are penicillin resistant. Similarly, *H. influenzae* and *Moraxella catarrhalis* strains frequently produce β-lactamase. The exact resistance patterns vary among communities, but amoxicillin-clavulanate rather than amoxicillin should be used as the initial empiric antimicrobial therapy. The prevalence of methicillin resistant *S. aureus* (MRSA) should also be considered when providing empiric therapy.

Adults are prescribed a penicillin with β-lactamase for 10 days with frequent review until there is definite improvement. This can usually be done as an outpatient. Children are also given β-lactamase resistant penicillin and frequently admitted to the hospital for close observation. Oral steroids decrease pain and inflammation; however, they prevent use of CBC and neutrophilia to monitor progress. As a result, clinicians' views vary on steroid usage. The sinuses should be addressed with nasal irrigations and a short course of decongestants to encourage sinus drainage of pus and mucus. It is also important to control diabetes or other immunodepressed states. If no improvement is noted after 24–36 hours, imaging (CT scan with contrast) is obtained to establish if an abscess has formed or to identify a potential nidus of infection which if present is addressed endoscopically. Endoscopic sinus surgery in acute infections can be challenging due to inflamed mucosa which bleeds easily.

Preseptal Abscess (Mortimore and Wormald IB)

If left untreated, the preseptal cellulitis can form into an abscess (Figs. 34.1 and 34.2). Initial management consists of antibiotics, though incision and drainage may be required if the patient does not improve. Like in preseptal cellulitis, sinus surgery may play a role.

Postseptal Orbital Cellulitis (Mortimore and Wormald IIA)

Infection of the postseptal region of the orbit can occur as a continuum of inflammatory/infectious changes in

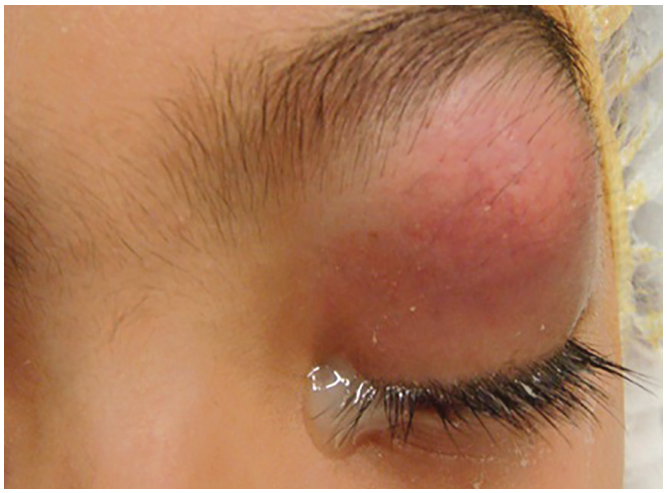

Fig. 34.1: Left eye of young male with preseptal abscess (Mortimore and Wormald class IB). Preseptal cellulitis looks clinically similar, though purulence is typically absent.

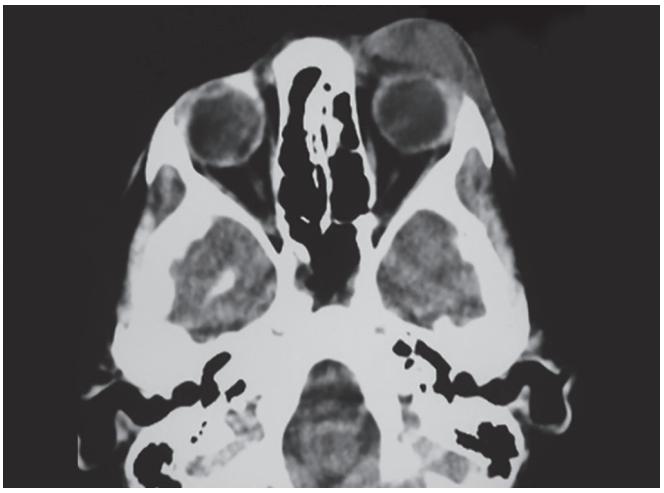

Fig. 34.2: Axial cut CT scan demonstrates the purulent fluid collection on the left. Note its position in the preseptal space. *Courtesy*: Daniel Cantero, MD, Santiago, Chile.

patients suffering with preseptal cellulitis, or it can form from direct seeding into the orbit. Orbital cellulitis (Chandler II) remains an infection of soft tissue without abscess formation. It has a similar etiology to preseptal cellulitis and affects similar populations, although the children tend to be older in the 7–10 year range.

When bacteria traverse the orbital septum, the significance of the infection becomes greater. On initial presentation, the manifestations may seem similar to preseptal cellulitis with unilateral eyelid edema, erythema, and pain. There may be associated purulent rhinorrhea or skin abrasions. Upon further examination, however, these patients are more acutely ill with higher fevers, headache, and general malaise. They suffer a greater degree of peri-orbital and retro-orbital pain and frequently complain of vision loss and diplopia. Due to edema of the orbital contents, proptosis and conjunctival chemosis are present.

The work-up is similar to preseptal cellulitis, but special attention must be paid to the ophthalmologic examination, including evaluation for optic neuropathy, acuity, visual fields, and ophthalmoplegia. A CT scan of the sinuses with contrast is often obtained to determine presence of cellulitis/phlegmon or abscess. Management is also similar, though all patients should be admitted to the hospital for intravenous antibiotics. Empiric therapy covers aerobic and anaerobic bacteria. IV clindamycin with a quinolone is typically adequate. Ophthalmology must closely follow the patient and endoscopic surgical intervention should be performed if the patient fails to improve or the vision deteriorates.

Postseptal Subperiosteal Abscess (Mortimore and Wormald IIB)

In fewer than 10% of patients with orbital cellulitis the infection progresses and one or more abscesses form beneath the orbital periosteum (Chandler III). Because the periosteum is loosely adherent, the abscess can spread within the orbit and even intracranially resulting in a rapidly deteriorating status. Initially, however, these patients clinically appear similar to patients with orbital cellulitis, and the differentiation is made on imaging.

Abscesses commonly form in the medial aspect of the orbit which is the site adjacent to the ethmoid sinuses. As a result of the abscess, the proptotic globe may be pushed laterally and out with significant ophthalmoplegia. In some patients this may be challenging to appreciate due to lid edema. In patients in whom the frontal sinus is the primary cause the abscess may form in the superomedial orbit. Vision is at risk and serial ophthalmologic examination is paramount. Presence of worsening color perception, afferent pupillary defect, increased intraocular pressure, ophthalmoplegia, resistance to retropulsion, papilledema, and optic nerve abnormality are all indications for surgical intervention. Systemically the patients have fever, pain, and are unwell.

Subperiosteal abscesses are readily seen on a CT scan of the sinuses and brain with contrast (Figs. 34.3 to 34.6). The CT remains the preferred diagnostic modality. Ocular ultrasound has been described, but is not readily available at many facilities and the quality of imaging is user-dependent.

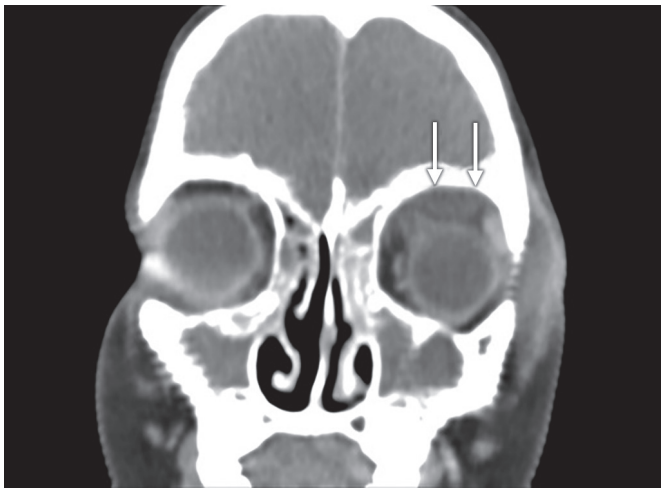

Fig 34.3: Accompanying axial CT scan reconstruction from referring hospital shows a subperiosteal abscess of the superior orbit (arrows) pushing the globe inferior. Note opacified maxillary and ethmoid sinuses.

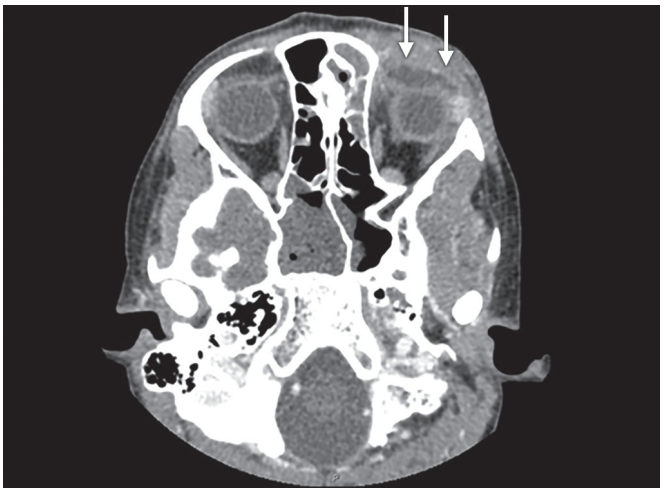

Fig. 34.4: Axial CT scan after cessation of steroids demonstrating persistent subperiosteal abscess (arrows) in the superior aspect of the orbit.
Courtesy: Derek Robinson, MD, Charlottesville, Virginia, USA.

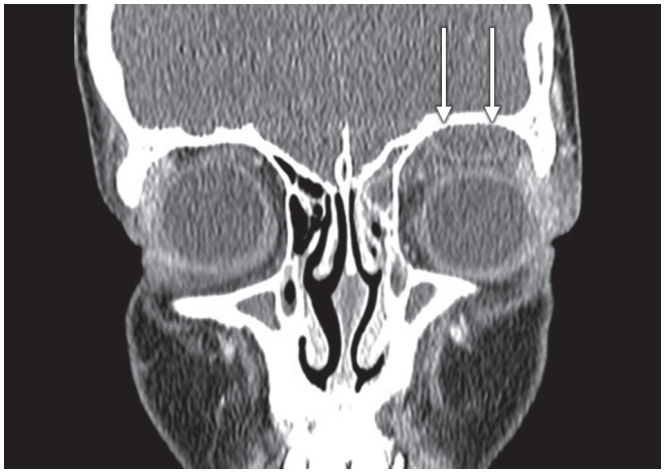

Fig. 34.5: Coronal ST scan after cessation of steroids demonstrating persistent subperiosteal abscess (arrows) in the superior aspect of the orbit.
Courtesy: Derek Robinson, MD, Charlottesville, Virginia, USA.

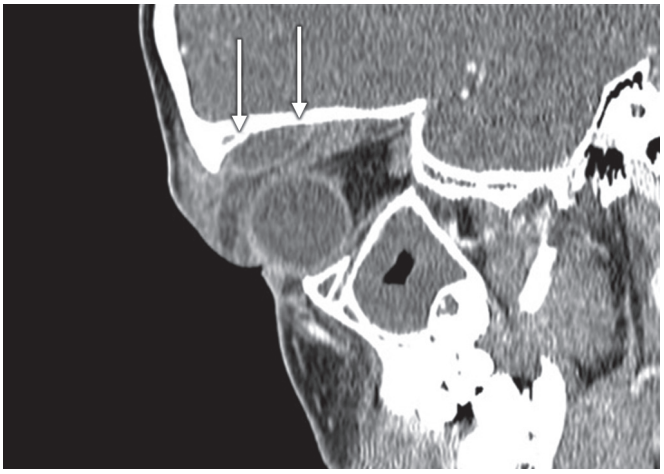

Fig. 34.6: Sagittal CT scan after cessation of steroids demonstrating persistent subperiosteal abscess (arrows) in the superior aspect of the orbit.
Courtesy: Derek Robinson, MD, Charlottesville, Virginia, USA.

Patients who have a confirmed abscess on CT and have visual compromise should be taken to the operating room for drainage. This is usually done endoscopically with the diseased sinuses being addressed at the same time. However, if the surgeon is not a rhinologist, external drainage with or without an external ethmoidectomy is an alternative. In addition, IV antibiotics and nasal decongestants and saline douches are given. Although some authors[7] have suggested that younger patients (<9 years) may be treated conservatively initially, this is not the authors' preferred approach (Figs. 34.7 and 34.8).

Surgery to drain a medially or superiorly located subperiosteal abscess was traditionally performed with a Lynch incision and external ethmoidectomy. Alternatively, drainage can also be performed endoscopically with a maxillary antrostomy, ethmoidectomy, and partial removal of the lamina papyracea. The endoscopic approach provides better visualization and clearance of abscess with wide removal of the lamina papyracea to allow continued drainage (Figs. 34.9 and 34.10). Rarely a combined endoscopic and open approach is necessary to adequately clear the infection.[8]

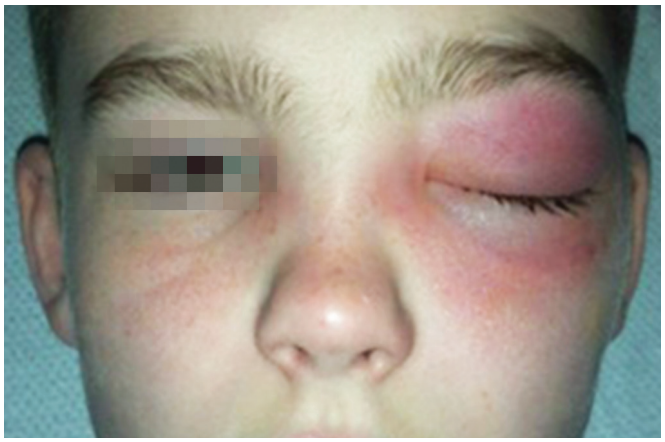

Fig. 34.7: Eight-year-old boy transferred to a tertiary care center for management of left eye swelling and erythema. No loss of vision at presentation.

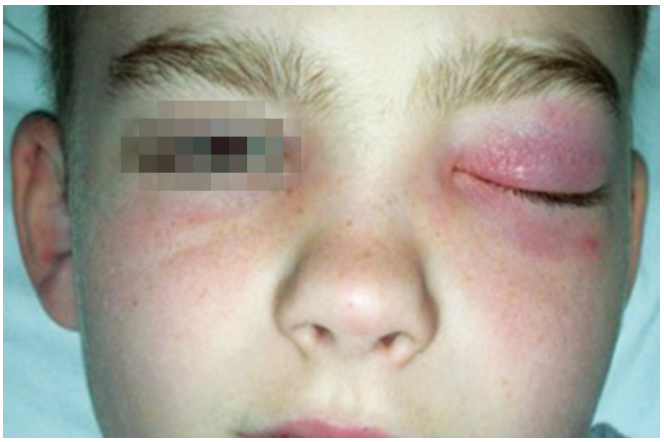

Fig. 34.8: After 3 days of IV antibiotics and steroids the patient's clinical status improved, though upon cessation of steroids his condition deteriorated again. He subsequently underwent endoscopic drainage of the abscess.

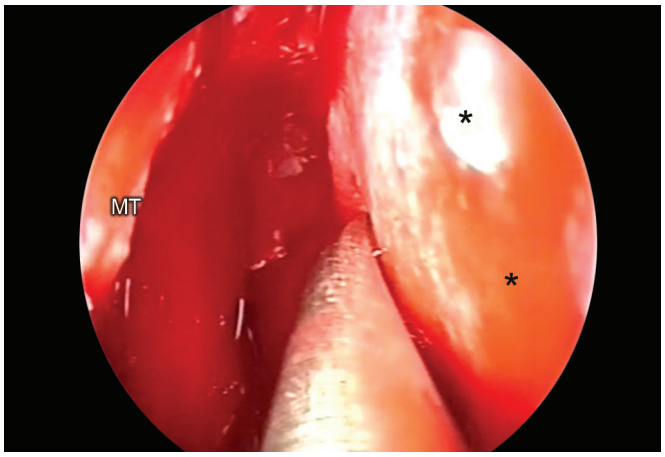

Fig. 34.9: Intraoperative photograph of endoscopic management of left superior subperiosteal abscess. Sinuses have been opened. The lamina papyracea has been removed to widely expose the soft left periorbita (asterisks). Middle turbinate (MT).

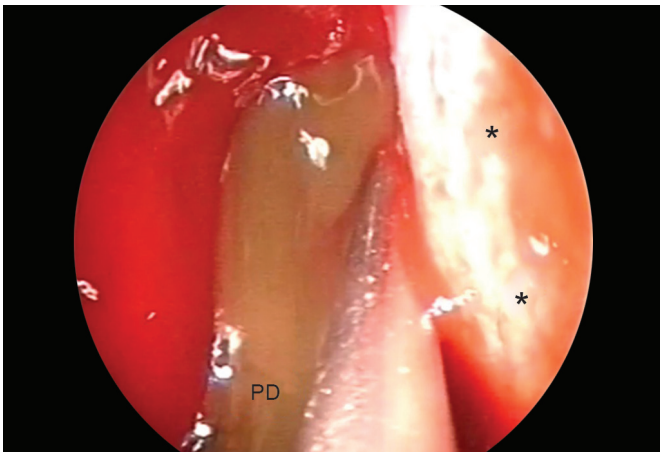

Fig. 34.10: Purulent drainage (PD) is seen after suction is placed into the abscess. Loculations were gently broken up Periorbita (asterisks).

Intraconal Orbital Cellulitis or Abscess (Mortimore and Wormald III and IV)

When a collection of pus lies within the soft tissue of the orbit and is no longer confined to the subperiosteal space, it is termed an orbital abscess (Chandler IV). This is a severe condition and fortunately only makes up about 1% of the orbital complications in the pediatric population.[9] Patients suffer considerable exophthalmos and chemosis with complete ophthalmoplegia.

Vision loss is common from edema of surrounding structures, stretching of the optic nerve from proptosis, and bacterial toxins leading to nerve inflammation and edema. Orbital apex syndrome can develop due to impingement of structures as they run through the orbital apex. This is manifest by the combination of visual loss (CN II), ophthalmoplegia (CN III, IV, and VI), and forehead numbness (first division CN V). Treatment consists of IV antibiotics and urgent surgical drainage in an effort to protect vision.

OSTEOMYELITIS

Acute or chronic frontal sinus infections can in rare circumstances result in osteomyelitis of the frontal bone. Bacterial seeding occurs when bacteria in the fontal sinus travel through the diploic veins to the subgaleal space.

Abscess formation in this space progresses to infect and erode the overlying frontal bone. The defect, combined with a subperiosteal collection of pus, leads to a soft area known as a Pott's puffy tumor. Spread can also proceed posteriorly to the intracranial space leading to meningitis or development of intracranial complications such as subdural empyema and cerebral abscess.

Frontal osteomyelitis occurs in both genders but carries a male preponderance. It presents at almost any age, and while is less likely in children prior to formation of frontal sinuses approximate 50 pediatric cases have been reported in past 10 years. An increased risk for development of osteomyelitis is seen in patients with prior sinusitis, head trauma, and cranial surgery.

The most common complaints include headache and periorbital or forehead swelling. Skin erythema, nasal congestion, purulent rhinorrhea, fever, and neurologic symptoms may be present. Pain and systemic effects are uncommon. Unless intracranial complications develop, these patients typically present without distress as an outpatient.

Diagnosis is primarily made with history and physical examination. Leukocytosis is often absent and inflammation markers (ESR, CRP) are typically of little benefit unlike in temporal bone osteomyelitis. Purulent rhinorrhea or drainage from the forehead is cultured if present. Paranasal sinus CT scan determines the extent of the erosion and whether the posterior table of the frontal sinus is involved.

Mortality was high in the preantibiotic era but has fortunately decreased significantly with long-term antibiotics and surgery. A standard sinus regimen is instituted consisting of nasal irrigation, nasal steroids, oral steroids, and short-term decongestants. Endoscopic sinus surgery is performed to clear the frontal ostium and frontal recess. A modified endoscopic Lothrop procedure is best in patients with prior failed frontal sinus surgery or those with chronic disease manifest with narrow outflow tract due to osteoneogenesis. If this fails to clear the osteomyelitis then and osteoplastic flap approach may be necessary for eradication of all infected bone. This may need to be done in conjunction with the neurosurgeons if intracranial complications are suspected. The cosmetically unfavorable anterior table defect is not repaired until resolution of the infection.

MUCOCELE

A mucocele is an expansile growth caused by a chronic collection of inspissated mucus within a sinus. The sinus mucosa constantly produces mucus that is swept by cilia to natural ostia of the sinuses. However, ostial obstruction can occur due to trauma, scarring, and inflammation (sinusitis). If the obstruction is not relieved, mucus accumulates and begins to expand leading to remodeling and thinning of surrounding bone. The frontal sinus is most frequently affected followed by the sphenoid sinus. The mucocele may expand into the orbit, sinuses, intracranium, or soft tissues under the skin.

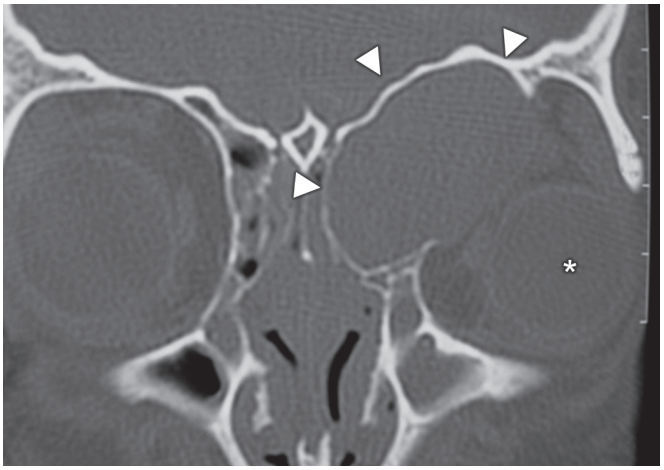

Fig. 34.11: Coronal CT scan demonstrating left frontal sinus mucocele with expansion into the ethmoid sinuses. Note the bowing of thin bone (arrowheads) and inferolateral displacement of the globe (asterisk).

Most patients report a history of sinus surgery or facial trauma; however, some have no prior history of sinus problems. Mucoceles may cause slow and progressive symptoms. Patients are often asymptomatic initially, but with time may develop blurred vision, diplopia, narrowed visual field, or visual loss. Further, when mucoceles become infected (mucopyocele) patients may present acutely. These patients may present with recurrent periorbital erythema and swelling, which may have required a drainage procedure in the past. Symptoms are typically localized, but if the posterior table of the frontal sinus or lateral wall of the sphenoid sinus is involved, meningitis, epidural abscess, subdural empyema, and cerebral abscess formation are possible.

Assessment is performed with a CT scan of the sinuses. The mucocele usually appears as a homogenous, well-circumscribed, opacified lesion with thinning and expansion of surrounding bone (Fig. 34.11). If there is evidence of intracranial or orbital extension, an MRI is useful to differentiate the mucocele from dura, brain parenchyma, or orbit.

These lesions are best dealt with by endoscopic techniques—even with intracranial extension. As long as the

dura is intact, the mucocele can still be marsupialized into the nose. External approaches can also be used but obliteration of the sinus not suitable if bone has been eroded and dura or orbital periosteum is exposed. It is very difficult if not impossible to remove all the mucocele mucosa from these soft structures, thereby risking a significant recurrence. For frontal sinus mucocele, the modified endoscopic Lothrop procedure carries a high rate of success in resolving frontal sinus mucoceles by providing a large cavity for easy in-office surveillance with minimal risk of ostial closure and recurrent mucocele formation.[10] Further, if there is an anticipation of a large dural defect, this can often be reconstructed endoscopically with the assistance of a neurosurgeon.

Mucoceles in other sinuses, most notably the sphenoid sinus, should be widely marsupialized. Routine surveillance is warranted since mucoceles have a tendency to recur. Image guidance navigation is helpful in recurrent cases when native anatomy has been distorted. As with the frontal sinus, the surgeon must be prepared to repair a skull base defect and cerebrospinal fluid leak should either arise.

INTRACRANIAL INFECTIONS

The incidence of intracranial complications due to acute and chronic sinusitis is fortunately low in the antibiotic era. The sequelae of intracranial complications can be devastating and therefore a high index of suspicion must be maintained, especially when patients do not improve as expected. Intracranial complications occur via direct extension of pathogens through the sinus wall or from thrombophlebitis through valveless veins. Primary intracranial complications include meningitis, subdural abscess/empyema, epidural abscess, cerebral abscess, and cavernous and venous sinus thrombosis. When an intracranial complication occurs, a team effort consisting of otolaryngology, neurosurgery, infectious disease, and on occasion ophthalmology is required.

Meningitis

Bacterial meningitis is an infection that affects the subarachnoid spaces and meninges resulting in inflammation. This irritation of the leptomeninges leads to the clinical signs associated with meningitis such as stiff neck and increased intracranial pressure (ICP). This is usually considered the most common intracranial complication of sinusitis.[5] Development of meningitis appears to occur more frequently in patients with existing skull base defects (i.e. after trauma, iatrogenic, and meningoencephalocele) and not necessarily due to acute and chronic sinusitis. The most common pathogens are *Streptococcus pneumoniae*, *S. aureus*, *anaerobes* (*Bacteroides* and *Fusobacteria*), and *H. influenza*.

Although meningitis is one of the more common intracranial complications, the pathophysiology of meningitis remains incompletely understood. A host of factors ultimately allows the pathogens to invade local mucosa and subsequently the meninges into the subarachnoid space.[11] Whether carried through the blood stream, retrograde movement along the cranial nerves, or directly traveling across the skull base, the bacteria violate the blood brain barrier to contact the meninges. Both inter- and transcellular mechanisms for meningeal invasion into the subarachnoid space have been implicated. The subarachnoid space is immunologically inert when compared with serum, with smaller populations of white blood cells and lower levels of immunoglobulins. This bacterial safe-haven explains the rapid evolution of meningitis into intracranial abscesses with corresponding rapid clinical deterioration.

Symptoms of meningitis are related to the systemic infection, meningeal irritation, and ICP. Bacteria results in complaints of fever and myalgias. Children often exhibit anorexia. Meningeal irritation causes neck stiffness, headache, cranial nerve palsies, and possible focal neurologic weaknesses. Patients may also complain of nausea and vomiting, photophobia, lethargy, confusion, and mental status changes due to increased ICP. Despite the number of potential symptoms, none are particularly sensitive or specific.[12] Only about 50% of cases in the literature report headache and 28% nausea and vomiting.

Meningitis classically presents with a triad of examination findings consisting of fever, nuchal rigidity, and altered mental status. While only about two thirds of patients have all three at presentation,[13] nearly all have at least one. Traditional teaching also describes the presence of Brudzinski's and Kernig's signs on physical examination secondary to meningeal inflammation and irritation. Brudzinski's sign is exhibited when the affected patient's neck is flexed and the knees flex in response. Kernig's sign is demonstrated by an inability to straighten the leg at the knee when the hip is flexed at a right angle. Attention should be paid to skin rashes, papilledema, hemiparesis and focal deficits, cranial nerve weaknesses,

and nystagmus. Overall, physical examination is superior to history in determining which patients warrant additional testing.

In addition to typical blood work including blood cultures, CT scan of the head is typically the first study ordered. Meningeal inflammation is not seen on CT, but it can show presence of sinus inflammation and other intracranial complications. Further, CT can suggest brain shift and elevated ICP that are contraindications for LP due to risk of brain herniation and cessation of respiratory drive. After it is determined that LP is safe to perform, the diagnosis of meningitis is based on these results. Bacterial meningitis results in elevated opening pressures, often 200–500 mm H_2O. Further, leukocytosis of 1000–5000/mL is common with a predominance of neutrophils. Glucose concentration is low and the CSF is often cloudy instead of clear. CSF should undergo Gram staining and culture for organism and antibiotic sensitivity.

Intravenous antibiotics are the mainstay of treatment, and many suggest it should be initiated as soon as meningitis is suspected. Initial therapy can be guided by Gram stain from the CSF. If no additional information is available, therapy consists of a third-generation cephalosporin (e.g. cefotaxime and ceftriaxone) in combination with vancomycin. These agents penetrate the blood–brain barrier and provide adequate coverage for common pathogens. While no prospective data exists, the consensus is that earlier treatment results in lower morbidity and mortality.[14,15] Adjunctive corticosteroid is given to decrease meningeal inflammation and potentially decrease neurologic sequalae including hearing loss.

Epidural Abscess

The dura mater is tightly adherent to the overlying skull bone. However, purulent collections can form in this extra-axial space between the dura and bone to form an epidural abscess. The opposition of the dura and bone explains many of the findings related to this life-threatening condition. As the abscess expands, pathogens frequently cross the emissary veins into the subdural space; thus, epidural and subdural abscesses are often found concomitantly. Infection within the frontal sinus is typically implicated as the source.

Clinically, there is no pathognomonic sign or symptom. As a result, diagnosis is often delayed. Akin to other intracranial complications, patient outcome is improved when early treatment is initiated. Onset is typically insidious since the adherent dura confines the infection.

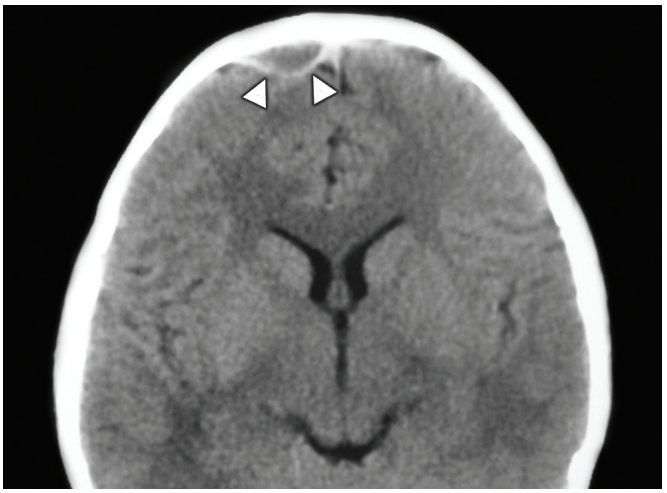

Fig. 34.12: Axial CT scan illustrating a small right frontal epidural abscess (arrowheads). Note the well-defined borders which are due to the tight adherence of dura to overlying skull bone.

Subsequent slow growth and expansion fails to produce the rapid intracranial shifts and changes required to produce neurologic deficits. Vague symptoms are secondary to sinusitis, bacteremia, and dural inflammation; therefore, fever, headache, nausea, and vomiting are the most common. Still, fever is found in only about half of patients and headache in about three fourths. It is not until late in the clinical course when mass effect leads to elevation of ICP with papilledema, hemiparesis, seizure, and mental status changes.

Blood cultures should be obtained immediately with subsequent administration of antibiotics. An LP is unhelpful and carries risk of brain herniation. Since the infection is extra-axial, CSF can be normal. CT brain with contrast is the first imaging study obtained, which reveals a rim-enhancing crescent-shaped fluid collection (Fig. 34.12). The smooth border of the crescent shape is secondary to the dura's attachment to bone that prevents wider spread. MRI with gadolinium is more sensitive and is the imaging modality of choice. In addition to the fluid collection, enhancement of the meninges is appreciated. Further, concomitant subdural empyema or other intracranial infections are more readily identified than with CT scan.

Urgent management is both medical and surgical, and appropriate consultations should be obtained. Therapy should be initiated with IV antibiotics, anticonvulsants to prevent seizure, steroids, and consideration of measures to decrease ICP (mannitol, acetazolamide, elevate head, hyperventilation). Empiric antibiotic treatment covers for MRSA (vancomycin), anaerobes (metronidazole), aerobic

gram-negative bacilli (third and fourth generation cephalosporin such as cefepime). Antibiotics are administered for at least 3–4 weeks, longer if overlying osteomyelitis is present. A craniotomy is performed for decompression and to clear the purulent fluid that is sent for Gram stain and culture. Consideration is given to endoscopic clearance of the sinuses as well.

Subdural Abscess/Empyema

A subdural abscess is a collection of pus between the arachnoid and dura mater. Once an infection reaches the subdural space there are few barriers to spread except for some arachnoid granulations. Most affect the frontal lobe and tend to be located near the falx cerebri. Along with meningitis, subdural abscess is one of the most common intracranial complications of bacterial sinusitis.[16] Sinusitis accounts for about 40–80% of subdural abscesses in adults, and this proportion is higher in children.[16,17] In adults, spread from the frontal and ethmoid sinuses is the most common. Patients suffer with rapid clinical deterioration and this condition was once uniformly fatal prior to the advent of antibiotics. Mortality rates remain 10–20% with current treatment regimens. Of note, as with epidural abscesses, survival rates are >90% for patients who are alert when the condition is diagnosed, thus demonstrating the importance of early diagnosis and intervention.[18]

Signs and symptoms are nonspecific and can be similar to those observed in meningitis due to an association with increased ICP, meningeal irritation, and mass effect on the brain. High fever >39°C is common with associated headache. Nausea and vomiting and mental status changes are present in about two thirds of patients due to increased ICP. Meningismus is present in up to 80%. Cranial nerve palsies and focal neurologic defects can progress to hemispheric defects (hemiparesis, hemiplegia) and seizure. The intracranial infection with cerebral herniation frequently causes lethargy that progresses to coma in untreated cases. Yet, a surprising proportion of patients (as many as a fourth) lack significant focal neurological symptoms, making diagnosis especially difficult.[19]

CT scan with contrast of the brain is useful in demonstrating an enhancing crescent shaped or elliptical hypodense fluid collection. The lesion may be intrahemispheric and can cause mass effect and edema. CT is often the first imaging obtained since it is quick and readily available, though MRI remains the study of choice. The margins are better defined and early loculations and empyema are more readily seen with MRI. The skull base and posterior fossa are also visualized with more detail using MRI. An LP is contraindicated due to risk of herniation and regardless, findings are not very helpful unless comorbid meningitis is present.

It is important to treat a subdural abscess as a medical emergency. With the exception of abscesses <1.5 cm that can (controversially) be treated with antibiotics alone, management consists of medical and surgical therapy. Akin to treatment of epidural abscess, IV antibiotics, anticonvulsants, and decrease of ICP are necessary. Antibiotics must cover for *S. aureus*, streptococci species, and anaerobes. Therefore, first-line agents often consist of β-lactamase-resistant penicillin, metronidazole, and a third-generation cephalosporin for 3–4 weeks. Vancomycin is also considered if MRSA is suspected.

Surgical drainage of the lesion with open craniotomy is the standard of care. The surgery provides wide exposure to clear the purulent collection. Burr holes over the site of abscess have been used with some success, but this method provides limited access with greater potential for incomplete drainage of the infection. Endoscopic clearance of the affected sinuses is performed at the same time.

Intracerebral/Brain Abscess

Intra-axial abscess due to sinusitis is fortunately uncommon. When it occurs the frontal sinuses are the most common cause, but abscess can also occur from hematogenous spread. The incidence of anaerobic pathogens appears higher than other intracranial complications. Symptoms can be vague at first and are related to an enlarging intracerebral lesion. Headache, mental status change, focal neurologic deficits, nausea, vomiting, seizure, meningismus, and papilledema are all possible, though none is sensitive. The presence of abscess is more evident after abscess rupture, but at this advanced stage the condition is rapidly fatal. The purulent fluid enters the arachnoid space leading to meningismus and the ventricles, resulting in increased ICP, hydrocephalus, and mental status changes.

CT scan of the brain with contrast is usually the first radiographic study obtained. The abscess is manifest by a ring-enhancing lesion at the gray–white interface. MRI with gadolinium has greater detail and surrounding edema of cerebral parenchyma is easier to appreciate. The abscess is less likely with MRI than CT to be mistaken for tumor. LP does not have a role in diagnosis of intracerebral abscesses.

Aggressive medical and surgical management follows other intracranial abscesses. Mass effect of abscess is relieved with craniotomy. Intravenous antibiotics, seizure prophylaxis, and lowering of ICP are warranted. The sinuses should be surgically managed at the same time.

CS Thrombosis (Chandler V)

CST was once considered the most severe and potentially fatal orbital complication arising from rhinologic disorders; however, today it is widely accepted to be an intracranial complication. Numerous valveless orbital veins drain into CS that allows pathogens to travel into this area. The right and left sides of the CS are connected by the superior and inferior intercavernous sinuses. Thus, when one side is affected, the contralateral sinus is often affected as well. *S. aureus* is isolated in 60–70% of patients. Historically mortality approached 50%, though fortunately this has decreased with better antibiotic therapy. However, many continue to suffer with long-term cranial nerve deficits, and visual loss is one of the most common residual deficits.

As with orbital abscesses, patients are toxic with periorbital edema, chemosis, painful ophthalmoplegia, malaise, and headache. The ache is often described as temporal or retrobulbar. An intermittent spiking "picket fence fever" may be observed that is classic for thrombophlebitis. Additional clinical manifestations relate to cranial nerve involvement within the CS. CST may present in the setting of either acute or chronic sinusitis. In acute disease, thrombosis and symptoms develop rapidly with frequent progression to bilateral eye involvement. In contrast, in chronic states, there is an indolent development of orbital effects and involvement of the contralateral eye occurs inconsistently.

Both CT scan of the brain with contrast and MRI scan with gadolinium show manifestations of CST. Contrasted CT scan demonstrates unilateral or bilateral multiple irregular filling defects in the enhancing expanded CS. There may be associated orbital inflammation. Further, the superior orbital vein may be engorged due to impaired drainage into the CS (Fig. 34.13). These findings may be subtle and about one-third of scans are considered normal in patients with CST. MRI shows high signal intensity of the thrombus on all sequences and increase in size of the CS. Of note, acute thrombosis is sometimes isointense and thus more difficult to diagnose. The margins of an enlarged CS may also enhance suggesting presence of a thrombus. MR venogram is helpful to show areas of cessation of blood flow.

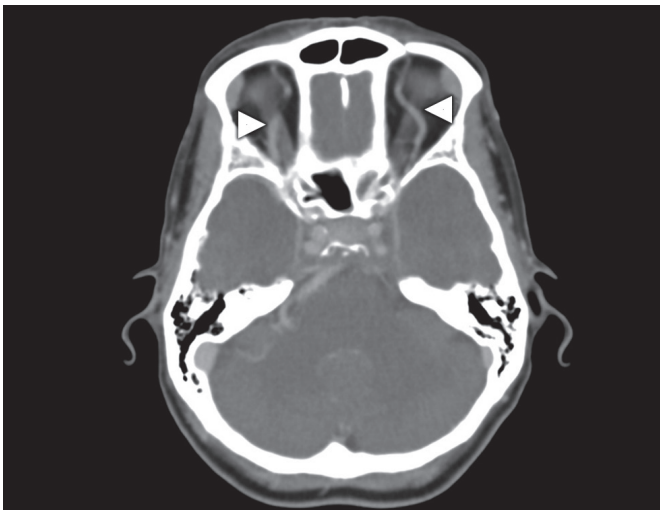

Fig. 34.13: Axial CT venogram. Both superior orbital veins (arrowheads) are engorged due to cavernous sinus thrombosis. Lack of enhancement of bilateral cavernous sinuses further suggests thrombosis.
Courtesy: Samuel Boase, BMBS, PhD, Adelaide, Australia.

Given the gravity of this complication, immediate management must be initiated with broad-spectrum intravenous antibiotics to cover gram-positive and gram-negative aerobic and anaerobic pathogens. If the infection originated from the sinuses, endoscopic surgery is performed to facilitate drainage. Steroids are often used to decrease inflammation and edema, but the actual benefit of steroids in preserving function remains unclear. The role of anticoagulant heparin therapy remains controversial.[20] The hypothesized benefits include cessation of progression and propagation of the thrombus. Retrospective data suggest morbidity decreases with anticoagulation, though mortality remains unchanged.

Venous Sinus Thrombosis

Pathogens can progress to affect the venous sinuses, leading to thrombosis and suppurative thrombophlebitis due to retrograde flow in valveless veins, usually from the frontal sinus.[21] As a result, *S. aureus* is most common, but any microorganism found to cause sinusitis can be causative including mucormycosis and *Aspergillus*. Conditions associated with increased blood viscosity are also associated with a higher risk of developing clots. The superior sagittal sinus is most commonly involved. Since thrombosis is a late manifestation of disease, other intracranial complications stemming from sinusitis are often present simultaneously.

Patients tend to be very ill upon presentation and specific symptoms depend on the venous sinus that is obstructed. Thrombosis of the superior sagittal sinus yields altered mental status, motor deficits, meningismus, and papilledema with elevated ICPs. Seizures occur in over half of affected patients. CST was discussed previously, and if clot propagates to block the inferior petrosal sinus, ipsilateral facial pain and lateral rectus muscle weakness are common. Symptoms associated with lateral sinus thrombosis are more gradual and the majority of patients complain predominantly of headache (>80% of cases), photophobia, and vomiting. The lateral sinus is most commonly affected by otologic etiologies.

CT scan of the brain with contrast is helpful to delineate thromboses, but is less sensitive than MRI. MR venogram is the imaging modality of choice to demonstrate a filling defect within the thromobosed sinus (Fig. 34.14). Sagittal sinus thrombosis is associated with a very high rate of mortality.

IV antibiotics for 3–4 weeks, anticonvulsants, and steroids are given. Measures to decrease ICP are considered. The diseased paranasal sinuses are surgically managed acutely. If the patient still fails to improve after sinus surgery and antibiotics, surgical drainage of the thrombus with open craniotomy may be indicated. At present, the efficacy of internal jugular vein ligation for lateral sinus thrombosis remains unclear. Further, the role of anticoagulants (heparin) to prevent clot propagation remains controversial.[20,22] Retrospective evidence suggests that addition of heparin to antibiotics may decrease mortality.[22] However, this must be weighed against the increased risk of intracranial venous and arterial hemorrhage with the addition of anticoagulants. These hemorrhagic complications can prove fatal in patients with already guarded neurological status. Nonetheless, it is the practice in many tertiary care centers to use anticoagulation unless active bleeding is present. Duration of anticoagulant therapy varies widely from a few weeks to the time of clot resolution. Regardless of treatment, many of these patients suffer with residual neurologic deficiencies after resolution of the thrombus.

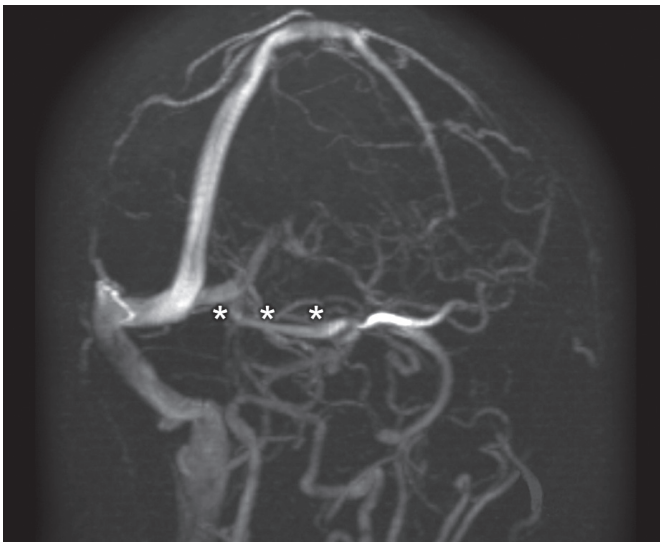

Fig. 34.14: MR venogram of thrombosis of right transverse sinus with complete absence of flow. Asterisks superimposed over the location of the right transverse sinus. Additional absence of flow through right sigmoid sinus and internal jugular vein.

CONCLUSION

Rhinologic disorders are common, yet significant complications arising from sinusitis remain relatively uncommon. Understanding the anatomy of the structures adjacent to the nasal cavity and sinuses helps the clinician diagnose complications when they arise. The history and physical examination are important, but often additional imaging is necessary to determine the precise nature and extent of the disease. Treatment often consists of antibiotics and surgical intervention. A high index of suspicion must be maintained at all times to prevent delay in diagnosis and the potential associated increase in morbidity and mortality.

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CHAPTER

35

Antibiotic Therapy in Rhinosinusitis

Patricia A Loftus, Abtin Tabaee, Marvin P Fried

INTRODUCTION

The role of antibiotic therapy for the various forms of rhinosinusitis has evolved in concert with developments in basic science and clinical research. Previously viewed as an infectious event, rhinosinusitis is now understood to be a heterogeneous group of disorders with different phenotypic endpoints and etiologic factors. Inflammation, rather than infection, is the primary pathophysiologic manifestation and may arise from a combination of host, environmental and pathogenic factors, only one of which is bacteria. Even in patients where the initiating event is a bacterial infection, the pathophysiologic cascade is defined less by the presence of bacteria than by the ensuing inflammatory response, mucosal injury, mucociliary dysfunction and, in a sub-set of patients, biofilm formation. Therefore, treatment of sinusitis includes not only antibiotic therapy to reduce the colony counts of the pathogenic bacteria but also anti-inflammatory therapies to restore normal sinonasal physiology. Interestingly, recent studies investigating the paranasal sinus microbiome in normal and diseased states suggests that the goal of antimicrobial therapy for sinusitis may be to restore a normal balance of nonpathogenic bacteria rather than eradicating all bacteria. Achieving this shift is complex, given the nonselective nature of antibiotic therapy. This chapter explores the clinical guidelines, seminal research findings, and unanswered questions regarding antibiotic use in rhinosinusitis.

ACUTE RHINOSINUSITIS

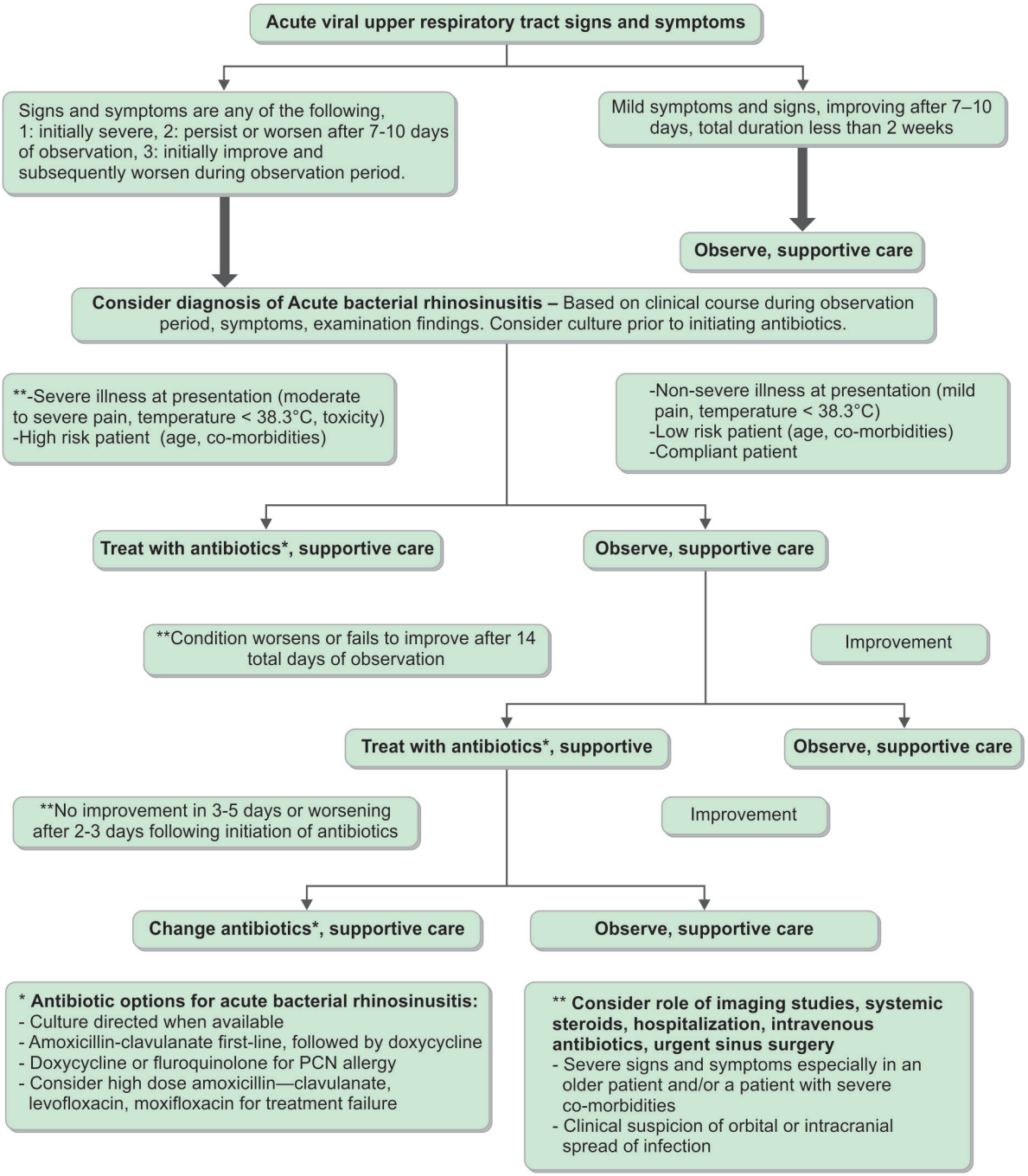
The majority of acute rhinosinusitis (ARS) events are caused by a viral infection and resolve without sequela within 7–10 days. In these cases, treatments consists of supportive care only, as antibiotics do not impact the disease course, are associated with increased cost, and can potentially result in medication-related adverse events such as allergic reaction, toxicity, and microbial resistance. Current clinical guidelines recommend an analgesic or antipyretic for the pain and/or fever associated with acute viral rhinosinusitis (AVRS). Decongestants may provide further symptomatic relief in many cases but do not affect the course of the disease. Antihistamines also produce a decongestant effect, although their impact on outcomes of AVRS is unknown. As with antibiotics, neither topical nor systemic steroids have proven effectiveness in the treatment of AVRS.[1]

Acute bacterial rhinosinusitis (ABRS) complicates AVRS in 0.5–2.0% of cases.[2] Similar to AVRS, ABRS may be a self-limited disease and does not necessarily require antibiotic therapy to resolve. However, antibiotics are recommended in ABRS that has not improved after a period of observation, not only to eliminate the infection but also to relieve symptoms, shorten the duration of illness, and prevent complications such as orbital or intracranial spread. Differentiating between AVRS and ABRS, and therefore deciding which patients would benefit from antibiotics, is challenging given the similar symptoms and examination findings. An "observation option" may be considered for select cases of ABRS. This entails symptomatic treatment alone for up to 7 days after the diagnosis of ABRS is made and is most appropriate in patients with mild symptoms who are deemed compliant with follow-up. This option is recommended based on the high rate of spontaneous improvement in patients not treated with antibiotics. For example, a Cochrane review

in 2012 regarding antibiotics for ARS demonstrated that 47% of participants were cured after one week and 71% after 14 days, irrespective of treatment with antibiotics or with placebo.[3] Furthermore, this review demonstrated a 2.10 odds ratio (95% CI) of experiencing side effects in the antibiotic group versus the placebo group.[3]

Antibiotics may be considered if symptoms have persisted after 7–10 days, if symptoms initially improve and subsequently worsen, if symptoms are atypically severe at any point in the disease course or if there is any concern for sinusitis-related complications.[4,5] Patients with severe illness in regards to pain and fever should be treated with antibiotics at the time of diagnosis. Antibiotic treatment should also take into account patient age and comorbidities. An algorithm for the proper diagnosis and appropriate management of ARS is outlined in Flowchart 35.1.

Flowchart 35.1: Treatment algorithm for patients with acute bacterial rhinosinusitis.



In addition to antibiotic usage, clinical guidelines for the management of ABRS stress the importance of pain control for symptomatic and quality of life (QOL) care during the disease process. Pain can be treated with acetaminophen, nonsteroidal anti-inflammatory drugs, or opioid medication, depending on the severity. Decongestants, corticosteroids, saline irrigation, and mucolytics can also be used for symptomatic relief in ABRS, although these medications have not yet been approved by the Food and Drug Administration for this indication.[1]

Studies concerning the efficacy of antibiotics in ABRS are confounded by heterogeneity in symptoms and difficulty differentiating between a viral and bacterial infection. Accordingly, Mandal and colleagues reported that the strongest evidence for antibiotic use in ABRS was found in studies with stringent entry criteria.[6] The same Cochrane Review from 2012 cited above demonstrated that antibiotics can shorten the time to cure, but only 5 more patients per 100 will cure faster at any time point between 7 and 14 days if they receive antibiotics instead of placebo (number needed to treat to benefit = 18).[3] Other studies have shown similar findings, but again are complicated by the difficulty in distinguishing between a viral versus a bacterial infection in the primary care setting.

In regards to the cost of prescribing antibiotics for ARS, a review of 58 trials between 1989 and 2002 illustrated that the most cost-effective approach for treating ABRS with antibiotics was failure to improve after 7 days, as opposed to treating based on clinical criteria or radiographic images.[7]

Antibiotic treatment is initiated empirically based on the microbiology of the most common organisms responsible for ABRS and the local community resistance patterns. Culture directed antibiotics may be considered, but is associated with a delay in initiating therapy. If warranted, a culture may be taken at the time of evaluation and empiric therapy can be started while awaiting results. Culture-guided therapy is especially indicated in immunocompromised patients, patients not responding to standard treatment, or patients with ABRS-related complications. The most common bacterial pathogens in ABRS are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (Table 35.1). Amoxicillin was the first-line agent in the past due to its appropriate spectrum of coverage and low cost, but increasing resistance to *S. pneumoniae* and *H. influenzae* led to the recommendation of amoxicillin with the β-lactamase inhibitor clavulanic acid to improve coverage. The 2012 Infectious Disease Society guidelines recommend the following in adult patients with ABRS[4] (Flowchart 35.1):

Table 35.1: Microbiology of acute and chronic rhinosinusitis.

Acute rhinosinusitis	*Chronic rhinosinusitis*	
	Anaerobic	*Aerobic*
Streptococcus pneumoniae	*Actinomyces*	Coagulase-negative *Staphylococcus*
Haemophilus influenzae	*Bacteroides*	*Enterobacter* species
Moraxella catarrhalis	*Fusobacterium*	*Escherichia coli*
Streptococcus pyogenes	*Peptostreptococcus*	*Haemophilus influenzae*
	Prevotella	*Klebsiella pneumoniae*
		Moraxella catarrhalis
		Proteus mirabilis
		Pseudomonas aeruginosa
		Staphylococcus aureus
		Stenotrophomonas maltophilia
		Streptococcus species

- Amoxicillin-clavulanate rather than amoxicillin alone as empiric antimicrobial therapy for ABRS in adults.
- "High-dose" (2 g orally twice daily) amoxicillin-clavulanate for adults with ABRS from geographic regions with high endemic rates (≥10%) of penicillin-resistant *S. pneumoniae*, those with severe infection, age >65 years, recent hospitalization, antibiotic use within the past month, and immunocompromised patients.
- Macrolides (clarithromycin and azithromycin) are not recommended for empiric therapy due to high rates of resistance among *S. pneumoniae* (~30%). Trimethoprim-sulfamethoxazole (TMP-SMX) is not recommended for empiric therapy because of high rates of resistance among both *S. pneumoniae* and *H. influenzae* (~30% and ~40%, respectively). Second- and third-generation oral cephalosporins are no longer recommended for empiric monotherapy of ABRS due to variable rates of resistance among *S. pneumoniae*.
- Doxycycline may be used as an alternative regimen to amoxicillin-clavulanate for initial empiric antimicrobial therapy of ABRS in adults because it remains highly active against respiratory pathogens.
- *Penicillin allergy*: Either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) are recommended as an alternative agent in adults who are allergic to penicillin.
- *Methicillin-resistant Staphylococcus aureus (MRSA)*: Although *S. aureus* (including MRSA) is a potential

pathogen in ABRS, routine antimicrobial coverage is not recommended during initial empiric therapy.

- *Pregnancy*: Amoxicillin-clavulanate (class B) is the first-line agent for pregnant patients, and azithromycin (class B) can be used for pregnant patients with a penicillin allergy.
- *Parenteral therapy*: Intravenous antibiotics are indicated in ABRS for severely ill patients or those with sinusitis-related complications. Parenteral therapy should be culture directed. Broad-spectrum antibiotics against the most likely pathogens based on the clinical picture may be initiated while waiting for culture results.
- *Treatment failure*: High-dose amoxicillin-clavulanate, levofloxacin, or moxifloxacin are recommended for second-line treatment if there is no clinical improvement after 3–5 days or if symptoms worsen after 2–3 days of therapy.

Duration of Treatment for ARS

Ten to fourteen days of empiric treatment has been recommended in the past.[8] However, IDS guidelines recommend a 5–7 day course of antibiotics for ABRS in adults, based on studies such as a meta-analysis from 2009 that suggested short-course antibiotic treatment has similar effectiveness to longer-course treatment for patients with uncomplicated ABRS.[9]

CHRONIC RHINOSINUSITIS

As reviewed throughout this book, chronic rhinosinusitis (CRS) is a complex and multifactorial disorder with hallmark findings of sinonasal mucosal inflammation, outflow tract obstruction, disordered physiology, and altered microbiology. Medical management focuses on decreasing mucosal inflammation, restoring normal sinus physiology, and removing inciting factors, which include infectious organisms. Therefore, it is overly simplistic to consider CRS purely a persistent bacterial infection as a number of other host, pathogenic and environmental factors act as disease cofactors. Antibiotics are, however, a mainstay of therapy to decrease the bacterial counts of pathogenic bacteria throughout the treatment course.

The pathologic flora in CRS is typically polymicrobial,[10] and the bacteria most commonly implicated in this disease process are listed in Table 35.1. It should be noted that anaerobes are not always isolated from CRS cultures, likely reflecting a lower test sensitivity. Gram-negative bacilli (GNB) may be present in CRS and especially in immunocompromised, diabetic, and cystic fibrosis patients. A systematic review in 2012 cited the prevalence of MRSA among culture isolates from nonhospitalized CRS patients as ranging from 1.8-20.7%, but the heterogeneity of treatment regimens precluded proper outcome studies in these cases.[11] Of note, in acute bacterial exacerbations of underlying CRS, the most common ABRS pathogens (S. pneumoniae, *H. influenzae*, and *M. catarrhalis*) should be suspected.

Antibiotics for CRS

Antibiotics are a mainstay of treatment for CRS since it is believed that the continuous inflammation of this disease process is in part due to a chronic infection that has not been sufficiently eliminated.[12] To date, no antibiotic has been approved by the US Food and Drug Administration for use in CRS. However, consensus guidelines and clinical practice patterns support their use as part of multimodality therapy.[13]

A number of research methodology issues have limited the performance of double-blind studies investigating the efficacy of antibiotics for CRS.[14] The Joint Task Force on Practice Parameters guidelines indicate that the role of antibiotics in CRS is controversial, but that antibiotics may be required for acute exacerbations of CRS.[15] Although high-quality studies investigating the therapeutic benefit of antibiotic therapy on the long-term management of CRS are limited,[16] antimicrobials are still considered a main component of the multimodality therapy for CRS.

For patients seen for the first time, the approach to antibiotic treatment in CRS is usually empiric toward both aerobic and anaerobic bacteria if cultures are not available.[10] MRSA coverage is added if risk factors for this pathogen are present, such as a past culture positive for MRSA. Recent antibiotic use as well as resistant bacterial strains endemic to the area should be considered when choosing an antibiotic for the treatment of CRS.

Macrolide therapy has been studied extensively in CRS due to its anti-inflammatory properties in addition to its antimicrobial properties. The most prominent effect of macrolides noted in vitro is the inhibition of proinflammatory cytokines such as interleukin-8, which results in the inhibition of neutrophil migration and adhesion.[17] Furthermore, a clinical study looking at long-term macrolide therapy for CRS that was not sufficiently treated by surgery or glucocorticoids showed very good results.[18]

In regards to the efficacy of other classes of antibiotics for CRS, Legent and colleagues treated 251 adult CRS patients in a double-blind manner with ciprofloxacin versus amoxicillin-clavulanate for 9 days. Nasal discharge disappeared in 60% and bacterial eradication rate was 89% in the ciprofloxacin group, and 56% and 91%, respectively, in the amoxicillin-clavulanate group, although these differences were not significant.[19] However, in patients who had a positive initial culture, there were significantly higher cure rates with ciprofloxacin than with amoxicillin-clavulanate. In a multicenter, randomized clinical trial in 2002, amoxicillin-clavulanate was compared with cefuroxime, both showing a similar clinical response (95% in the amoxicillin-clavulanate group and 88% in the cefuroxime group). However, clinical relapse was significantly higher in the cefuroxime group.[20] Of note, in a double-blinded placebo-controlled study in 2008, low dose doxycycline (a tetracycline) treatment for 3 weeks demonstrated a clinically relevant effect on polyp size, but larger controlled trials of doxycycline treatment in patients with CRS and nasal polyposis are needed before recommendations can be made.[21]

Overall, there are not enough data to make a relevant grade of recommendation regarding antibiotic choice for CRS,[22] although amoxicillin-clavulanate, clindamycin, macrolides, and fluoroquinolones have all been used successfully as antimicrobial monotherapy. In clinical practice, culture directed antibiotics as part of multimodality therapy allows for individualized treatment.

Antibiotics versus Surgery

In the majority of patients, surgical intervention for CRS is indicated only after failed medical management. This makes it difficult to generalize about antibiotic treatment versus surgical treatment, as surgery is most commonly performed in selected patients who are not sufficiently responsive to medical therapy. A prospective study in 2004 randomized 90 patients with CRS to 3 months of an oral macrolide or endoscopic sinus surgery and followed these patients for over a year. The authors assessed symptoms, QOL, nasal nitric oxide, acoustic rhinometry, saccharine clearance time, and nasal endoscopy. Both groups showed improvement, and there was no significant difference between the two groups.[23] However, 2 prospective, multi-institutional studies by Smith and colleagues in 2011 and 2013 clearly demonstrate a QOL benefit of surgical management versus medical management for the treatment of CRS. The earlier study evaluated outcomes in patients who failed initial medical management and then selected either continued medical management or surgery coupled with continued medical management. Medical management patients (n = 55) had better baseline QOL, while surgical patients (n = 75) had significantly greater improvement than medically managed patients in QOL outcomes (rhinosinusitis disability index [RSDI], $p = 0.015$; chronic sinusitis survey [CSS], $p < 0.001$), as well as fewer oral antibiotics ($p = 0.002$), oral steroids ($p = 0.042$), and missed days of work/school ($p < 0.001$) after surgery.[24] The later study evaluated 1-year outcomes in three cohorts of CRS patients: medically managed, surgically managed, or crossover (from medical to surgical). With 1 year of follow-up, the surgical cohort (n = 65) had statistically significant greater improvement than the medical cohort (n = 33) based on both the RSDI ($p = 0.039$) and the CSS ($p = 0.018$). Furthermore, QOL in the crossover cohort (n = 17) improved after sinus surgery (RSDI, $p = 0.035$; CSS, $p = 0.070$).[25]

MRSA

For culture positive MRSA, clindamycin is recommended, as this antimicrobial also has anaerobic coverage. TMP/SMX also has MRSA coverage, but an antimicrobial effective against anaerobes must be added to this regimen. Culture directed sensitivity patterns are necessary for MRSA management.

Immunocompromised Hosts

Pseudomonal coverage should be considered for diabetics, cystic fibrosis patients, or any patient with an immunodeficiency such as HIV. In these cases, culture directed therapy is useful to guide treatment.

Parenteral Therapy

The role of outpatient parenteral antibiotic therapy in patients without intraorbital or intracranial complications has not been universally established. A higher rate of complications is associated with this form of treatment, such as catheter-related infections and thrombosis, neutropenia, and systemic toxicity.[26] Typically, this type of therapy is reserved for severely ill patients, infectious complications, treatment of resistant organisms, or patients with

compliance issues. Another indication advocated by some authors is hyperostotic sinusitis, citing higher serum levels of antibiotic when delivered intravenously as the reason these patients do better with parenteral over oral antibiotics.[27] A study by Gross and colleagues looked at 14 patients who underwent intravenous antibiotic treatment for CRS for resistant organisms (50%), inability to tolerate oral antibiotics, or extranasal complications. Fourteen of the 16 patients completed therapy successfully, although 3 patients (19%) experienced line-related complications such as thrombophlebitis or deep vein thombosis.[28] The authors concluded that outpatient intravenous antibiotics are a well-tolerated adjunct for the treatment of CRS, but that catheter-related complications can be significant. In a prospective study by Anand and colleagues in 2003, 45 CRS patients who either failed or refused surgical intervention were treated with 6 weeks of culture-guided intravenous antibiotics. All showed symptom improvement, concluding that outpatient parenteral antibiotics are an excellent alternative to failed or refused surgery.[29]

As stated in this aforementioned prospective study, antimicrobial choice in CRS should be culture guided. However, parenteral antibiotics with both aerobic and anaerobic coverage can be initiated while awaiting culture results. These include ampicillin-sulbactam, piperacillin-tazobactam, clindamycin, moxifloxacin, carbapenems, and second-generation cephalosporins. Intravenous antibiotics effective against MRSA include vancomycin, daptomycin, and linezolid. The role of parenteral antibiotics in the treatment of CRS deserves further investigation as its use has not been universally established.

Nebulized Therapy

Conventional medical therapy for CRS is not effective for all patients, which has led to experimentation with nebulized antibiotics.[30] The thought behind this therapy is that nebulization allows for particles to be distributed over a larger area of mucosa, which is especially ideal for postsurgical patients with large sinus openings. A study by Desrosiers and Salas-Prato treated 20 patients who failed sinus surgery with 4 weeks of a tobramycin-saline solution or a saline only solution. The authors found that large-particle nebulized aerosol therapy improved symptomatology and objective parameters of rhinosinusitis, but the addition of tobramycin added minimal benefit.[31] Accordingly, most other studies have been unable to show a proven benefit with this form of pharmacotherapy[32] and therefore it is not approved for use in the treatment of CRS at this time.

Antibiotic Irrigations

Since topical irrigation with mupirocin significantly reduces *Staphylococcus aureus* biofilm in vitro, a review of the literature was performed to assess the efficacy of topical antibiotics in CRS. Results demonstrated that physiologic saline irrigation is beneficial in the treatment of CRS, but only low-level evidence supports the effectiveness of topical antibiotics in the treatment of CRS.[33,34] A more recent systematic literature review by Lee and Chiu in 2014 verified these results, showing that topical anti-infective solutions are not recommended as first-line therapy for routine CRS but may be considered as a potential option for patients with refractory CRS who have failed traditional medical and surgical intervention.[35] Furthermore, a recent systematic review of the literature by Rudmik and colleagues in 2013 provides evidence-based recommendations regarding the use of topical medications in the treatment of CRS, with the majority of included studies containing a level of evidence of 2b or higher. The evidence does not recommend routine use of topical antifungal or antibiotic sprays for CRS, and research regarding antibiotic therapy delivered via other methods (such as irrigations) is lacking. However, as mentioned previously, saline irrigations and topical nasal steroids have proven to be efficacious and are recommended as topical treatment for CRS based on the available evidence.[34] Additional research is needed to determine which patients would benefit from irrigation regimens.

Duration of Treatment for CRS

No prospective studies have been performed to demonstrate the optimal length of antibiotic treatment course for CRS. The recommendation for a 3–6 week course followed by repeat assessment is based on clinical practice.[13] The total duration may be extended up to 12 weeks for patients with severe symptoms, previous failures, or infectious complications.

In the 2012 European position paper on rhinosinusitis and nasal polyps, Fokkens and colleagues define long-term treatment with antibiotics for CRS as treatment duration longer than 4 weeks. They note that the number of placebo-controlled trials concerning this topic are limited, but that open studies are available that demonstrate improvement of symptoms in CRS with nasal polyposis patients when given a 12-week course of lose-dose macrolide therapy, with reduction in symptoms ranging between 60% and

80% in these studies.[36] Larger placebo-controlled studies are necessary to better answer the question of antibiotic duration in the treatment of CRS.

Concern for antimicrobial resistance, as well as patient specific side effects such as elevated liver enzymes, gastrointestinal upset, and dermatological disease, should be considered when prescribing long courses of antibiotics for the treatment of CRS.[37]

CONCLUSION

Although it is now well understood that the development of both acute and chronic forms of rhinosinusitis is a multifactorial process, with bacteria being only one etiologic and pathogenic factor, antibiotics continue to be a mainstay of the multimodality therapy for this disease. Antibiotics are prescribed not only to eradicate the infection and improve symptoms, but also to decrease the pathogenic bacterial counts within the nasal cavity and paranasal sinuses in the hope of restoring the normal microbial balance. Although some of the clinical decisions regarding antibiotic use are supported by primary literature and consensus statements, other questions, such as the role of antibiotics in the management of chronic rhinosinusitis, would benefit from further placebo-controlled prospective studies.

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CHAPTER

36 Anti-Inflammatory Therapy for Rhinosinusitis

Alla Y Solyar, Donald C Lanza

INTRODUCTION

Medical opinion is varied over which treatments are best to manage the various forms of rhinosinusitis. However, most agree that there is an important role for anti-inflammatory therapy since sinus inflammation is the hallmark of this condition.

Exogenous etiologies for sinus inflammation include, but are not limited to, infection (e.g. bacteria, viruses, and fungi), allergens, trauma, noxious substances, and medications such as aspirin in sensitive individuals. Endogenous factors associated with sinus inflammation include disorders of immunity, autoimmunity, the endocrine system, ciliary dyskinesia, cystic fibrosis, neoplasm, and extra-esophageal reflux (Fig. 36.1).

The pathophysiology of sinonasal inflammation is complex and can differ in acute rhinosinusitis (ARS) vs. various forms of chronic rhinosinusitis (CRS). Inflammatory mediators in rhinosinusitis include neutrophils, eosinophils, T and B lymphocytes, mast cells, interleukins, leukotrienes, major basic protein, immunoglobulins, tumor necrosis factor, interferon gamma, and numerous other cytokines. Histopathologic evaluation of sinonasal mucosa during an inflammatory response reveals submucosal presence of a mixed inflammatory cell infiltrate, which may include mature lymphocytes, plasma cells, eosinophils, histiocytes and neutrophils, along with submucosal edema, intermittent presence of surface mucosal squamous metaplasia, minimal fibrosis, and vascular proliferation[1] (Fig. 36.2).

Some diagnostic methods can help identify inciting factors and thereby help determine which anti-inflammatory treatments may be appropriate for a given individual. Therapies directed at reducing sinus inflammation are the subject matter of this chapter and include corticosteroids, antihistamines, leukotriene modifiers, and antimicrobials with anti-inflammatory properties. Proton pump inhibitors may be used as part of an anti-inflammatory regimen when laryngopharyngeal reflux is suspected; however, these are discussed elsewhere in this textbook.

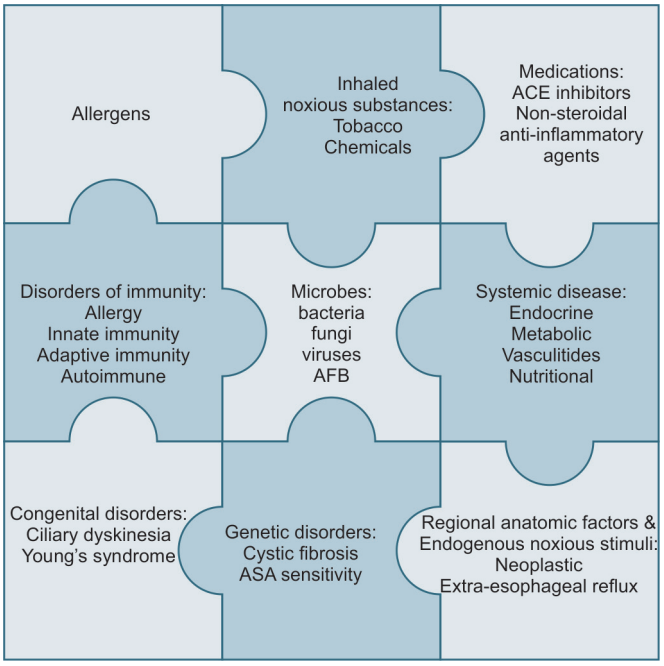

Fig. 36.1: Factors associated with rhinosinusitis inflammation.

Table 36.1: Corticosteroids[8]

Name	*Approximate equivalent dose (mg)*	*Anti-inflammatory potency*	*Mineralocorticoid potency*	*Half life (h)*
Betamethasone	0.6–0.75	20–30	0	36–54
Cortisone	25	0.8	2	8–12
Dexamethasone	0.75	20–30	0	36–54
Fludrocortisone	n/a	10	125	18–36
Hydrocortisone	20	1	2	8–12
Methylprednisolone	4	5	0	18–36
Prednisone	5	4	1	18–36
Prednisolone	5	4	1	18–36
Triamcinolone	4	5	0	12–36

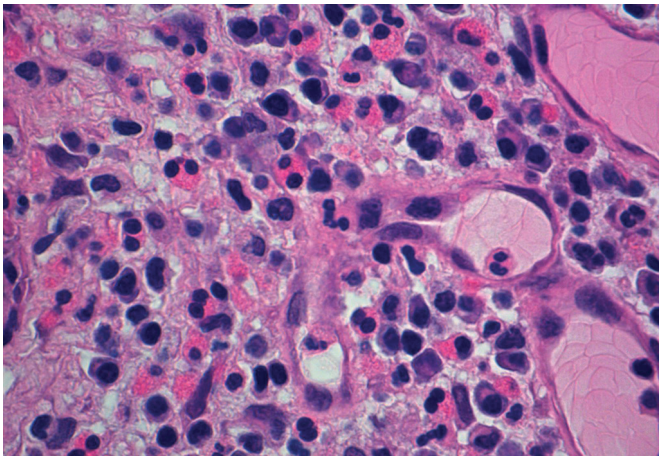

Fig. 36.2: 400 × HE histophotomicrograph of CRS with polyps in patient with eosinophilia, elevated total IgE, and asthma.

STEROIDS

Mechanism of Action

Glucocorticoids (GCs) are a type of corticosteroid hormone that binds the glucocorticoid receptor (GR) and possesses anti-inflammatory properties. The GR is virtually present in all cells but its expression varies. Steroids exert their effects through multiple signaling pathways. GCs are widely used in the setting of allergic and nonallergic rhinitis and CRS with multiple oral and topical forms available. Whether via topical or oral administration, the unbound steroid molecule diffuses across the cell membrane to enter the cytoplasm where in binds to a GR. This forms a steroid-receptor complex, which then translocates into the nucleus and binds specific areas on the DNA where it regulates the transcription of certain target genes.[2] One mechanism of action in the setting of inflammatory disorders is via the inhibition of synthesis of cytokines and inflammatory mediators.[3] Specifically, treatment with topical steroids has been shown to reduce production of IL-4 and IL-13 and inhibit infiltration of inflammatory cells, including eosinophils, T-lymphocytes, basophils, and mast cells.[4,5] Additionally, expression of IL-4 receptor, IL-5 receptor, and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor mRNA was found to be reduced with topical steroid treatment.[5] Eosinophil survival is curtailed as a result of steroids by enhancing eosinophil apoptosis by reducing the effects of cytokines such as IL-5 and GM-CSF. Interestingly, while the GCs suppress the adaptive immunity, they do not appear to downregulate the innate immune system in the respiratory epithelium, and in some cases may even enhance it though the activation of Toll-like receptors.[6,7]

Oral Steroids

Forms

Hydrocortisone is a naturally produced human glucocorticoid that plays an important role in metabolic, cardiovascular, immunologic, and homeostatic function. There are multiple forms of synthetic oral steroids, which are listed in Table 36.1. Variability among various formulations includes glucocorticoid potency, mineralocorticoid potency, and half-life. Mineralocorticoid activity pertains to sodium and water retention.

Oral Steroids in ARS

While treatment of ARS typically involves supportive therapy and at times antimicrobial therapy, the role of oral steroids for ARS is controversial. Yet, a Cochrane review

concluded that oral steroids may be a useful adjunct to antibiotics in the treatment of ARS for short-term relief of symptoms.[9] Data, however, are limited. Consideration of risk vs. benefit to patient must be applied when considering the use of this medication for what can be a self-limiting condition.

Oral Steroids in CRS

Oral steroids are widely used in both CRS with and without polyps. Although GCs are a mainstay of therapy for nasal polyposis, not all nasal polyps are as sensitive to this therapy. This appears to stem from a variation in the expression of the GR. Altered expression of GRs, namely GR-α and GR-β, is a potential mechanism underlying GC insensitivity in some nasal polyps.[4,10] Multiple studies of varying quality, but including some highly rigorous trials, show improved subjective symptoms scores and endoscopy findings in patients with CRS with polyps treated with oral steroids.[11–17] Brief courses of oral steroids are generally preferred for the short-term alleviation of symptoms and reduction of polyp burden. In one study, patients with CRS with polyps were randomized between three study arms, one receiving methylprednisolone, the second group receiving antibiotic doxycycline and the third group receiving a placebo.[14] Both the doxycycline and the steroid group showed substantial improvement with regard to polyp size as compared to the placebo group. Interestingly, the effect of doxycycline was more moderate but longer lasting than the steroid. Both medications reduced different inflammatory markers in nasal secretions: methylprednisolone significantly decreased levels of eosinophilic cationic protein (ECP), IL-5, and IgE, while doxycycline significantly reduced levels of myeloperoxidase, ECP, and matrix metalloproteinase 9. Temporary reduction in blood eosinophils was observed in the steroid group but not the doxycycline group. Most patients in the steroid group experienced a rebound eosinophilia after the treatment was discontinued.

Steroid use in CRS without polyps is not fully established. Available studies examining systemic steroid treatment in this patient group used the oral steroid as part of a multimodality medical therapy, which frequently included an oral antibiotic, topical steroid, and topical decongestant.[11] Therefore while objective and subjective improvement was observed in most patients with this approach, there is insufficient evidence to advise this approach for all CRS patients without polyps. Clinicians are advised to use systemic steroids on a basis of an individual approach to each patient.

Oral corticosteroid therapy is also useful in management of patients with allergic fungal rhinosinusitis (AFRS).[11] Multiple studies evaluated the use of oral steroids as an adjunct to surgical treatment.[18–20] The evidence from literature suggests that oral corticosteroids are useful in both preoperative and postoperative periods in the management of AFRS. However, many studies varied with regard to other concomitant therapies (topical steroids, antifungal medication, antacid) and oral steroid dose. In one study, a group of patients in the steroid arm received 1 mg/kg (50–80 mg/day) for 10 days before surgery and then a 6–9 day postoperative taper.[18] Another study treated their experimental group with 0.5 mg/kg for one month postoperatively.[19] Finally, 50 mg of oral prednisolone was administered to postoperative patients for 6 weeks, followed by another 6 week taper in a prospective randomized double-blind placebo-controlled trial.[20] Though there was a statistically significant difference between the control and experimental groups in these studies with regard to improvement of symptoms and symptom recurrence, further study is needed to determine optimal dose and duration of therapy. Consideration needs to be given to the increased risk of adverse effects with prolonged steroid intake. Rupa et al.[20] had a longer course of oral steroid intake duration and reported the most significant side effects. All 12 patients developed transient weight gain, 42% developed Cushingoid features, and one patient developed steroid-induced diabetes mellitus (DM) that resolved after steroid therapy was completed.

Oral steroids are recommended for perioperative use in patients with polyps, with multiple studies showing surgical benefits including shorter operative times, improved visibility and improved postoperative appearance, but no significant reduction in blood loss.[21–23] Based on these studies, a review by Poetker et al.[17] has surmised that 30 mg of prednisone daily started 5–7 days before surgery and continued for 9 days postoperatively may be efficacious for perioperative use. There was no added effect from increased dosage. The authors of this chapter typically use a perioperative prednisone taper for all patients who can tolerate them, starting at 15 or 20 mg for most patients 5 days prior to surgery and continuing for another 4–13 days depending on certain variables involved specific to the patient. Steroid use is part of comprehensive medical management of this chronic condition. Oral steroids are also frequently used as part of maximal medical therapy in an effort to avoid surgical treatment. Lal et al. evaluated a group of 145 patients that had polyp and nonpolyp CRS disease, treated with a multimodality therapy

that included 4 weeks of antibiotics, 12-day steroid taper, nasal steroid sprays, rotating use of topical decongestants for 4 weeks and nasal saline rinses. A total of 55% of patients in the CRS with nasal polyps cohort had complete resolution of symptoms and 31% had ongoing symptoms with subsequent elective surgery. CRS patients without nasal polyps had a 46% successful treatment rate in their cohort with 37% electing to proceed with surgery. There was no significant difference with regard to response to multimodality therapy between the two groups of patients. Given the use of multimodality treatment, it was not possible to analyze the specific effect of oral steroid on ability to avoid surgery.[24]

Systemic Steroid Side Effects

The list of oral steroid side effects is extensive and includes Cushingoid changes with redistribution of adipose tissue, hyperglycemia, susceptibility to infection, delayed wound healing, osteopenia/osteoporosis, avascular necrosis (AVN), cataract formation, glaucoma, dermal thinning, gastritis, adrenal suppression, myopathy, hypertension, and mood disorders.

Cushingoid changes include truncal obesity, moon facies, and dorsocervical fat pad known as buffalo hump. These may occur in 33–40% patients who have been treated with an average dose of prednisone equaling 23 mg/day after 8–12 weeks of treatment.[25] Hyperglycemia may occur as a result of increased gluconeogenesis in the liver and insulin resistance. This effect may occur in as little as 12 h after initiation of therapy[26] and is more potent with synthetic corticosteroids such as prednisone and dexamethasone. Patients with high and/or prolonged courses of corticosteroids are at a greater risk of developing steroid induced DM with resolution of hyperglycemia upon cessation of treatment. Oral corticosteroids should be used cautiously in patients with known DM.

Hypertension may occur early in the corticosteroid treatment course. However, this side effect is thought not to be secondary to synthetic steroid mineralocorticoid activity. In addition to this, there is also an increased risk of a cardiovascular or cerebrovascular event. Rare episodes of cardiac arrhythmias have been reported after a pulse of steroids. The pathophysiology remains to be elucidated; however, dyskalemia has been postulated as a possible factor.[25]

There is a risk of osteoporosis with prolonged steroid use, which is increased in postmenopausal women. The fracture risk is higher with prolonged corticosteroid duration, higher doses and patient characteristics that include female gender, lower body weight, and older age. Supplementation with calcium and vitamin D may effectively prevent bone loss associated with osteoporosis; bisphosphonates may also be used for prevention and treatment of corticosteroid-induced osteoporosis.

One of the most feared complications of oral steroid therapy is AVN, a complication that is associated with high steroid dose and most frequently involves the head of the femur, though other bones may be affected. In one study, the mean time from treatment to onset of symptoms was 16.6 months and in another study a risk of AVN was 0.03% in a population with a mean age of 26 receiving a mean cumulative dose of 673 mg of prednisone over a mean duration of 20 days. Corticosteroids may also affect skeletal muscle and cause reversible muscle weakness.[26]

Patients using corticosteroid therapy are more likely to complain of peptic ulcer–like symptoms. However, there is no evidence that there is an association between ulcer development and prednisone use based on several large meta-analyses of randomized, placebo-controlled studies.[25] There is also no evidence of increased risk of ulcer hemorrhage or perforation with corticosteroid use.

A well-known side effect of steroid treatment is the suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Natural production of cortisol in a healthy, unstressed adult by the adrenal gland is approximately 10–20 mg per day, which correlates with 5–7 mg prednisone per day. Exogenous intake of prednisone produces a negative feedback on the HPA axis, resulting in decreased cortisol secretion from the adrenal glands. The suppression may occur with as little as 10 mg of prednisone per day taken for 4 days.[26] Though the suppression is present on objective data, the risk of clinical corticosteroid-induced adrenal insufficiency is much lower and its incidence is unknown.

Multiple ophthalmologic side effects of corticosteroids exist and they are beyond the scope of this chapter. The most common ophthalmologic side effects are cataract formation and increased intraocular pressure. Cataract formation is associated with a lengthy steroid course with some investigators reporting a need for at least a year of 10 mg of prednisone or more daily prior to cataract development.[26] Certain factors associated with a higher risk of developing increased intraocular pressure include open-angle glaucoma, DM, high myopia, rheumatoid arthritis, hypertension, history of migraines, and first-degree relatives with open angle glaucoma.[26] Given the risk of visual field loss with increased intraocular pressure,

a consultation with an ophthalmologist is prudent to obtain prior to initiation of corticosteroid treatment in any individual who may be susceptible to developing an ophthalmic complication.

The same mechanisms that allow steroids to decrease inflammation and provide symptom relief may expose a patient to its immunosuppressive effects and result in decreased resistance to infections. Those with the highest risk of infection such as invasive fungal infections, pneumocystosis, and viral infection include patients who have undergone bone marrow transplantation and are being treated with GC. Corticosteroids may also affect wound-healing process, resulting in wound-healing delay and decreased tensile strength.

There is a wide range of variability with regard to incidence of psychiatric side effects with corticosteroids. The most common ones include anxiety, agitation, distractibility, fear, hypomania, indifference, insomnia, irritability, lethargy, mood lability, pressured speech, restlessness and tearfulness.[26] It is important to educate patients regarding these side effects prior to therapy initiation; a clinician should recommend that the patient alert their family to this as well. Given the risk of sleep disturbance, the authors of this chapter typically advise that the steroid be taken in the morning, shortly after arising, to mimic the circadian rhythm of cortisol release. This, along with lower doses, can mitigate steroid associated insomnia.

Corticosteroids prescribed during first trimester of pregnancy may be associated with a higher risk of cleft lip or cleft palate.[25] Prednisolone is labeled category C by the FDA (i.e. animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans), but potential benefits may warrant use of the drug in pregnant women despite potential risks. Prednisone and Medrol are not formerly assigned a category by the FDA. Inhaled budesonide is given category B by the FDA (i.e. animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women). Steroids can be transmitted to the newborn via breastfeeding as well. Corticosteroid-induced menstrual disorders may be present in a substantial number of female patients.

As seen from the above summary on the side effects of corticosteroid treatment, there are multiple potential complications that may occur. Patients should be counseled regarding these side effects prior to initiation of steroid therapy. In the setting of a plethora of potential complications, it may be beneficial to provide a patient with an educational handout reviewing the counseling they received in the office.

TOPICAL INTRANASAL CORTICOSTEROIDS

Formulations, Safety, and Side Effects

Topical corticosteroids are widely used for alleviation of symptoms of allergic and nonallergic rhinitis as well as acute and chronic rhinosinusitis. Their potent anti-inflammatory activity, effectiveness in the relief of nasal symptoms of congestion, their topical route of administration, reduced systemic bioavailability as compared to oral steroids, and long-standing safety record make them an attractive treatment option in managing the symptoms of patients with rhinosinusitis. Multiple formulations as well as routes of administration exist, and each one differs in terms of systemic bioavailability, lipid solubility potency, and half-life. Currently available intranasal corticosteroids (INCs) include flunisolide (Flu), triamcinolone acetonide (TAA), beclomethasone dipropionate (BDP), budesonide (Bud), fluticasone propionate (FP), fluticasone furoate (FF), mometasone furoate (MF), and ciclesonide (Cic). As with any corticosteroid, there is a concern for adverse effects (as listed in the previous section) resulting from absorption into the systemic circulation. The likelihood of a systemic adverse effect varies between INCs and is dependent on systemic bioavailability of the drug, which is listed in Table 36.2. As shown, newer second generation INCs such as MF, FP, FF, and Cic have a significantly lower systemic bioavailability than the older compounds. As opposed to the inhaled corticosteroids where the systemic availability is determined by the amount of drug absorbed from the

Table 36.2: Systemic bioavailability of inhaled nasal corticosteroids[27]

Intranasal corticosteroid	*Systemic bioavailability*
Flunisolide	49%
Triamcinolone acetonide	46%
Beclomethasone dipropionate	44%
Budesonide	34%
Fluticasone propionate	<1%
Fluticasone furoate	0.5%
Mometasone furoate	<0.1%
Ciclesonide	Undetectable

lungs and from the gastrointestinal (GI) tract, the systemic bioavailability of INCs is a sum of absorption from the nasal cavity and the GI tract. The overall steroid burden from the INCs is lower than that from the inhaled corticosteroids.[27] There are no recent comparative bioavailability data for topical intranasal dexamethasone or betamethasone, both of which are generally more potent GCs and are associated with systemic side effects.[28–30] Steroids such as MF and FP possess higher topical potency and lipid solubility.[31] Enhanced lipophilic activity means that the substance possessing of this quality is absorbed through the nasal mucosa at a faster and higher rate, has greater retention within the target tissue and increased GR binding in that area, resulting in less unbound drug to interact with systemic GRs and therefore less probability of adverse systemic effects.[27] With each intranasal administration of INC, 30% is deposited in the nose and 70% is swallowed. The INC that passes through the GI tract is subject to first-pass hepatic metabolism that varies between different agents, with for example 90% for Bud and 99% for FP and MF.

The most common local adverse effects associated with INCs are epistaxis, dryness, burning, and pharyngitis. Most of these adverse effects are mild, self-limited, reverse with discontinuation of treatment but usually do not require therapy cessation.[27,32] Certain formulation additives may contribute to the above-mentioned side effects. Traumatic insertion of the nasal applicator tip may also contribute epistaxis. A more severe but rare side effect of INCs is septal perforation. Correct administration technique, holding the nozzle away from the septum intranasally while spraying into the center of the nasal cavity, may help prevent septal mucosal injury leading to ulceration and perforation.[27]

Potential systemic adverse effects of INCs are similar to oral corticosteroids. However, given the limited bioavailability of these medications, systemic adverse effects observed with prolonged oral glucocorticoid therapy are rarely encountered with long-term INCs. The majority of trials show that INCs have a negligible effect on the HPA axis.[32] Multiple studies have shown no growth suppression with use of INCs in children, when appropriate dosing was used.[27] Because release of growth hormone in prepubertal children is pulsatile, with initiation of secretion at nighttime, corresponding to low levels of plasma cortisol, it is important that INC is administered once daily during the morning in this patient population.[32] Twice daily INC use in children may lead to suppression of growth hormone production. Additionally, given their extremely low systemic absorption rate, second-generation INCs are considered safe during pregnancy.[27]

INCs do not appear to have a negative effect on bone metabolism. The risk of ocular adverse effects such as cataracts or glaucoma also appears to be negligible with INCs and two recent 2-year studies evaluating ocular effects of INCs in adults and children did not reveal adverse effects with regard to intraocular pressure or cataract formation.[33,34] Nevertheless, many patients may have glaucoma or cataract formation prior to initiation of INC; consequently, ophthalmology clearance prior to initiation of therapy and regular ophthalmology evaluations during treatment may be warranted. In addition, many patients are treated with other topical and oral steroids, thus increasing the total corticosteroid burden.

Topical Corticosteroids for ARS

Topical corticosteroids have been shown to be a useful adjunct to oral antibiotic therapy for the treatment of uncomplicated acute bacterial rhinosinusitis.[35,36] In fact, one study showed that patients with acute uncomplicated rhinosinusitis treated with MF as monotherapy did better with regard to their symptoms than patients treated with amoxicillin alone.[37] Another trial showed that topical steroids were more likely to be effective in those patients with a milder form of rhinosinusits.[38] Use of topical steroids during initial phase of a viral upper respiratory infection has long been advised against since there was a theoretical concern they could promote worsening of the viral infection. This concern, however, has not been borne out in limited research.[39,40]

Topical Steroids in CRS

Topical delivery of medications such as corticosteroids into the sinuses is an attractive alternative to frequent oral corticosteroid intake and the potential side effects associated with oral steroids. Advantages of topical steroid over oral steroid administrations include direct delivery of a drug to the diseased tissue, ability to use higher concentration locally, and minimal systemic absorption. Disadvantages include local adverse effects from the drug or application device, variable sinus penetration, and time consumption when using nasal irrigation (extra time to perform the nasal rinse, prepare the solutions and sterilizing irrigation devices). In patients with CRS, topical drug delivery to diseased sinus mucosa may be enhanced after endoscopic sinus surgery. There are

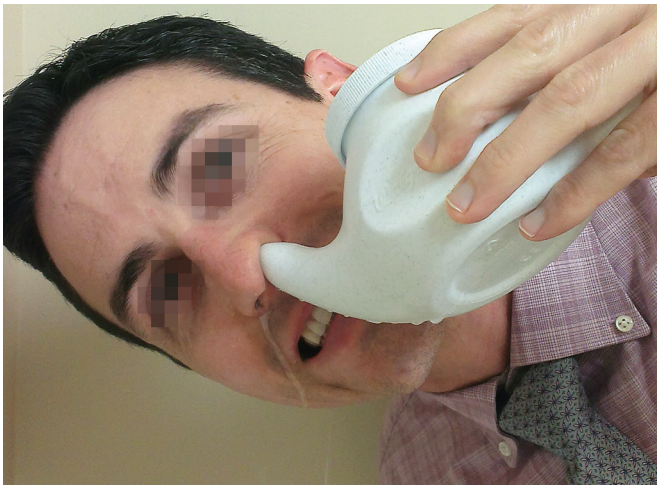

Fig. 36.3: The Neti pot is a gentle method of sinonasal lavage (especially for the unoperated patient).

Fig. 36.4: Sealed container of compounded budesonide nasal irrigation with obvious signs of microbial growth. This adverse compounding event was reported to the Florida Department of Health.

different methods of topical steroid delivery and these include the FDA-approved metered-dose nasal sprays or non-FDA approved irrigation or nebulization methods.

Multiple studies have shown that there is objective and subjective improvement in patients with CRS with and without polyps when using INC via a standard metered-dose delivery device.[41,42] Use of nasal steroid sprays improves sinonasal symptomatology, endoscopic appearance, and reduces polyp size. Though multiple reports in the literature demonstrate that distribution of topical steroid sprays is superior in operated sinuses, subgroup analysis of a Cochrane review of topical steroid use in CRS without polyps showed no difference in efficacy in patients with or without surgery. It is important to consider that factors such as positive pressure, irrigant volume, and size of the ostia play a role in topical solution distribution.

Off-label topical intranasal steroid delivery includes the use of nebulization and high volume irrigation with a variety of devices available. Drugs commonly used in these delivery methods include budesonide, mometasone, and betamethasone. Another less common nonstandard INC delivery route includes low volume solutions such as intranasal dexamethasone ophthalmic drops, prednisolone ophthalmic drops, tobramycin/dexamethasone ophthalmic drops, and ciprofloxacin/dexamethasone otic drops. The drops may be useful in the treatment of CRS; however, consideration must be given to potential adverse effects associated with high-dose steroids. Combinations containing aminoglycosides may have additional adverse risk including nephro- and ototoxicity. Vertex to floor head position held for 5 min improves the medicated drop delivery to the olfactory cleft region.[43] High volume topical steroid delivered via a Neti Pot (Fig. 36.3) or a squeeze bottle may be beneficial for treatment of patients with CRS by providing better local drug delivery and simultaneous mechanical lavage.[41] Endoscopic sinus surgery provides a corridor for a more effective topical therapy delivery to the sinuses, with larger ostial size providing better penetration.[44,45] Furthermore, high volume nasal irrigation with a squeeze bottle has demonstrated superior particle distribution than a nasal nebulizer in an operated cadaver model.[46] Even though a large volume of the medication makes contact with the mucosa, drug exposure is limited when corticosteroids are administered via nasal irrigation as the residual fluid volume after the rinse is small (2.5% ± 1.6%).[47]

A few studies have shown efficacy of both nasal steroid sprays and nasal steroid irrigations after surgery; however, the results have not been consistent.[48] A retrospective study by Jang et al. suggested that budesonide nasal irrigation may be superior to conventional steroid sprays in their postoperative patient population, which consisted of patients with and without nasal polyps as well as those with AFRS.[48] It is advised that the off-label nature of the topical steroid administration via nebulization or irrigation is disclosed to the patient. Frequently these medications are prepared at compounding pharmacies, which may have inconsistent standards and variability in policy and procedure protocols. Contamination of the solution used for rinse is possible when sterile technique is not adhered to (Fig. 36.4). Patient education and clinician's

awareness as to the source of the product and reliability of the manufacturer is important.

Recent advances in the postoperative therapy of patients with CRS have brought forth corticosteroid coated sinus stents. The first such device is a mometasone eluting stent, which is composed of MF imbedded in a biodegradable polymer and is deployed within the middle meatus at the time of surgery.[49] In addition to eluting corticosteroid in the sinonasal cavity after surgery, the stent may also act as a spacer, maintaining a separation between the middle turbinate and the lateral nasal wall, thereby preventing synechia formation. Trials have shown that steroid eluting stents downregulate inflammation and new polyp formation after endoscopic sinus surgery. The three clinical trials that have investigated the use of this new device found only a limited number of adverse effects and demonstrated overall safety and short-term efficacy in their study population.[49]

Another less utilized method of corticosteroid delivery into diseased tissues is direct injection of the steroid solution into the inflammatory polyps. The use of intraturbinal/intranasal steroid had declined after reports of blindness began to emerge. This complication is believed to be associated with large particle corticosteroid injection directly into the mucosa of the inferior turbinate and the septum, allowing retrograde flow of these particles through the ethmoidal circulation and into the central retinal artery.[50] Measures to prevent visual loss with steroid injection include using a small particle steroid, small gauge needle, adequate topical vasoconstriction of the area prior to injection, and possibly injecting only the polyp tissue. A few recent reports suggest potential benefits, such as control of symptoms and surgery avoidance.[50,51] Patients should be informed about the risks associated with intrapolyp steroid injection as well as the fact that this type of steroid administration is off label.

NASAL SALINE IRRIGATIONS

Nasal saline irrigations (NSIs) are frequently one of the first lines of treatments and represent a mainstay of therapy in a CRS patient. Though the effectiveness of NSI as an adjunct treatment for ARS has not been determined,[52] its use in a CRS patient population has been well established and validated by multiple studies.[52,53] Theories as to the mechanisms of the therapeutic effect of normal saline include its role in enhancement of mucociliary clearance, mechanical removal of biofilm, allergens and other irritants.[52–54] A 2009 Cochrane review evaluating NSI in CRS found that it was tolerable and possessed beneficial effects.[53] Buffered hypertonic saline has been shown to be more effective in the enhancement of mucociliary clearance than normal saline secondary to rheologic alterations such as decreased viscosity of the mucous blanket.[55] The improvement in nasal patency with buffered hypertonic saline is not secondary to decongestion. In fact, an increased sensation of nasal obstruction may ensue with its higher tonicity.[54] It has been theorized that Dead Sea salt solutions may have anti-inflammatory properties and thus may be superior to standard saline preparations.[56] A recent study showed that CRS patients who used hypertonic Dead Sea salt nasal rinse had significant symptomatic improvement from their baseline that was similar to improvement seen in a group of CRS patients using topical intranasal steroid and hypertonic saline irrigation.[56] A randomized controlled trial by Pynnonen et al.[57] showed that NSIs were superior to nasal saline sprays with regard to symptom alleviation in patients with sinonasal complaints.

Minor side effects of NSI such as burning, irritation, and nausea may be experienced by some patients. There is a concern that host immune defenses may be removed with frequent NSI.[54,58,59] An in vitro study that evaluated the fungicidal activity of lysozyme (an innate immune peptide present in mucus secretions) found that this activity was inhibited by commercial sinus irrigation solutions.[58] So far the literature supports evidence of benefit as opposed to adverse effects with NSI. Sterility of the water source for the saline as well as careful attention to sanitation of the irrigation devices appears to be very important. Rare cases of primary amoebic encephalitis may be associated with intranasal tap water use. Inadequate cleansing of irrigation devices and spray bottles may create a breeding ground for bacterial organisms and possible contamination of sinonasal mucosa.[60,61] Patients on a low salt diet and with congestive heart failure should be counseled regarding importance of not swallowing the saline solution during irrigation. Other adverse effects include impact on the patient's daily life and a requirement to expend time and resources on preparation and delivery of the irrigant as well as upkeep of irrigation devices. Benzalkonium chloride is a frequent preservative used in commercial nasal sprays, including certain brands of nasal saline sprays. A concern for its role in nasal mucosal damage has been raised in the literature;[54] however, the evidence remains inconclusive.

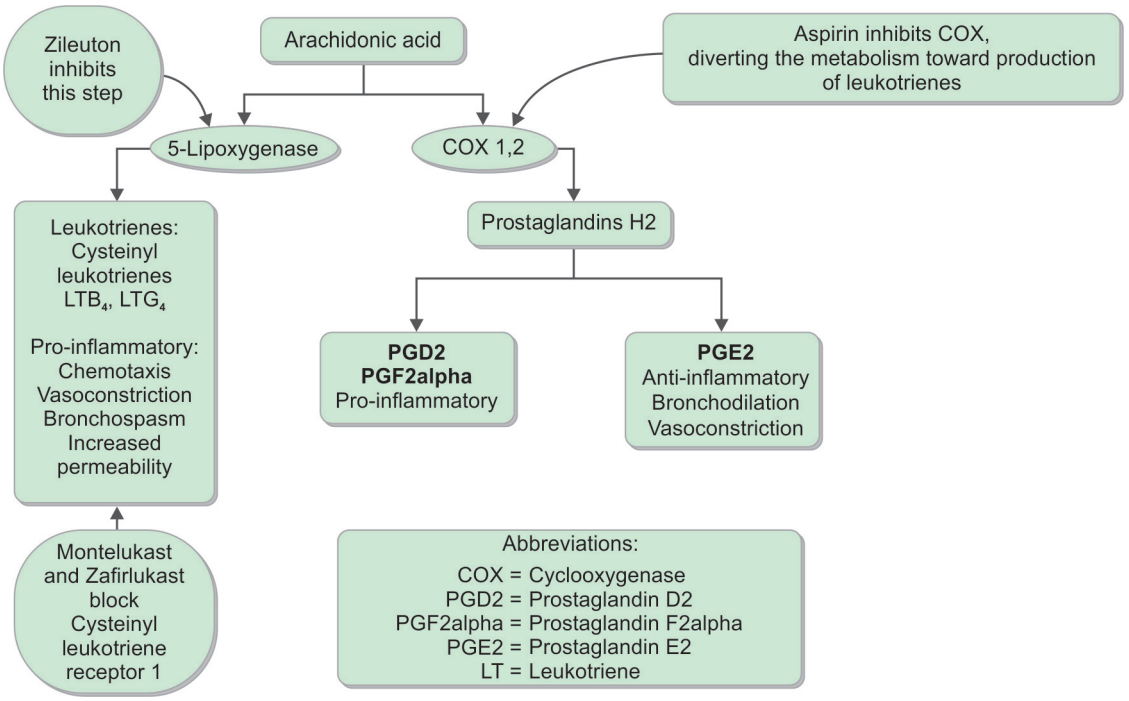

Fig. 36.5: Arachidonic acid metabolism. Note site of action for ASA, Zileuton, Montelukast and Zafirlukast.

LEUKOTRIENE MODIFIERS AND ANTIHISTAMINES

Leukotrienes (LTs) are a group of inflammatory mediators secreted by basophils, eosinophils, mast cells, macrophages, and monocytes and are thought to play a prominent role in asthma and allergic disease as well as in some forms of CRS with polyps. Topical leukotriene D4 (LTD4) has been shown to increase nasal blood flow and nasal resistance.[62] Moreover, surgery for asthmatics who have CRS with polyps has been shown to decrease postoperative urinary leukotriene E4 excretion for both aspirin sensitive polyp patients as well as in polyp patients without aspirin sensitivity. This suggests a broader role of these LTs in CRS with polyps as well as a beneficial, albeit temporary, anti-inflammatory effect of sinus surgery.[63]

LT inhibitors include zileuton that blocks the 5-lipoxygenase pathway (inhibits formation of LTs) and montelukast and zafirlukast that block the action of cysteinyl LTs by binding the CysLT1 receptor on target cells (Fig. 36.5). These drugs are widely used in management of asthma and allergic rhinitis. Though there are currently no randomized, controlled trials describing the use of LT receptor antagonists in patients with CRS, there are multiple uncontrolled trials that show a potential benefit of antileukotrienes in patients with nasal polyposis.[62,64] Unfortunately, the results of multiple studies with LT modifiers are difficult to interpret, as they were conducted with LT modifiers as an additional treatment to oral or topical steroids.[64,65] Theoretically, LT modifiers may provide benefit in certain types of CRS [especially associated with hypereosinophilia and aspirin exacerbated respiratory disease (AERD)] via direct reduction of eosinophil recruitment and ability to decrease eosinophilopoiesis.[65]

While there is no evidence that anti-histamines are efficacious in management of nasal polyp size, there is evidence of symptom improvement. A double-blind placebo-controlled study by Haye et al. evaluating CRS patients who have undergone ethmoidectomy, were left with small residual or recurrent polyps and treated with cetirizine or a placebo, found that cetirizine had no effect on the polyp size.[66] The investigators reported a significant improvement in symptoms of nasal obstruction, rhinorrhea, and sneezing in the cetirizine group. Concomitant treatment with an antihistamine and antileukotriene has a synergistic benefit in diminishing inflammatory mediators typically seen allergic rhinitis as well as those in rhinosinusitis.[67]

Generally, antihistamines and leukotriene modifiers are well tolerated and have few side effects. Antihistamines may have a sedating effect, though this is less common with the newer generation H1 receptor antagonists. Other

side effects of antihistamines include dry mouth, blurry vision, urinary retention, and potential for weight gain. Leukotriene inhibitors' most commonly reported side effects are headaches and GI issues.[64] Zileuton therapy may result in liver injury; therefore, monitoring of liver enzymes when using this medication is important. Patients should also be alerted as to the possibility of a relationship between the use of LT modifiers and development of Churg-Strauss syndrome. It is important to point out that this may not be a direct effect of the drug but rather a presence of Churg-Strauss in patients treated with LT modifiers prior to initiation of therapy with this drug. Although uncommon, there may be a potential link between suicidal thought and the use of leukotriene modifiers. From 1998 to 2009, there were 838 suicide-related adverse events associated with leukotriene modifying agents reported to the FDA, prompting the FDA to issue a warning for the entire class of LT modifiers. Most of the reports involved montelukast and nearly all cases were reported in 2008 and 2009 (96.1%) after the FDA warnings were issued. Despite the FDA warnings, there are no well-designed studies supporting the link between LT modifiers and suicide. Furthermore, there is a greater incidence of suicidal ideation and suicide attempts in an asthmatic population. Caution and careful monitoring should be used in patients prescribed LT modifiers, especially those with elevated risk for suicide.[68]

ROLE OF NSAIDs IN THE MANAGEMENT OF RHINOSINUSITIS: ASPIRIN DESENSITIZATION FOR CRS

Though there are a variety of over the counter nonsteroidal anti-inflammatory drugs (NSAIDs) available for symptomatic management of ARS, there is a paucity of literature with regard to their efficacy in this condition. More is known about the role of aspirin in the management of CRS classified under AERD. AERD constitutes a triad of rhinosinusitis, bronchial asthma, and aspirin intolerance. AERD is a type I pseudoallergic non-IgE-mediated reaction, occurring as a result of 5-lipoxygenase driven excessive production of leukotrienes when the COX pathway is blocked[69] (Fig. 36.5). The increased production of leukotrienes results in mast-cell degranulation, release of inflammatory mediators leading to respiratory symptoms that include nasal congestion, rhinorrhea, and bronchospasm. The typical onset of AERD entails sinonasalcomplaints initially, progression to nasal polyps, and finally aspirin-intolerant asthma. It is not uncommon in these patients for nasal polyps to recur soon after surgery. The prevalence of AERD ranges from 0.3% to 0.9% in general population to 30–40% in patients with CRS and nasal polyposis.[69,70] About one-third of patients with AERD are atopic. Oral aspirin challenge under medical supervision is the gold standard for diagnosing AERD in the United States.[70] Major goals in management of AERD include reduction of mucosal inflammation, prevention of new polyp development, and improved asthma control. The management options are limited and include NSAID avoidance or aspirin desensitization followed by uninterrupted aspirin therapy. Even with aspirin avoidance it is not uncommon for patients with AERD to suffer from CRS and asthma despite medical and surgical therapy.

Aspirin desensitization is a form of therapy where progressively increasing doses of oral aspirin are administered on a daily basis. It has been shown in multiple studies to improve symptoms of CRS and asthma, reduce new polyp formation, reduce the number of sinus surgeries, and need for systemic steroid intake.[69,70] Though polyp growth and recurrence is diminished with this form of therapy, there is no evidence that pre-existing polyps are consistently affected.[69,70] Multiple theories as to the mechanism of action of aspirin desensitization exist; however, the exact mechanism is yet to be elucidated. Furthermore, NSAIDs other than aspirin have not been shown to be efficacious in desensitization. Candidates for aspirin desensitization include AERD patients with stable asthma who display ongoing symptoms despite appropriate medical and surgical interventions, those with aggressive polyp formation, or AERD patients who require aspirin for management of coronary artery disease. Continuous therapy after desensitization is important as interruption leads to a rapid recurrence of sensitivity and return of symptoms. Despite multiple authors investigating lower aspirin maintenance doses, the commonly accepted daily dose is 325–650 mg twice daily.[69] Contraindications to aspirin desensitization include peptic ulcer disease, pregnancy, unstable asthma, and bleeding disorders. A potential for side effects such as bronchospasm, laryngospasm, gastric irritation, and cutaneous reaction has resulted in caution with regard to utilization of this treatment modality among clinicians.

More recently, attention in the literature has focused on other routes of aspirin administration in an effort to avoid the risk of severe reaction seen with oral form of treatment. Lysine-aspirin is a soluble form of aspirin that may be administered intranasally for aspirin desensitization.

A prospective, randomized, double-blind, placebo-controlled, crossover trial by Parikh et al. did not reveal a significant benefit in AERD patients receiving intranasal lysine-aspirin.[71] However, a subsequent non-placebo-controlled trial demonstrated an improvement in nasal inspiratory peak flow and nasal polyp size reduction; lung function was not affected.[72] Both studies were limited by small number of participants. Larger placebo-controlled, double-blind trials are needed. Other forms of aspirin delivery such as bronchial and intravenous are being explored as well.

IMMUNOMODULATION

Immunotherapy in CRS

The role of allergic rhinitis as a risk factor for the development of ARS has not been well defined. Furthermore, there is a paucity of literature evaluating the role of allergy treatments such as avoidance, pharmacotherapy, and immunotherapy in prevention of recurrent ARS.

The understanding of the role that allergy plays in the pathogenesis of CRS is even more complex. Undoubtedly, IgE, mast cells, and eosinophils play a prominent role in certain forms of CRS; however, the role of allergy in the pathophysiology of CRS is controversial. Data regarding the prevalence of systemic allergy in CRS is varied with some reports showing a high association and others not.[73–75] Mucosal IgE in patients with CRS may be elevated as a response to local bacterial and fungal products. Additionally, other immune mechanisms may be at play as opposed to being the result of classical type I IgE mediated hypersensitivity.

Allergy is proposed to have causality in AFRS and by definition is present in all cases of AFRS.[76] Despite the definition, the dominance in the role of allergy in the pathogenesis of AFRS is questionable.[73] There is no clear evidence that subcutaneous immunotherapy is beneficial for AFRS.[77] Furthermore, the role of sublingual immunotherapy for the management of CRS has not been rigorously evaluated.

Gammaglobulin Therapy

Recurrent upper respiratory infections including ARS may be associated with a low IgG level in conditions such as selective IgG deficiency, X-linked agammaglobulinemia, hyper IgM syndromes, and common variable immune deficiency. Intravenous immunoglobulin (IVIG) is a blood product prepared from donor serum and used in the management of the above-mentioned immunodeficiency disorders as well as multiple immune and inflammatory diseases. Patients with antibody deficiencies receive a "replacement dose" of IVIG, different from the "high dose" IVIG given as an anti-inflammatory agent in autoimmune disorders.[78] IVIG mechanism of action is complex and depends on the disease and the dose. Some of its immunomodulatory effects include competition of pathogenic IgGs for activation of Fcγ receptors, suppression of T-cell proliferation, reduction of T-cell adhesion to extracellular matrix, inhibition of dendritic cell maturation, downregulation of certain cytokines, and induction of other ones.[78,79] Other effects include interference with antibody-dependent cellular cytotoxicity and modulation of complement activity.[78,79] Interestingly, IVIG can act synergistically with dexamethasone in suppressing lymphocyte activation and has also been used as a glucocorticoid sparing agent in asthma.[80] Though IVIG therapy is effective at reducing the number of upper respiratory infections in immunodeficient individuals, its role as an anti-inflammatory or glucocorticoid sparing agent in rhinosinusitis has not been studied. IVIG therapy is not without adverse effects, some of which include abdominal pain, nausea, rhinitis, asthma, chills, low-grade fever, myalgia, and headache. More severe reactions include anaphylaxis, Stevens-Johnson syndrome, hypotension, myocardial infarction, thrombosis, cytopenia, hemolysis, stroke, seizure, loss of consciousness, and pulmonary complications.[81]

Monoclonal Antibody Therapy—Anti-IgE and Anti-IL-5

IgE plays an important role is certain forms of CRS; therefore, its inhibition is an attractive target to explore as a potential therapeutic option for CRS patients. Omalizumab is an anti-IgE monoclonal antibody indicated for treatment of moderate to severe persistent asthma associated with inhalant allergies. It has also been effective for the management of patients with perennial allergic rhinitis.[82] Omalizumab inhibits binding of the IgE to the IgE receptor on the surface of mast cells and basophils. A number of case reports and uncontrolled studies demonstrated benefit of omalizumab therapy in CRS.[82–84] A randomized, double-blind, placebo-controlled trial of anti-IgE for CRS showed a small, clinically irrelevant effect of omalizumab on CRS.[85] However, this study was limited by a small number of subjects. Common side effects of

omalizumab include local reaction at the injection site, upper respiratory infections and headache. Anaphylaxis is also a potential adverse reaction of anti-IgE therapy. There was a concern for higher rate of malignancy among patients treated with omalizumab; however, recent pooled analysis of the data from 67 phase I through IV clinical trials did not suggest a causal relationship between omalizumab and malignancy.[86]

IL-5 plays an important role in eosinophil survival and maturation and thus is a significant player in the modulation of inflammatory response in the setting of allergic disease. It is no surprise that high levels of IL-5 and intense eosinophilic inflammatory response have been identified in nasal polyps. A double-blind, placebo-controlled, randomized safety and pharmacokinetic study evaluated the use of reslizumab (anti-IL-5 monoclonal antibody) in patients with grade 3 or 4 bilateral nasal polyps.[87] Patients in the treatment groups were randomized to receive a single intravenous infusion of reslizumab with the dose of 3 or 1 mg/kg depending on the group. Approximately half of the subjects in the treatment arms demonstrated improvement in the total nasal polyp score for a variable number of weeks. When comparison of responders vs. nonresponders was performed, patients with significantly higher levels of IL-5 in the nasal secretions were found to respond better to treatment. Biologic activity analysis revealed a significant decrease in blood eosinophil counts in the treatment groups; however, 24 weeks after the initial injection, a significant rebound eosinophilia was observed. Treatment with a single injection of reslizumab at 3 mg/kg was shown to be safe and well tolerated in the subjects studied. Larger studies are required to further evaluate the clinical efficacy of anti-IL-5 therapy in patients with CRS and polyps.

VASOACTIVE DECONGESTANT THERAPY

Various oral and topical decongestants are readily available to patients for relief of symptoms associated with nasal congestion secondary to ARS. Topical forms include oxymetazoline and neosynephrine, which are selective α-1 agonists; oxymetazoline is also a partial α-2 agonist. The mechanism of action is via vasoconstriction of the blood vessels. There is a concern regarding inappropriate prolonged use of these medications with subsequent complications including rhinitis medicamentosa and septal perforation. Interestingly, topical oxymetazoline was shown to decrease rhinovirus titers in volunteers inoculated with the virus.[88]

Oral preparations that are vasoactive decongestants include phenylephrine and pseudoephedrine. Phenylephrine is another α-adrenergic receptor agonist while pseudoephedrine is both an α- and β-adrenergic receptor agonist. A meta-analysis that identified studies evaluating effect of pseudoephedrine on heart rate and blood pressure found that pseudoephedrine caused a slight but significant increase in systolic blood pressure and heart rate.[89] Another sympathomimetic agent phenylpropanolamine was removed by the FDA from over-the-counter availability because of increased risk of hemorrhagic stroke in women. There are no well-controlled studies demonstrating efficacy of any of these agents in ARS or CRS.

ANTI-INFLAMMATORY ANTIMICROBIAL THERAPIES

Perhaps unrelated to their direct antimicrobial effect, certain antibacterial and anti-fungal medications reduce inflammation.[90] As discussed above, doxycycline possesses anti-inflammatory properties.

Macrolides

Macrolide antibiotics were first identified as having anti-inflammatory properties by Japanese clinicians who used it for management of a chronic inflammatory pulmonary condition called diffuse panbronchiolitis (DPB). DPB had a high mortality rate until macrolide therapy was used for patients with this disease in the mid-1980s.[91] Long-term macrolide therapy was found to be also beneficial in CRS. Immunomodulatory mechanisms induced by macrolides include inhibition of pro-inflammatory cytokines such as IL-8 and TNF-α and suppression of neutrophil migration.[92] A double-blind, randomized, placebo-controlled trial evaluating the use of long-term (3 months), low-dose macrolide in the treatment of CRS demonstrated improvements in both objective and subjective outcome measures.[93] This effect was particularly prominent in patients with low IgE levels. A prolonged course of macrolide was necessary to observe improvements and the benefit was not sustained after the cessation of therapy.

NOVEL ANTI-INFLAMMATORY THERAPIES

Many agents are known to have anti-inflammatory effects and are undergoing research in rhinosinusitis. These

include statins, resveratrol (a component of wine and fruits with inhibitory effects on influenza virus replication), vitamins, and herbal therapies (Sinupret).[94–98]

KEY POINTS

1. Rhinosinusitis is an inflammatory condition with various potential etiologies, triggering the inflammatory response. As the correct etiology is often difficult to identify, management of CRS is often directed at treating inflammation as opposed to the root cause.
2. Anti-inflammatory therapy can play a limited role in the management of acute uncomplicated rhinosinusitis. Topical nasal steroids can be used for management of ARS either in conjunction with antimicrobial therapy or alone.
3. Anti-inflammatory therapy plays a significant role in the management of CRS. Patients are frequently managed long term with topical corticosteroids with an addition of nasal irrigations, short tapers of oral corticosteroids, and long-term macrolides in selected cases.
4. Preoperative and postoperative therapies may differ based on ability to deliver topical treatments to surgically created passageways in the sinonasal cavities.
5. A clinician must not only be familiar with the side effects of prescribed treatment, but also should be able to educate patients regarding potential side effects through personal conversation by a physician, an allied health professional, another member of the staff or pre-made handouts.
6. Additional placebo-controlled studies on indications, dosing, safety and efficacy of the various anti-inflammatory therapies are warranted.

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CHAPTER

Complementary Therapy and Integrative Medicine in Sinonasal Disease

37

Roheen Raithatha, Sezelle Gereau Haddon

BACKGROUND

The NIH's National Center for Complementary and Alternative Medicine (NCCAM) defines complementary and alternative medicine (CAM) as "a group of diverse medical and healthcare systems, practices, and products that are not generally considered part of conventional medicine."[1] Alternative medicine is the use of such modalities instead of conventional medical treatments. Integrative medicine (IM) combines conventional medicine and CAM for which there is high-quality evidence of efficacy and safety.

Perhaps the best and most broadly accepted definition of integrative medicine is the one most recently developed by the Consortium of Academic Medical Centers for Integrative Medicine (CACHIM) in 2009. CACHIM consists of some 55 medical centers throughout the United States, Canada, and Mexico. The Consortium has espoused the mission "to advance the principles and practices of integrative health care within academic institutions."[2] The Consortium members provide opportunities for training in Integrative Medicine practice and research from the medical student level through residency, fellowship and postdoctoral training. Their definition is the same as the one adopted by the American Board of Integrative Medicine:

- "Integrative Medicine is the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing."[3]

The most recent attempt to canvas Americans for their usage of CAM was in 2007 with the National Health Interview Survey. An estimated 38% of Americans have used such therapies. Within those same 12 months, Americans spent $33.9 billion out-of-pocket on CAM products and services. This is approximately 11% of total out-of-pocket expenditures on health care.[3a] While statistics regarding numbers of chronic rhinosinusitis patients using such therapies is not directly available in the United States, a 2009 study looked at patient use in a rhinology clinic in the United Kingdom. A total of 65% of patients had used CAM and only 43% had informed their physicians of such use.[4] Shakeel and collaborators looked at CAM usage among patients scheduled for elective otolaryngologic surgery in a hospital in Scotland. They found that 36% of subjects had used these therapies in the previous year. The vast majority (92%) felt that the therapies were useful. Less than half (43%) of the subjects had discussed their use of these therapies with their family doctor.[5]

Rigorous, well-designed clinical studies supporting the use of CAM is generally lacking in the medical literature. As such it is often unclear whether or not therapies are effective, particularly as compared to conventional medications. Furthermore, safety profiles and drug–drug or drug–herb interactions have not been investigated. Physicians are generally unfamiliar with such treatments, and are reticent to recommend, much less encourage, their use for patients. Medical doctors are also often not knowledgeable of sources to learn more about these therapies, even if patients choose to share their use with them. Condoning or recommending use of such therapies

Table 37.1: Selected internet resources for integrative medicine

Source	*Website/link*
• Cochrane Summaries	• http://summaries.cochrane.org
• Consumer Lab	• Consumerlab.com
• NCCAM Health Topics	• http://nccam.nih.gov/health/atoz.htm
• Natural Medicine Comprehensive Database	• http://naturaldatabase.therapeuticresearch.com
• Natural Standard Database	• http://www.naturalstandard.com

can be viewed as fraught with the potential for litigation should a patient encounter an adverse effect, either from use of remedies or from deferring use of more conventional medical treatment.

Many resources exist for the naïve practitioner who would like to learn more about integrative therapies. Excellent online databases exist, some of which are included in Table 37.1.

ISSUES WITH CAM RESEARCH

There are a number of challenges to performing and interpreting research in the area of IM. Many CAM providers are not physicians (chiropractic, homeopathic, naturopathic), often utilizing techniques and tools that would be considered more experimental than evidence based by allopathic doctors. CAM also bases diagnosis and treatment on a different paradigm of healing often without any regard to the actual underlying diagnosis according to Western-based medicine. Physicians use International Classification of Diseases diagnostic codes, whereas CAM disciplines are much more individualized in both diagnosis and treatment. CAM practitioners also are concerned about getting to the root of disease, which can be different depending on the orientation of the individual IM modality.

Blinding is a large methodological issue in many areas of CAM research. How does one blind the taste of fish oils or scent of peppermint oil? Or whether or not an acupuncture needle has penetrated the skin? Thus, despite the thousands of randomized controlled trials (RCTs) in CAM, the risk of bias makes interpretation of the results challenging. To this end, Bloom et al. evaluated more than 5000 trials, but only 258 were RCTs. The main cause for rejection (>90%) was that the study was not an RCT or had no blinding. The authors concluded that the overall quality of evidence for CAM RCTs is poor but improving slowly over time, at about the same rate as that of biomedicine. Thus, most CAM services are provided without a level of evidence of benefit that is acceptable to allopathic practitioners.[6]

Much of the CAM research that relates to sinonasal issues deal specifically with the treatment of allergy. Throughout this chapter we chose to refer to these articles as many of these modalities can be considered in the treatment of sinusitis as well.

ISSUES OF LIABILITY

Legal guidelines do exist for incorporating CAM therapies into one's practice. Michael Cohen, a lawyer who has worked with IM legal issues for many years, has devised a common sense way to advise patients on its use. This algorithm is summarized in Table 37.2.[7]

INTEGRATIVE MODALITIES FOR SINUSITIS

One way to approach CAM for sinonasal disease is to look at the modalities as they are thought to work. Though some therapies will not strictly fall within such categories, with some exceptions, this approach allows one to analyze them in the way they are traditionally viewed and to incorporate them into a patient's treatment as such:

- Dietary manipulations
- Immune modulation
  - Management of the microflora
  - Herbal immune enhancers
- Antiallergy (mast cell stabilizers/leukotriene inhibitors)
- Mucolytics
- Indigenous medical systems
  - Homeopathy
  - Chinese medicine—acupuncture and Chinese herbals
- Nasal irrigants
- Vitamins, minerals, and supplements.

DIETARY MANIPULATIONS

Certain dietary interventions are frequently proposed for patients with sinusitis.[8] Among these are:

- Elimination of dairy products
- Elimination of processed sugar
- Elimination of alcohol
- Elimination of wheat products
- Food intolerance and elimination diets

Table 37.2: Potential for malpractice liability with IM therapies

Evidence supports safety but efficacy is unclear	**Evidence supports safety and efficacy**
Therapeutic posture: Tolerate with caution but monitor effectiveness closely	***Therapeutic posture:*** Recommend, but monitor
Example: Anti-inflammatory diets for sinusitis	***Example:*** Dead Sea salt nasal irrigation for rhinitis
Liability risk: Potential exists, but acceptable	***Liability risk:*** Unlikely
Evidence supports significant risk or clear inefficacy	**Evidence supports efficacy, but safety is unclear**
Therapeutic posture: Avoid use and actively discourage patient	***Therapeutic posture:*** Consider tolerating with caution and closely monitor side effects
Example: Ear candling for cerumen impaction	***Example:*** Ginkgo biloba for tinnitus
Liability risk: Probably liable	***Liability risk:*** Potential exists, but most likely acceptable

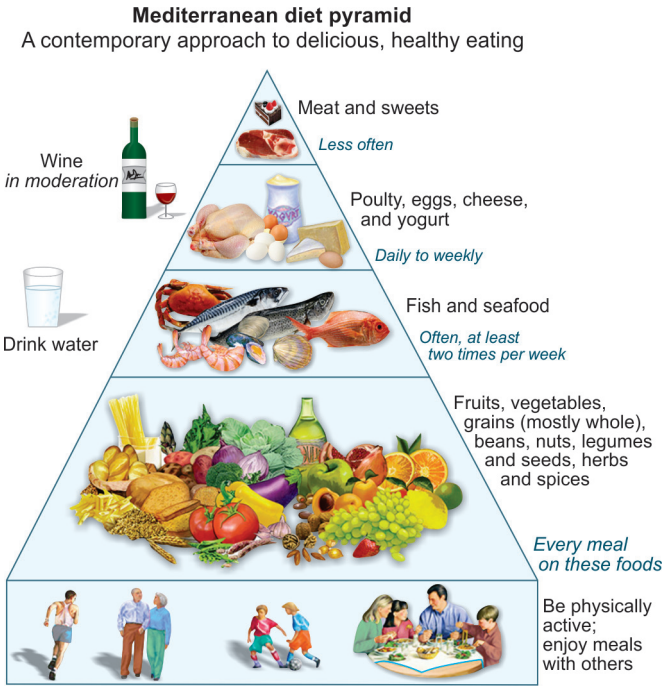

Fig. 37.1: Mediterranean diet.
Source: Redrawn from Rakel D. Integrative Medicine, 3rd edition. Saint Louis, MO: Saunders; 2012. p. 796.

- Antifungal dietary regimens
- Anti-inflammatory dietary regimens

In the absence of true food allergy, clear evidence supporting any of these interventions is lacking, and much of the data that exists refers to patients with asthma and/or allergies. Confounding variables and effect modification affects interpretation of many of these studies.[9] While there is no clear supporting evidence for elimination of dairy products, alcohol, processed sugar or wheat, there appears to be a correlation between the development of asthma and atopy and consumption of junk food in teenaged children.[10] It has also been shown that adherence to the Mediterranean diet is associated with a lower incidence of asthma in 10–12 years olds.[11] The Mediterranean diet pyramid is displayed in Figure 37.1.[12]

There is a general trend in the integrative community to attribute chronic rhinosinusitis (CRS) to an overgrowth of yeast. It is unclear if this approach is as classic allergic fungal sinusitis (AFS), or thought of as presence of fungus in the sinus cavity, or an issue of chronic systemic candidiasis. Others conjecture that the yeast itself acts as a "super-antigen," residing in the sinus cavity protected by biofilm, or in the gut, resulting in general dysbiosis.[13] Yeast- and carbohydrate-free diets are commonly recommended to patients with nasal symptoms of various sorts. These sometimes are combined with antifungal agents, such as Diflucan, Nystatin, Itraconazole, or herbal antifungals such as Candibactin BR or Candisol.

Candibactin BR is a proprietary herbal blend that contains a number of plants, including *Coptis chinensis, Berberis aquifolium, Berberine, Scutellaria baicalensis, Phellodendron chinense, Zingiber, Glycyrrhiza uralensis,* and *Rheum officinale*. While there are no human studies supporting its use for this purpose, some of its components have been shown in vitro and in animal studies to have activity against a number of types of yeast. Berberine in particular has been shown to have strong anti-Candida activity and appears to have a synergistic effect with Fluconazole.[14,15]

CRS has been associated with both TH1 and TH2 inflammatory patterns and production of arachidonic acid.[13] One could argue that foods that seem to inhibit these reactions are beneficial for patients with rhinosinusitis. A list of food inhibitors of arachidonic acid production is included in Table 37.3.[16] Intake of such foods is encouraged in patients with recurrent sinonasal symptoms.

Table 37.3: Food inhibitors of arachidonic acid (AA)

Onions
Apples
Turmeric
Curcumin
Rosemary
Red pepper
Capsaicin
Ginger

Table 37.4: Anti-inflammatory diet

- Total daily dietary protein to ≤10–15%
- Use plant proteins preferentially
- Eliminate milk and dairy, possibly gluten
- Include natural antioxidants – fruits, vegetables
- Eat organic when possible
- Eliminate saturated fats and transfatty acids
- Increase intake of omega 3 essential fatty acids

Anti-inflammatory diets are thought to generally reduce inflammation in the body. They are based on fresh fruits and vegetables, beneficial dietary fats, whole grains and plant based proteins. Anti-inflammatory diets are proposed for a number of conditions thought to be related to chronic inflammation, including atopy. An example of one such diet is outlined in Table 37.4.

IMMUNE MODULATION WITH CAM THERAPIES

Hundreds of botanicals are claimed to have immunomodulatory effects, but clear evidence that they are able to regulate immunological responses against defined antigens is lacking. While one can measure changes in white blood cell function in response to a product, it is impossible to know what that does to the system as a whole, or that the specific effect is the one desired therapeutically. In fact, one might argue that allergy, atopy, chronic inflammation, and infection are the result of an already over-stimulated immune system.

Screening botanicals for immunomodulatory activity after oral ingestion is difficult due to unknowns such as bioavailability (depending in part on issues such as formulation and concomitant food intake), the amount of active ingredient in the botanical selected, optimal dose, and appropriate assay.[17] Many herbal remedies are combination products, and it is unclear which product or individual component within the product imparts the desired effect.

Of those herbal preparations reviewed, those included had either the clearest in vitro or in vivo clinical evidence supporting efficacy, or are commonly recommended in the integrative community. Appropriate dosages for both adults and children and common side effects are reflected in Table 37.5. Note that for many of these products pediatric dosages are unknown.

IMMUNE ENHANCEMENT

Management of the Microflora

Probiotics

Probiotics are defined as live microbial food ingredients beneficial for health. By definition they are safe for ingestion, stable to acid and bile, and able to adhere to the intestinal mucosa. It is also important that their beneficial physiological effects have been proven scientifically.[18]

There are thought to be two distinct effects of oral probiotics on immune responses. One is the suppression of an undesired immune response, such as allergic and autoimmune reactions. The second is a generalized immunostimulatory effect. These two effects are thought to be achieved via a variety of mechanisms, some via direct action on the mucosa of the gut, others by absorption and interaction with various cell types in immune competent tissues. Overall, these actions are outlined in Figure 37.2.[19]

Interestingly, it is also clear that dendritic cells from different anatomical sites respond differently to specific probiotics, and that individual probiotic strains affect different responses depending on the site in which their effect is expressed (i.e. different in the gut than the spleen). In addition, these organisms are in constant surveillance, able to monitor their environment, and may alter their behavior and characteristics depending on host characteristics.[20] Phagocytosis, in response to probiotics, occurs differently in allergic versus healthy subjects. For example, probiotics help healthy individuals to mount an immunostimulatory effect, in response to antigens, whereas in allergic subjects there is more of a downregulation of the immune response.[21] Therefore, the same probiotic bacteria appear to have the ability to respond directly to the immunologic state and needs of the host.

These beneficial bacteria are most frequently *Lactobacillus* or *Bifidobacterium* species. Many species already

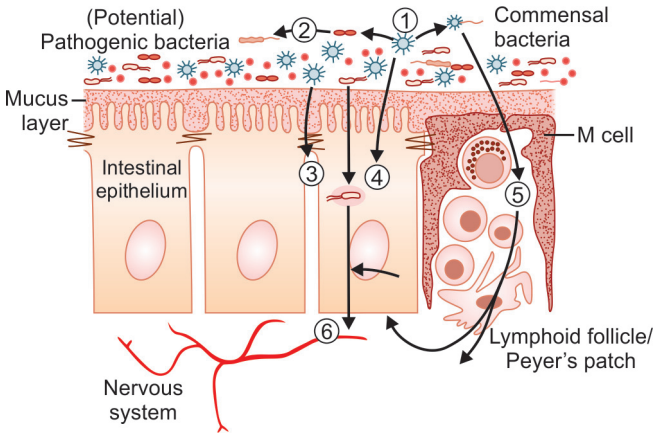

Fig. 37.2: Proposed mechanisms of action of probiotics.

1. Direct antibacterial action on potential pathogens
2. Production of local and systemic secretory IgA
3. Enhancement of intestinal barrier function
4. Interaction with intestinal epithelial cells with modulation of the maturation and phenotype of dendritic cells.
5. Uptake of organisms by M cells or directly by dendritic cells to coordinate antigen presenting cells and T cell responses.
6. Interaction with the enteric parasympathetic nervous system which can modulate efferent vagal discharge, releasing neuropeptides that inhibit macrophage activation and modulating systemic inflammatory responses.

Source: Redrawn from Rakel D. Integrative Medicine, 3rd edition. Saint Louis, MO: Saunders; 2012. p. 799.

exist in human commensal microbiotia. Human monocytes and mononuclear cells incubated with certain lactobacilli show a downregulation of the TH2 response and shifting toward TH1 including increased production of IL-12, IL-18, and IFN-g.[22]

Daily consumption of a fermented dairy product containing *Lactobacillus casei* increased specific antibody responses to influenza vaccination in nursing home subjects.[23] A study of Finnish children in day care centers who consumed *Lactobacillus rhamnosis GG* enriched milk for 7 months in winter had 17% fewer upper respiratory tract infections compared to controls.[24] A reduction in the common cold and enhanced T suppressor cells (CD8+) and T helper cells (CD4+) was noted in patients supplemented for 3 months during the winter and spring with *Lactobacillus gasseri, Bifidobacterium longum,* and *Bifidobacterium bifidum*.[25]

Some common in patients with allergies and/or sinus disease probiotics that have been used for immune modulation include:

- *Lactobacillus strains*:
  - Acidophilus
  - Bulgaricus
  - Casei
  - Plantarum

Table 37.5: Dosages and side effects of selected herbals and supplements

Product	*Daily dose - adult*	*Daily dose-pediatric (4 and older)*	*Formulation comments*	*Possible side effects*
1,8-cineol	200 mg TID	Not recommended for children	Eucalyptol	Heartburn, gastritis, headache, hypoglycemia, cytochrome P450 interactions
Andrographis Paniculata	60-300 mg daily standardized to 4-6% andrographolide	200 mg per day standardized to 11.2 mg andrographolide		Allergy, infertility
AHCC	up to 3 g daily	Not recommended for children		Nausea, diarrhea, bloating, headache, fatigue, and foot cramps
Bromelain	200-400 mg TID	Not recommended for children		GI upset and diarrhea, cross allergenicity with wheat flour, celery, papain, carrot, fennel, cypress , ragweed and grass pollen, potentiates the effects of Amoxicillin and Tetracycline.
Butterbur	50-75 mg of standardized extract BID	6-9 years old 25 mg BID-TID > 9 years old 50 mg BID-TID		Hepatotoxicity, cross allergenicity with ragweed pollen

Contd..

Contd..

Product	*Daily dose - adult*	*Daily dose-pediatric (4 and older)*	*Formulation comments*	*Possible side effects*
Candibactin AR	One softgel TID daily	Not recommended		Nausea, vomiting, diarrhea, dizziness, wheezing, high blood pressure, allergic reactions, hepatotoxicity, cross reactivity with ragweed allergy
Dead Sea Salt	1.8% irrigation 2 sprays/ nostril TID daily	Same		Nasal mucosal irritation (burning , stinging, or dryness
Eleutherococcus senticosus	2–3 g whole herb or 300–400 mg of extract	Not recommended		Can elevate Digoxin levels
Esberitox	3 tabs TID	4-6 years old 1-2 tabs TID 6-12 years old 2 tabs TID		Avoid in patients with autoimmune disorders, or who have known allergy to the components.
Kan Jang	60–300 mg of andrographolide	2 pills TID or standardized to 30 mg andrographolide	Standardized extract of Andrographis paniculata SHA-10, 85 mg, containing 5g. 25 mg andrographolide and deoxyandrographolide with extract of Eleutherococcus senticosus 9.7 mg.	allergy, infertility
Larix arabinogalactan	3-9 gm of powdered extract daily	Please consult resource for proper dosage for preparation used		Bloating and flatuence, Can intefere with immunosupressive medications
N-acetylcysteine	600 mg BID	Can be used as young as one month old. Please consult resource for proper dosage for route of administration		Nausea, vomiting, abdominal pain, constipation, urticaria, bronchospasm in asthmatics, Rarely, generalized urticaria with mild fever, sulfhemoglobinemia, headache, hypotension, rash, and hepatotoxicity, allergy
Panax Ginseng	1–2 g of whole herb, or 200 mg extract standardized to 4% to 7% ginsenosides	Not recommended		Insomnia, blood pressure and cardiac abnormalities, headache, loss of appetite, diarrhea, itching, rash, dizziness, mood changes; avoid in patients on coumadin, or patients with autoimmune disease or breast cancer
Panax quinquefolium (Cold FX)	400 mg daily × 4 months	Not recommended		GI, CNS and CV adverse effects similar to placebo
Pelargonium Sidoides	30 gtts TID of standardized extract	20 gtts tid of standardized extract		Abnormal bleeding, allergy, GI upset
Phytocort	3 caps BID-TID	n/a		Weight gain, GI upset

Contd..

Contd..

Product	*Daily dose - adult*	*Daily dose-pediatric (4 and older)*	*Formulation comments*	*Possible side effects*
Quercitin	400-500 mg TID	n/a		Do not give concomitantly with quinolone antibiotics as can lessen effects
Resist Aid	1–2 "shots" daily	1 shot daily	Proprietary blend combines 1500 mg of Larch arabinogalactan with Inulin and 120 milligrams vitamin C	Abdominal cramping
Reboost	1-2 puffs TID	Same		
Sinupret	2 tablets TID	check resource for children's formulation dosage		GI side effects and allergic reactions
Tinospora cordifolia	300 mg TID	n/a	Tinofend	Nasal pain, headache, hypoglycemic effects, might intefere with immunosupressive drugs
Urtica dioica	300 mgs leaf extract 3–7 × daily	n/a		Hypotension, hypoglycemia, diuretic effect, can affect androgen and estrogen metabolism
Xylitol	12 mg dissolved in 240 mL water; 120 mL per nostril once daily for 10 days	Same		Sweet taste, sore throat, can intefere with absorption of copper
Zinc	4.5-24 mg every 1-3 hours for 3-14 days.	Check resource for children's formulation dosage		Bad taste, nausea

  - Rhamnosis GG
  - Reuteri
  - Gasseri
- *Bifidobacterium strains*:
  - Lactis
  - Longum
  - Bifidum

Dosage should be 6–10 billion colony-forming units daily.

Herbal Immune Enhancers

Sinupret

Sinupret is a trademarked German herbal preparation for treatment of sinusitis that is available in either liquid or tablet form. It has gained popularity in the United States and contains five herbal extracts: *Gentiana lutea*, root; *Primula veris*, flower; *Rumex* sp., herb; *Sambucus nigra*, flower; *Verbena officinalis*, herb. A number of studies have examined its use for rhinosinusitis. In a study performed in 1984, Sinupret was compared to placebo for patients with maxillary and frontal sinusitis, confirmed by sinus X-rays and physical examination. Results showed improvement in 12 of 16 patients, but it is unclear how such improvement was documented, and statistical significance was not reported.[26]

Other trials in the literature compare Sinupret as an adjunct to antibiotics and/or decongestants in patients with acute rhinosinusitis. Ninety patients were randomized to receive Doxycycline alone, Doxycycline plus Sinupret, or Esberitox. Radiographic improvement of sinusitis was used as an end point of treatment. Both herbal preparation groups had greater statistically significant improvement than with antibiotics alone.[26] A second such study showed similar trending but failed to reach statistical significance.[27] More recent studies have demonstrated in vitro antiviral activity of both dry extract and oral drops against a variety of common upper respiratory pathogens.[28]

Esberitox

Esberitox is another herbal immune enhancer containing the herbs *Thuja occidentalis, Baptisia tinctoria,* and *Echinacea*

angustifolia. Native Americans traditionally use these herbs for various immune disorders. This product has been shown to activate macrophages and is thought to nonspecifically induce immunoglobulin production.[29] In patients with chronic bronchitis, Esberitox has been shown to shorten time to improved FEV 1 when combined with macrolide antibiotics, as compared to placebo.[30]

Mushrooms

Certain mushrooms, particularly of the *Shiitake* and *Maitake* species have been investigated for many years for their ability to upregulate various immune factors. The β-glucans are thought to be responsible for much of this effect. β-glucans are a group of glucose polymers, found in the cellular structure of fungi, algae, and some bacteria and plants. They have the ability to stimulate cells of the innate human immune system and have been shown in vivo to have antimicrobial properties against viruses, bacteria, and fungi.[31]

Active Hexose Correlated Compound

Active hexose correlated compound (AHCC) is a food product widely used in Japan. It is formulated from shiitake and other mushrooms fermented in rice bran. In addition to activating NK cells and macrophages, an increase in circulating dendritic cells has also been noted.[32] AHCC enhances CD4(+), CD8(+), and T-cell immune responses (IFN-γ and TNF-α) in persons 50 years and older taking 300 mg twice daily for at least 30 days. This effect remained for up to 30 days after discontinuing treatment with this compound.[33] There have been no studies examining its use specifically in patients with sinusitis. Human studies have confirmed its safety, even with intraperitoneal administration, though it induces CYP450 2D6, which could decrease the activity of any drugs taken concomitantly.[34,35]

Ginsengs

Three different herbs are commonly called ginseng: Asian or Korean ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*), and Siberian ginseng (*Eleutherococcus senticosus*). Ginseng is considered in the class of herbs known as adaptogens. Adaptogenic herbs are thought to help the body adapt to stresses of various kinds, cause no side effects, and be effective in treating a wide variety of illnesses, regardless of their origin.[36]

P quinquefolius seems to have some efficacy for fighting colds and flu. Cold FX, a proprietary extract from North American ginseng root contains mainly poly-furanosyl-pyranosyl-saccharides, unlike other Asian or American ginseng products, which contain more polysaccharides and ginsenosides. Studies in mice show Cold Fx is capable of enhancing the production of splenic lymphocytes. It has also been shown to increase the production of interleukin IL-i, IL-6, TNF-α, and nitric oxide from peritoneal macrophages in vitro, and to increase the production of mouse serum Ig G levels.[37] Two double-blind, placebo-controlled studies support the use of this product taken at 400 mg daily for 4 months to prevent the common cold.[34,38]

E senticosus, while loosely related to this family of herbs, is commonly referred to as Russian or Siberian ginseng. There are several double-blind studies that support its use in conjunction with the herb Andrographis for treatment of upper respiratory tract infections (URTIs).[39,40]

Andrographis Paniculata

A paniculata is a shrub used in India, Asia, and Scandinavia for immune enhancement, and is known as "Indian Echinacea." It is unclear which chemical constituents of this herb account for its therapeutic activity, but it has been commonly attributed to the andrographolide and arabinogalactan proteins.[41] A 2004 meta-analysis found seven double-blind, controlled trials, for a total of 896 participants, evaluating the use of a proprietary *A. paniculata* extract (Kan Jang) for the treatment of acute respiratory infections. The combined results suggest that this extract is more effective than placebo for cold symptoms.[42,43]

The effect of Kan Jang appears to be particularly helpful for nasal congestion and rhinorrhea, though improvements have also been noted in sore throat, fatigue, and earache.[44] As with many herbal therapies, Andrographis should be started within 24-72 hours of onset of symptoms.[45]

Larix Occidentalis

Arabinogalactan is a branched polysaccharide extracted from the bark of the larch (*Larix occidentalis*) tree. This substance has been shown to stimulate innate immunity by increasing NK cell cytotoxicity and enhancing the phagocytic capacity of macrophages and monocytes in cultured human blood cells.[46] A total of 199 patients were examined in a recent double-blinded, placebo-controlled randomized trial examining a proprietary Larch blend for symptoms of the common cold. During the study period, participants received 4.5 g of this blend (Resist Aid) versus placebo. Using a self-reported infection rate and

symptom diary, it was documented that study subjects had statistically significant less incidences of URTIs and a decrease in symptoms during such attacks.[47] Larix has also been shown to increase IgG responses to the 23-valent pneumococcal vaccine.[48] No significant side effects were noted.

Pelargonium Sidoides

Pelargonium sidoides is a South African plant, the roots of which are used to formulate the herbal compound EPs7640, marketed as Umckaloabo. Its effect on URTIs is thought to occur through a number of actions. In vitro studies suggest that polyphenols in Umckaloabo can stimulate release of TNF and interleukin activity, resulting in interferon production and increased NK cell activity.[49] This product can also promote phagocytosis and decrease adhesion of bacteria to tissues.[50] In addition, *P sidoides* is thought to have mucolytic effects, improve cilia function, and increase production of secretory IgA.[51] It is used for the treatment of self-limited URTIs.

The Cochrane database examined eight randomized clinical trials of *P sidoides* with acceptable methodologies. Two trials showed that *P sidoides* was effective in relieving all symptoms, in particular cough and sputum production in adults with acute bronchitis. Similarly, *P sidoides* was effective in resolving symptoms of acute bronchitis in 819 children studied, but the evidence was considered low quality in both age groups. In acute sinusitis and the common cold, *P sidoides* was effective in resolving all examined symptoms including headache and nasal discharge in adults when taken for an extended time period. There was no valid data for treatment of other acute URTIs.[48,52]

ANTI-ALLERGY, MAST CELL STABILIZERS, LEUKOTRIENE INHIBITORS

Antiasthma Herbal Medicine Intervention

Antiasthma herbal medicine intervention (ASHMI) is an extract of three Chinese herbal medicines: LingZhi (*Ganoderma lucidum*), Ku Shen (*Sophora flavescentis*), and Gan Cao (*Glycyrrhiza uralensis*). It has received FDA investigational new drug approval and is currently in clinical trials in the United States. In mice, it has been shown to decrease allergen-specific IgE and Th2 cytokine levels and also to increase IFN-γ. These changes persist at least 8 weeks posttherapy.[53] In a trial of 51 children with allergic rhinitis (aged 5–14 years), subjects were randomized to receive either inhaled corticosteroid and placebo or steroid and ASHMI. The steroid with ASHMI group showed a greater reduction in total IgE, serum eosinophilic cationic protein, and significantly increased IFN-γ and serum cortisol levels compared to steroid plus placebo. Symptoms were also significantly lower in the experimental versus the control group.[54]

The herbal product currently marketed in the United States known as Phytocort contains similar ingredients along with noni fruit. Dosage is three capsules TID or twice daily for maintenance.

Butterbur (*Petasites hybridus*)

The leaves and rhizomes of the butterbur plant contain a form of eremophilan-type sesquiterpenes known as petasin. They are pharmacologically active and exist in iso and neo isomers and their sulfuric analogs. These molecules have been shown in vitro to inhibit leukotriene synthesis, histamine binding, intracellular calcium mobilization, phospholipase activity and degranulation of certain inflammatory mediators. Petasins have been shown in vivo to inhibit Th2 cytokines Il-4 and Il-5, thereby affecting allergic airway inflammation and hyper-responsiveness.[55]

In a randomized, double-blind parallel group of 125 participants, butterbur was just as effective as cetirizine for ocular and nasal allergy symptoms.[56] The subjects were scored on number of allergic symptoms, including sneezing, rhinorrhea, itchy nose, and congestion. Although symptom-specific outcomes were not individually examined, overall, butterbur's effects were similar to those of cetirizine. There were no significant side effects noted with butterbur, although the cetirizine group noted an increased incidence of drowsiness.

A specific preparation of Butterbur, Ze339 used for 2 weeks in either low (16 milligrams of Petasin) or high (24 milligrams of Petasin) dose has been shown to have a dose-dependent effect on symptoms of allergic rhinitis, both superior to placebo. There was no significant difference in reported side effects for all 3 groups.[57] Care should be taken in patients with ragweed allergy, as there is potential cross reactivity. Preparations should be free of pyrrolizidine alkaloids which are hepatotoxic.

Quercetin

Quercetin has a number of properties that make it ideal for use in patients with recurrent sinusitis. In vitro it exhibits anti-inflammatory activity via inhibition of cyclooxygenase and lipoxygenase, thus potentially a regulator of leukotriene and prostaglandin metabolism. In addition, in vitro studies utilizing human nasal epithelium have shown that quercetin is able to stabilize mast cells and inhibit the release of histamine, even after IgE activation. It does so more effectively than cromolyn sodium.[58] It has been shown to decrease the frequency of URTIs in elite athletes, without a definitive change in immunomodulators being demonstrated.[59]

Quercetin is a dietary flavonoid that occurs abundantly in foods such as red wine, tea, onions, kale, tomatoes, broccoli, green beans, asparagus, apples, and berries, but absorption from food sources is highly variable.[60] Most studies have used 400–500 mg two times daily. While no side effects have been reported, quercetin may lessen the effects of quinolone antibiotics, and these should not be taken simultaneously.

Nettles (*Urtica dioica*)

Nettles are micronutrient dense herbs that have been shown in vitro to prevent mast cell degradation and inhibit COX enzymes.[61] A double-blind randomized study of 69 participants noted symptomatic improvement in allergy symptoms slightly more than placebo.[62] Notably, stinging nettles have traditionally been used as a food in pregnant and lactating women and are used in some cultures as a lactogogue. As their safety in pregnancy and breastfeeding has not been established, their use in medicinal form is not recommended at this time. In order to be most effective, nettles should be started at the first symptoms of allergy.

Tinospora Cordifolia

Widely used in Ayurveda (traditional Indian medicine) for fever, cough, and asthma, *Tinospora* is commonly called guduchi. While this herb has many immunostimulatory effects, in allergic rhinitis it is thought to work by inhibiting mast cell degranulation. It contains an α-glucan polysaccharide that can activate NK, T and B cells, thus inducing production of ILs-1,6,12,18.[63] In a randomized, placebo-controlled trial of 75 subjects with symptoms of allergic rhinitis, a significant reduction in sneezing, nasal discharge, obstruction, and pruritus was noted in the *Tinospora* group versus controls. There was also a statistically significant decrease in eosinophil and neutrophil, goblet cells in nasal smears, versus an increase in these factors in the control group.[64] Three hundred milligrams of the aqueous stem extract is typically used for up to 8 weeks. There is some concern that it can produce hypoglycemic effects, so it should be used with caution in patients on medications to lower blood sugar.

MUCOLYTICS

Bromelain

Bromelain is derived from the stem and the fruit of pineapple and is composed of a mixture of various thiol endopeptidases and other enzymes such as phosphatase, glucosidase, peroxidase, cellulase, escharase, and several protease inhibitors. In vitro and in vivo studies demonstrate that bromelain exhibits various fibrinolytic, antithrombotic, and anti-inflammatory activities. In vitro experiments have shown that bromelain has the ability to modulate surface adhesion of molecules to T cells, macrophages, and natural killer cells and that it can induce the secretion of IL-1β, IL-6, and TNF-α.[65] It inhibits prostaglandins and serves as a mucolytic and anti-inflammatory.[66] A 2005 German study did demonstrate statistically significant faster recovery in children with sinusitis treated with bromelain compared to other therapies.[67]

N-acetylcysteine

The route of administration might affect the mucokinetics of N-acetylcysteine (NAC). Nebulized, NACs reputation as a mucolytic stems from the ability of its sulfhydryl group to bind to and cleave disulfide cross-linkages, making smaller, less viscous components.[68] A 2000 meta-analysis of double-blind, placebo-controlled trials of patients with chronic bronchopulmonary disease showed a statistically significant difference compared to placebo when used for at least 3 months.[69] Given orally, NAC may act as an antioxidant, as it is required for glutathione synthesis, which protects against free radical damage.[70] In a randomized, placebo-controlled, double-blind clinical trial of 262 Italian seniors, 600 mg of NAC taken twice daily for 6 months significantly decreased the frequency (51% vs 29%) and severity of influenza-like episodes.[71]

Volatile Oils

A number of essential and volatile oils have been suggested as mucous thinners, particularly in cough and cold

preparations. Very few of them have been well researched, but traditional use is widespread. Eucalyptol (1,8-cineol) has been investigated in a double-blind, placebo-controlled study examining steroid-dependent asthmatics. Daily prednisone requirements were decreased 36% with eucalyptol use compared with a 7% decrease with placebo.[72]

OTHER MODALITIES

Acupuncture

For certain world populations, acupuncture remains a mainstay for treatment of sinusitis. A 2006 systematic review of CAM for rhinitis and asthma published in the *Journal of Allergy and Clinical Immunology* argues that the majority of studies on acupuncture and allergic rhinitis and were not randomized, controlled, or descriptive.[73]

Some studies do support the use of acupuncture for nasal symptoms. In 2009, a randomized, placebo-controlled study by Fleckenstein et al. examined acupuncture versus placebo electro-acupuncture for a number of parameters associated with allergic rhinitis: nasal obstruction, rhinorrhea, sneezing, postnasal drip, itching, watery eyes, headache, ringing or popping sensation in the ears, which they termed "nasal sickness score." There was a significant difference in the treatment versus placebo group, but the total number of participants in the study was small (24 total). Also, direct measurement of nasal patency using acoustic rhinomanometry failed to show a post-treatment difference in either group.[74]

In a study of over 200 participants, acupuncture versus sham acupuncture versus no acupuncture was compared looking at certain nasal symptoms including nasal obstruction, rhinorrhea, sneezing, and itching. Other quality of life (QOL) issues were also assessed. In this study, sham acupuncture consisted of light acupuncture at non-acupuncture points. The acupuncture groups received treatment three times weekly for 4 weeks. Differences were noted between all three groups in the nasal symptom scores, with the acupuncture group having the most significant change as compared to the sham and non-acupuncture group. There was no difference in the QOL parameters between the acupuncture and sham acupuncture group other than sleep, but there was a significant difference between the acupuncture and nonacupuncture group on all study parameters.[75]

In a study of children with sinusitis, Ng et al. studied 72 children ages 6–20 years, randomized to receive either acupuncture or sham acupuncture for 8 weeks. During both the treatment period and the 12-week follow-up period, the acupuncture group reported significantly better daily rhinitis scores and more symptom free days. There were, however, no significant differences found in use of relief medication, nasal or blood eosinophil counts, or serum immunoglobulin E levels. None of the benefits persisted beyond 10 weeks.[76] Xue et al. found similar results in a study of 30 adults in a randomized, placebo-controlled crossover study.[77] These studies suggest that acupuncture could be effective in relieving SAR symptoms, but treatment duration and frequency need to be further examined.

In one of the few studies that look at acupuncture specifically for sinusitis, Rossberg et al. performed a randomized, single-blinded three-armed study of patients with CT-documented mucoperiosteal thickening and symptoms of sinusitis. Patients were randomized to one of three study arms: 2–4 weeks of conventional medication (with antibiotics, corticosteroids, nasal saline irrigations, and local decongestants [$n = 21$]), 10 treatments with traditional Chinese acupuncture ($n = 25$), or 10 treatments with sham acupuncture (minimal acupuncture at nonacupoints [$n = 19$]). Results included documented changes in CT scan, reported nasal symptoms, rhinorrhea, midfacial headache, nasal congestion, frontal headache, anosmia, and generally feeling well. Other QOL issues were also examined. Radiographic confirmation of improvement of sinusitis was seen only in the conventional group. There were other signs of improvement in symptoms over 4 weeks in all three groups. Four-week changes in symptom scores showed a nonsignificant difference between the conventional medicine and the sham group, and less difference between the conventional medicine and the traditional Chinese acupuncture groups. No differences were noted between the groups after 12 weeks or 12 months which the authors conjecture could indicate a lack of long-term effect of treatment.[78]

The evidence to date does not strongly suggest including acupuncture alone as a treatment for chronic sinusitis. It is important to note that traditional Chinese medicine is meant to be a medical system, combining not only acupuncture but herbs, dietary interventions, massage and movement, such as Qi Gong or Tai Chi. It is also important to understand that study design in acupuncture is fraught with issues of randomization, how the diagnosis is formulated, what constitutes placebo, type of acupuncture performed (sham versus electro-acupuncture versus light acupuncture versus none for controls), which points are included, etc. Because it is such an individualized form of treatment, it is difficult to formulate appropriate clinical studies.

Homeopathy

Homeopathy is based on the principle of "similitude," or like cures like and the nanopharmacology of "ultrahigh dilutions," where the more dilute the preparation, the more potent.

Samuel Hahnemann, considered by most to be the father of homeopathy, self-administered cinchona bark, and reported symptoms of malaria. Hahnemann collected and administered a number of such substances and recorded the symptoms that resulted. This process, in homeopathic medicine, is known as "proving." Today, homeopathic formulations use these same substances, macerated with alcohol, producing what is known as a "mother tincture." One portion of this tincture is then diluted in 99% alcohol, shaken a certain number of times, to formulate what is known as a 1C dilution. At the 12C level, the substance has been diluted to a solution of 10^{-24}. Thus by Avogadro's number it is impossible for there to be any molecules of the original substance in the remedy. This preparation is then administered as medicine according to homeopathic principles.

While it can be argued that homeopathic remedies are merely placebo, Linde et al. published a meta-analysis in the Lancet, which showed that the odds ratio was 1.66 that the effects were due to placebo alone.[79] The authors conclude that while it is unlikely that all the effects of homeopathy can be accounted for by placebo effect, there is insufficient evidence to support that it works for any single clinical condition. A 2003 review examined some 93 randomized or double-blind, controlled trials for efficacy of homeopathy verses placebo. Hayfever and upper respiratory tract infections were among eight conditions for which homeopathy appeared to have a positive effect.[80]

Homeopathy can be used in low or high dilution, as a single remedy, or in combination. Of the single remedies utilized for allergic rhinitis, *sulfur, calcarea carbonica, lycopodium, pulsatilla, silicea, arsenicum album, and Nux vomica* were the most frequently mentioned products that demonstrated clinical success.[81]

Some combination products are noteworthy. A French homeopathic remedy, L52 containing *Eupatorium perfoliatum, Aconitum napellus, Bryonia alba, Arnica montana, Gelsemium sempervirens, Cinchona, Belladonna, Drosera,* and *Senega* showed promising results compared to placebo in a double-blind study examining its use for symptoms of upper respiratory tract infection.[82]

Three combination products marketed here in the US deserve mention. *Euphorbium*, currently sold under the trade name Reboost, has been shown to decrease symptoms of rhinitis.[68] An in vitro study using virus plaque reduction assays showed its antiviral activity against RSV and HSV-1. A minimal antiviral effect was also noted against influenza A virus and human rhinovirus.[83] Similarly, a nasal spray for allergic rhinitis, *Luffa compositum*, has shown efficacy when compared to Cromolyn sodium. Another product, marketed as Grippheel, was examined in a multicenter, observational cohort study of patients with mild viral URTIs. Results suggested equivalent effectiveness of homeopathy and conventional medications.[84]

NASAL IRRIGANTS

Dead Sea Salt Spray (Lavi)

Hypertonic saline has been shown to provide a greater improvement in mucociliary clearance, as compared to normal saline. This is due to the fact that hypertonic saline is a mildly alkaline solution, and thus, keeps mucus in sol phase and thereby reduces the mucociliary transit time. Its most commonly reported side effect is nasal mucosal irritation.

Dead Sea salt (DSS) solutions have long been used to treat various dermatologic conditions (like allergic dermatitis, atopic dermatitis, and psoriatic dermatitis) based on their observed anti-inflammatory properties. DSS solutions differ from regular saline solutions with regards to their unique mineral content (Ca, K, Br, Zn, Mg). Magnesium salts, which comprise 35% of DSS solutions, have the ability to bind water, enabling them to influence epidermal proliferation/differentiation and to enhance permeability barrier repair. Thus, it has been shown that skin bathed in the Dead Sea (or DSS solutions) demonstrates decreased inflammation, increased hydration, and decreased redness.[85]

Prior studies have shown the value of DSS in the treatment of allergic rhinitis or has shown its superior effectiveness compared to hypertonic saline alone.[86,87] A recent study by Friedman et al. compared DSS irrigations versus hypertonic saline plus fluticasone. Patients were included if they had a confirmed diagnosis of CRS based on the Rosenfeld criteria and nasal endoscopy findings. They were then blinded to either 1.8% DSS solution (2 sprays/nostril three times daily) or 1.8% hypertonic

saline/fluticasone. Patients completed a SNOT-20 questionnaire and University of Pennsylvania Smell Identification Test (UPSIT) at their initial visit as well. Upon their return at 4 weeks following daily treatment, patients underwent repeat nasal endoscopy, UPSIT, and SNOT-20. The post-treatment SNOT-20 scores between the two groups was significantly reduced from baseline in both cases; however, was not statistically different between the two treatment groups, thus proving the efficacy of DSS solutions.[88]

Given that DSS is well tolerated as an intranasal spray, it should be considered as therapy for CRS given its effectiveness compared to a topical intranasal steroid and hypertonic saline solution.

Xylitol (Xlear)

Xylitol is a five-carbon sugar alcohol that has been show to enhance the body's innate bactericidal mechanisms. The idea of the therapeutic role of xylitol in chronic rhinosinusitis comes from basic research on the airway surface liquid (ASL), which coats the apical surface of airway epithelia and is known to contain multiple antimicrobial agents like lactoferrin and lysozyme.[89] It has been shown that in respiratory epithelium affected by inflammation, irritation, and CF, the ASL chloride concentration is higher than normal.[90] Increasing chloride concentrations causes the antibacterial properties of normal ASL to diminish. When xylitol has been applied to CF respiratory epithelium, it has been able to lower the ASL chloride con-centration to values seen in normal samples. Moreover, common airway pathogens in CF (*Pseudomonas aeruginosa, Staphylococcus aureus*, coagulase-negative *Staphylococcus,* and *Staphylococcus saprophyticus*) were unable to utilize the xylitol for growth.[89] In the same study, colony counts of *S aureus* were significantly reduced with xylitol sprays as compared to saline.

A recent prospective, randomized, double-blinded, controlled crossover pilot study[91] was undertaken to compare xylitol versus saline irrigations in the management of chronic rhinosinusitis in patients who had previously undergone endoscopic sinus surgery. SNOT-20 and visual Analog scores (VAS) were the primary outcome measures. There was a statistically significant decrease in SNOT-20 scores in the xylitol group as compared to saline group; however, the VAS remained unchanged. Xylitol as a spray is very well tolerated. One out of 20 subjects reported transient stinging, but it did not cause the patient to stop using the spray. Further studies with longer treatment courses and more subjects, however, will be needed to further delineate these findings, but this study proves that xylitol nasal sprays may have a role in the future.

The dose of xylitol used was 12 mg dissolved in 240 mL water. 120 mL was then irrigated into each nasal cavity once a day for 10 days total.

VITAMINS, MINERALS, AND SUPPLEMENTS

Omega-3-Fatty Acids

Fish oil contains eicosapentaenoic and docosahexaenoic acids, which are omega-3-polyunsaturated fatty acids.[92] They have anti-inflammatory effects and there is a link between declining consumption of them and a rise in the prevalence of allergic diseases.[93] This was shown as maternal perinatal consumption of fish oil and omega-3-polyunsaturated fatty acids has been postulated to prevent the development of allergic disease in infants. Recent evidence has also shown that the intake of omega-3 polyunsaturated fatty acids may be associated with a reduced prevalence of allergic rhinitis.[94]

Selenium

A previous study showed that blood samples from 44 children undergoing tympanostomy tube placement had lower levels than adults of eicosapentaenoic acid, vitamin A, and selenium.[95] Selenium is a trace metal that is a component of glutathione peroxidase, which decreases reactive oxygen species.[96] A recent study[95] treated four pediatric patients with chronic/recurrent sinusitis with lemon-flavored cod liver oil and a children's multivitamin (mineral with selenium). Three out of four patients had a positive response with decreased sinus symptoms, fewer episodes of acute sinusitis, and fewer doctor visits. This was a small, open-label, dose-titration study. Thus, a definitive, large, well-controlled study will need to be performed before any definitive conclusions can be made.

Vitamin D

Cholecalciferol is the naturally occurring form of vitamin D and is obtained from dietary sources or from 7-dehydrocholsterol (7-DHC). 7-DHC absorbs ultraviolet B rays, which causes it to be transformed to cholecalciferol. Calcidiol (25-hydroxyvitamin D) is a prehormone that is made from cholecalciferol and is what is tested when

measuring vitamin D blood levels. Calcitriol (1,25-dihydroxyvitamin D) is made from calcidiol (mainly in the kidneys) and is the active form of vitamin D.[97]

Helper T1 (Th1) and Th2 cells are direct targets of calcitriol. Activation of CD4+ T cells results in a fivefold increase in vitamin D receptor expression, enabling calcitriol to regulate at least 102 identified genes.[103,104]

There have been multiple studies showing the importance of vitamin D in asthma and allergic rhinitis. One showed a positive correlation between vitamin D deficiency in individuals with asthma as compared with control individuals.[98] Another showed that allergic rhinitis increased with serum levels of vitamin D.[99] A third found that higher maternal intake of vitamin D during pregnancy was associated with a lower risk of allergic outcomes in children by 5 years of age.[100] There has been a lack of literature with regards to chronic rhinosinusitis and the role of vitamin D. One study found that vitamin D levels were significantly lower in African American patients with CRS as compared with age-matched and sex-matched controls.[101] Moreover, a recent study out of Poland evaluated the role of vitamin D in vitro in the reduction of fibroplast proliferation from nasal polyps in patients with CRS. Tissue samples were treated with varying doses of calcitriol and a tacalcitol, with and without budesonide. There was a statistically significant decrease in fibroblast proliferation with treatment with calcitriol and tacalcitol, nothing that higher dose concentrations had more of an effect than lower doses. This is a beginning step in the potential use of topical vitamin D analog for the treatment of CRS.[102]

Zinc

Zinc inhibits rhinoviral replication by preventing the formation of viral capsid proteins and has been tested in trials for the treatment of the common cold. Human rhinovirus attaches to nasal epithelium via intracellular adhesion molecule (ICAM)-1 to cause most colds. It is presumed that zinc has an affinity for ICAM-1 and may exert an antiviral effect by attaching to ICAM-1.[105] A recent Cochrane review[105] identified 15 RCTs, enrolling 1360 participants of all age groups, comparing zinc with placebo. It was found that zinc (either lozenges or syrup) was beneficial in reducing the duration and severity of the common cold in healthy people, when taken within 24 hours of onset of symptoms. It was seen that people taking zinc were less likely to have persistence of their cold symptoms beyond 7 days of treatment. In those that took zinc supplementation for at least five months, they were found to have a reduced incidence of the common cold, less school absenteeism, and reduced need of antibiotics. However, they were more likely to experience adverse effects, such as bad taste or nausea. No studies were undertaken in patients with underlying medical problems, thus the use of zinc cannot be recommended in patients with underlying chronic illness, immunodeficiency, or asthma. Also given the variability in the populations studied, dose, formulation, and duration of zinc used in the included studies, more research is needed to address these variabilities and determine the optimal duration of treatment as well as the dosage and formulations of zinc that will produce clinical benefits without increasing adverse effects, before making general recommendations for zinc in treatment of the common cold.

CONCLUSIONS

CAM is widely used among patients in the United States, and for many worldwide is the mainstay of treatment for chronic sinonasal conditions. As the literature continues to evolve and the field of Integrative Medicine emerges, allopathic physicians will be required more and more to counsel patients in various therapies. There are clear ways to approach such remedies from an objective evidence base while remaining open to other possibilities of healing. As always, the otolaryngologist will be called upon to counsel patients in the best way to approach conditions of the ear, nose, and throat. It serves us well to be prepared to respond to patients' needs, truly practicing in a fashion that integrates the best that medicine has to offer.

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CHAPTER

38

Refractory Chronic Rhinosinusitis

Whitney Zirkle, Rakesh Chandra

INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common health-care problems in the United States today, affecting up to 15% of Americans.[1] With the prevalence of disease continuing to rise, CRS has been estimated to affect even more people than common chronic diseases such as hypertension and arthritis, which place a huge demand on medical practitioners.[2] Perhaps more concerning than the immense economic burden related to caring for these patients is the detrimental impact on quality of life (QOL), which has been shown to be more severe in refractory cases of CRS than in other chronic diseases such as angina, hypertension, head and neck cancer, migraine, and chronic obstructive pulmonary disease.[3]

The majority of patients with CRS will respond to first-line medical therapies including nasal steroid sprays and oral steroids, nasal saline, and courses of oral antibiotics. Patients who fail these medical therapies undergo the next accepted step in treatment, which is functional endoscopic sinus surgery (FESS). While most studies suggest FESS to be effective in approximately 80% of patients, this leaves a significant subset of patients with persistent signs and symptoms of CRS despite appropriate medical and surgical therapy.[4] This refractory group of patients has led researchers and clinicians to take a closer look at the possible underlying mechanisms for the pathogenicity of more severe forms of CRS in order to develop more effective medical and surgical therapies. The heterogeneity within the CRS population as a whole is also seen within the subset of patients with recalcitrant disease, suggesting the possible need to tailor treatments to the individual patient and specific disease phenotype.[4]

PATHOPHYSIOLOGY OF REFRACTORY CHRONIC RHINOSINUSITIS

Most cases of CRS are idiopathic with the underlying etiology of disease like a multifactorial process with various modifying influences. CRS is really a group of disorders, including chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). Chronic inflammatory processes appear critical to the development and persistence of disease and are believed to occur primarily at the sinonasal mucosal level. This mucosal interface between the host and environment is thought to be the setting for a dysfunctional immune response to exogenous factors that then leads to the clinical signs and symptoms of CRS.[5,6]

Proposed contributing and predisposing factors for CRS include exogenous factors such as microbial infections and environmental irritants as well as host factors such as atopy and asthma, mucociliary dysfunction, osteitis, sinonasal obstruction, and genetic and epigenetic variation.[5,7,8] The heterogeneity of patient responses to therapies targeting many of these proposed factors suggests that there is still much to be learned in order to better direct our treatment strategies. Researchers and clinicians have worked to further delineate possible mechanisms responsible for the subset of patients who continue to complain of symptoms despite proper medical and surgical management. Disease outside of the paranasal sinuses can contribute to the signs and symptoms of CRS and may prevent successful treatment if not properly identified and managed. Immune deficiency is gaining more and more interest as a contributor to refractory disease with many arguing the importance of screening in this subset of CRS patients.

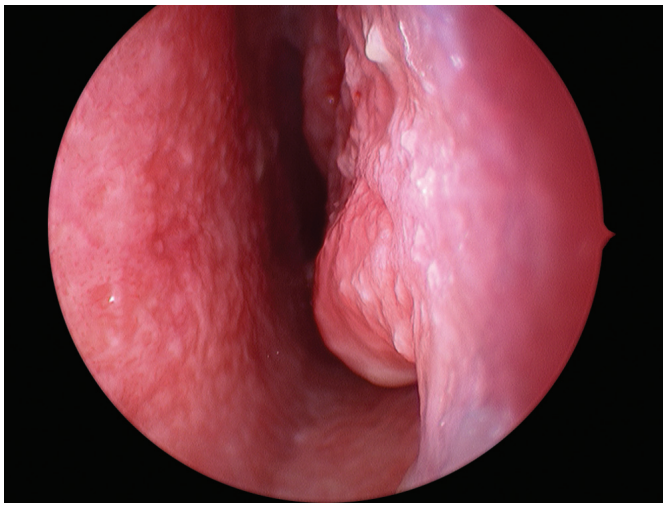

Fig. 38.1: Characteristic sinonasal involvement with sarcoidosis. This is an endoscopic view of granulomatous infiltration with associated submucosal nodularity, which is particularly common on the nasal septum and turbinates.

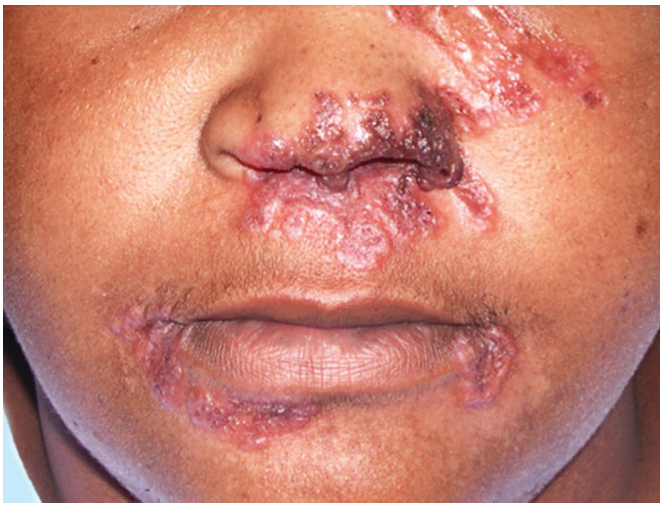

Fig. 38.2: Lupus pernio in a patient with sarcoidosis. Reddish or violaceous inflammatory lesions are characteristic of lupus pernio and result from cutaneous granulomatous infiltration. Note the involvement of the skin of the cheek, perioral area, and nasal dorsum with significant soft tissue erosion and resulting deformity of the nasal alar rim.

Also, the role of biofilms and the underlying impact of osteitis on refractory CRS are key areas of interest in refractory disease.

Systemic Disease and CRS Imitators

In a small subset of patients, the etiology of CRS can be traced to an underlying systemic disease including certain genetic disorders affecting mucociliary function and granulomatous diseases with widespread intrinsic mucosal inflammation.

Kartagener's triad (sinusitis, bronchiectasis, and situs inversus) and cystic fibrosis (CF) affect mucociliary transport through ciliary dysmotility and increased mucous viscosity, respectively.[9] The resultant ineffective trapping and clearance of foreign materials and potential antigens from the sinonasal mucosa is thought to explain the increased rates of CRS, which is often difficult to manage and can lead to exacerbations of lower airway disease in these patients.[10] The saccharine mucociliary transport test can be used to test for general mucociliary transport dysfunction. Diagnostic confirmation through histologic demonstration of the 9:2 dynein arm configuration in Kartagener's syndrome and the sweat chloride test in CF should at least be considered in the refractory subset of CRS patients.

Granulomatous disorders such as sarcoidosis, Wegener's granulomatosis, and systemic lupus erythematosus (SLE) can present with significant sinonasal mucosal inflammation, nasal crusting, rhinorrhea, and congestion with progression of disease leading to complications such as septal perforation and orbital complications[11] (Fig. 38.1). Characteristic cutaneous lesions of the face, such as the malar 'butterfly' rash of SLE or lupus pernio of sarcoid, may be the first clues for diagnosis but are not always present (Fig. 38.2). Biopsy results showing vasculitis with granuloma formation along with a positive C-ANCA can confirm Wegener's granulomatosis. SLE can be diagnosed through testing for antinuclear antibody, antidouble-stranded DNA, and anti-Smith antibodies, and sarcoidosis is typically associated with noncaseating granulomas on biopsy, elevated angiotensin-converting enzyme, and perihilar nodules on chest X-ray. Left undiagnosed and untreated, these disorders can contribute to treatment failure for CRS and increasing frustration for the patient and physician.

Foreign bodies within the nose and paranasal sinuses may present with nasal congestion, sinus pain or pressure, and rhinorrhea that may be purulent and foul-smelling. While children are known for placing any number of objects up their noses, adults may harbor foreign bodies as well. Examples include metallic filings or other inhaled debris among construction or factory workers, loose hardware in patients with previous surgery for facial trauma, and other retained materials from prior surgery (Fig. 38.3). Failure to identify and remove these objects may result in persistent symptoms despite medical therapies and can lead to significant soft tissue injury in some cases.

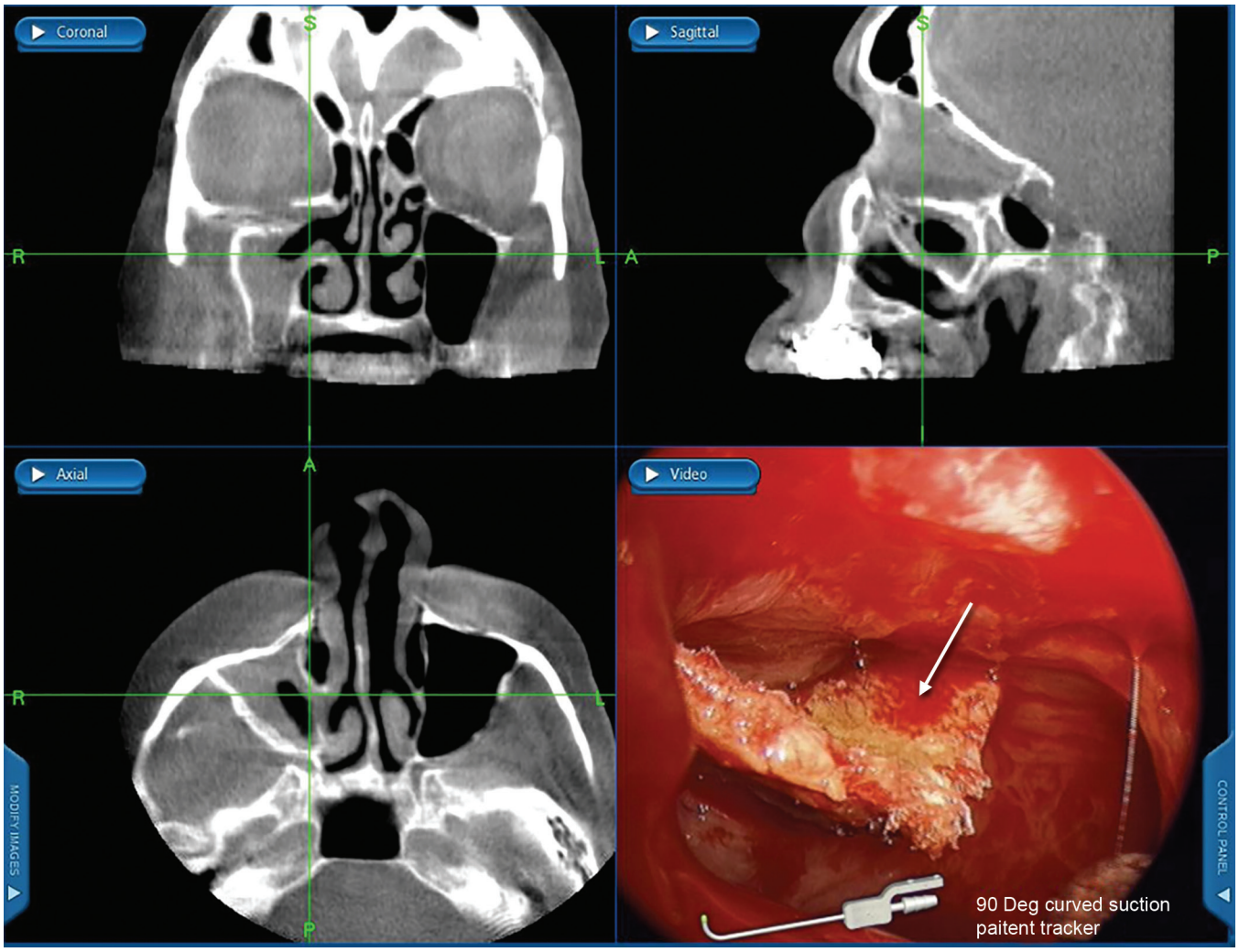

Fig. 38.3: Retained maxillary sinus foreign body. Computed tomography and endoscopic images demonstrate an infection of the right maxillary sinus associated with a piece of Gore-Tex originating from a prior orbital floor reconstruction (arrow).

Pathologies outside of the sinuses may impact sinus symptoms, preventing effective treatment for CRS if left undiagnosed and untreated. Dental disease particularly involving the maxillary tooth roots can contribute to maxillary sinus disease (Fig. 38.4). Evaluation with sinus computed tomography (CT) may show periapical lucencies warranting further dental evaluation. While not identified as a cause of chronic sinusitis, extra-esophageal reflux disease may also contribute to CRS symptoms such as postnasal drip, limiting subjective improvement after CRS treatment. Other nasopharyngeal processes such as a Thornwaldt cyst or enlarged adenoids can also become inflamed with production of thick postnasal drip and congestive symptoms that may be missed if nasopharyngeal exam is not included during endoscopic evaluation. Allergic rhinitis may also mimic or exacerbate CRS symptoms and can sometimes be difficult to discern from CRS especially with perennial allergies.[11] A thorough physical exam with allergy testing may be important in these patients to further direct appropriate management as worsened surgical outcomes for CRS have been associated with failure to treat allergic rhinitis.[12]

Immune Defects

While chronic immunosuppression and severe immunodeficiency (i.e. HIV) are known to be associated with more severe forms of CRS, there is a growing amount of evidence to suggest that even more subtle immune deficiencies have an increased prevalence in the refractory CRS population.[13] It has been suggested that in the CRS population, an abnormal sinonasal mucosal immune response may accompany exposure to certain triggers including fungi,

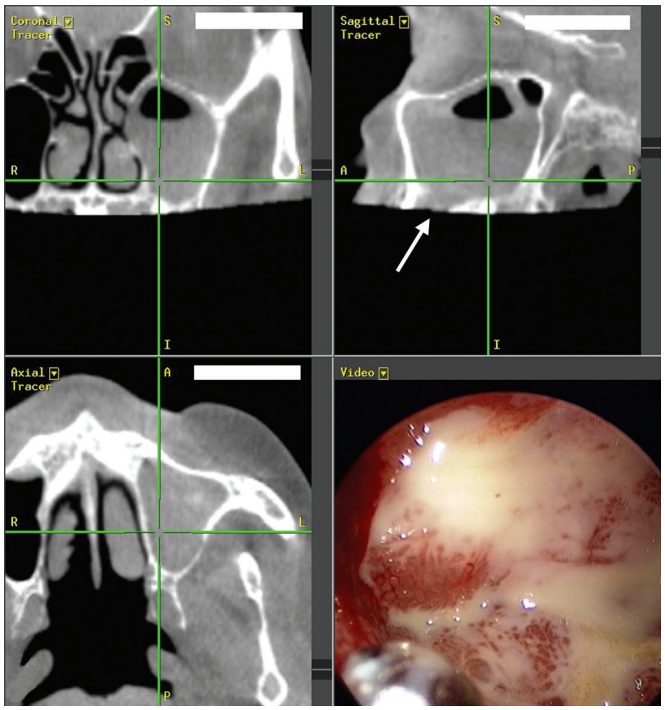

Fig. 38.4: Odontogenic sinusitis. Computed tomography images demonstrate left maxillary sinusitis resulting from an infection of the maxillary dentition. The arrow points to the bony dehiscence in the floor of the maxillary sinus at the location of the now extracted infected tooth. On endoscopic view, retained purulent secretions are noted within the left maxillary sinus.

Staphylococcus aureus (*S. aureus*), and bacterial biofilms. The fact that exposure to many of these agents does not typically generate a chronic inflammatory process in healthy individuals suggests an additional immune dysfunction underlying CRS.[14] Several alterations of immune marker expression have been discovered in the CRS population and may provide insight into the underlying pathogenesis of disease. More specifically, alterations in innate and adaptive immunity within the recalcitrant CRS population may help predict which patients are less likely to respond to therapy.

A prospective study of medically recalcitrant CRSwNP patients undergoing FESS showed increased expression of inflammatory genes associated with the innate immune response including those encoding for MIP-1α, RANTES, GM-CSF, and TLR2, a member of a family of pattern recognition receptors expressed in airway epithelial cells called the Toll-like receptors (TLRs).[15] TLRs work through recognition of certain pathogen-associated molecular patterns (PAMPs) to activate nuclear transcription factors in an inflammatory cascade.[16] In patients with early recurrence of polyps after sinus surgery, MIP-1α is increased but TLR2 and TLR9 are decreased compared with responders to surgery.[15] TLR9 is associated with Th1 skewing of the adaptive immune response, with decreases in expression potentially leading to a Th2-dominant inflammatory response, which is often seen in CRSwNP.

An in vitro study analyzing epithelial cells from medically and surgically recalcitrant CRSwNP patients showed an increase in mRNA expression of the inflammatory cytokine IL-33 in comparison to responsive patients.[14] IL-33 is released by sinonasal epithelial cells and promotes a Th2 polarization of the adaptive immune response with increased production of IL-4, IL-5, and IL-13 inflammatory cytokines in addition to eosinophilia. CRSwNP patients are known for recalcitrant disease with as many as 50% of patients showing recurrent polyps despite long-term systemic steroids with 30% requiring revision surgery. Although levels of Th2 cytokine have not been directly correlated with severity of disease, Il-33-driven increases in Th2 cytokine expression after surgery may promote return of polyps in patients with recalcitrant disease.[14] Polymorphisms in IL-33 receptor gene may further show a protective effect against the development of severe forms of CRS.[17]

Alterations in the adaptive humoral response may also play a role in recalcitrant CRS. A retrospective review of 79 patients with medically and surgically recalcitrant CRS showed an unexpectedly high prevalence of quantitative immunoglobulin deficiency with common variable immunodeficiency (CVID) identified in 9.9%, low IgG in 17.9%, low IgA in 16.7%, and low IgM in 5.1% of patients. Selective IgA deficiency was also found in 6.2% of patients, while 26.3% of 60 tested patients showed a decreased response to T cell mitogens.[13] A 2011 retrospective review by Carr et al. found a prevalence of specific antibody deficiency (SAD) of 11.6% in 129 patients with medically recalcitrant CRS undergoing FESS.[18] SAD is diagnosed when a patient demonstrates an impaired response to immunization with polysaccharide antigens in the setting of normal quantitative immunoglobulin levels. The most common manifestation of SAD is recurrent pyogenic sinopulmonary mucosal infection with polysaccharide-encapsulated organisms commonly including Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, and S. aureus.[19] The immune workup in refractory CRS patients has been suggested to include immunization with pneumococcal vaccine in order to exclude a polysaccharide-specific immunodeficiency. Interestingly, the study by Carr et al. also found a 72% rate of low baseline antipneumococcal antibody titers

among patients prior to vaccination, which raises the question of whether low baseline antibody levels or SAD may contribute to the severity of CRS or the need for surgery.[18]

Biofilms

Bacterial biofilms are thought to play a role in the pathogenesis of CRS and have been of particular interest in recalcitrant disease. Biofilms are highly organized structures encasing bacteria in an extracellular matrix that provides physical protection in addition to observed phenotypic and genotypic changes promoting bacterial survival.[20-22] Implicated in other chronic otolaryngologic diseases including otitis media with effusion, chronic tonsillitis, and cholesteatoma, biofilms are thought to create a relapsing and remitting disease state based on periodic shedding of pathogen, with the inability to eradicate the biofilm through traditional therapies leading to persistence of disease.

Most studies fail to show sinonasal biofilm formation in non-CRS patients, while the prevalence among CRS patients has been cited between 40% and 80%.[20] Biofilms have been associated with polymicrobial infections and individual bacteria including S. aureus, H. influenzae, Pseudomonas aeruginosa, and various anaerobes. S. aureus in particular has been linked to more severe CRS and has been associated with fungal biofilms in some patients.[21] While a direct role for bacterial biofilms in the pathogenesis of CRS is yet to be confirmed, the presence of specific features of certain bacterial pathogens in the setting of defective host immunity may allow for biofilm formation and associated chronic mucosal inflammatory changes. An example of this host immune dysfunction is the downregulation of the antimicrobial peptide lactoferrin that has been shown in CRS patients, particularly in the presence of biofilm formation.[20] Scanning electron microscopy studies of bacterial biofilms have shown evidence of epithelial destruction with loss of cilia, which suggests a link between biofilm formation and mucociliary dysfunction.[23] Biofilm formation has been linked to recalcitrant disease through studies showing more severe preoperative disease in addition to worsened postsurgical outcomes and increased risk of multiple surgeries in patients with known biofilm formation.[20,24]

Biofilms have also been suggested to play a role in the fostering of intracellular infection of sinonasal epithelial cells by S. aureus, which has been proposed as a potential reservoir of pathogenic organisms leading to persistent/recalcitrant CRS. In a prospective study of CRS patients undergoing FESS, confocal microscopic studies of sinonasal mucosa in combination with fluorescent in situ hybridization showed intracellular S. aureus in 56% of CRS patients (in comparison to 0% of controls). The presence of biofilms was seen in 100% of patients with intracellular S. aureus versus 50% of patients with CRS and no evidence of biofilm formation.[25] Intracellular S. aureus may influence the recalcitrant nature of CRS with one study showing significantly higher risk of late clinical and microbiological relapse in patients with intracellular S. aureus and biofilm formation versus patients with biofilm alone.[26] Limitations of this study, however, include potential confounding factors that were not controlled for the higher rates of nasal polyps and revision surgeries in the group of patients positive for intracellular S. aureus. Intracellular S. aureus may avoid medical therapies and host defenses through the ability to undergo phenotype switching, whereby bacteria alter their phenotype upon internalization into a cell to become more antibiotic resistant (thicker cell walls, lysozyme resistance).[26]

Osteitis

While mucosal changes, defects in local immune response, and biofilms have generally gained more attention within the CRS literature than osteitis, some studies have suggested a potential role for osteitis in CRS. Osteitis, as opposed to osteomyelitis, is an inflammatory process involving bone that lacks a marrow space, such as the bones of the paranasal sinuses. Osteitis has been used interchangeably with terms including bony inflammation and remodeling, neo-osteogenesis, and hyperostosis. While there is no gold standard test for the diagnosis of osteitis, identification of histologic changes (such as periosteal changes, osteoclast proliferation and bone resorption, new bone formation, fibrosis and cellular infiltrates) is considered to be the most accurate diagnostic method, although its routine use for diagnosis is somewhat impractical. Bony involvement can be diagnosed on CT or SPECT by signs of irregular bony thickening and increased bone density (Fig. 38.5). Many different CT staging systems have been proposed for osteitis, although none have been standardized. The prevalence of bony changes associated with CRS on CT imaging ranges from 2% to 64% in the literature.[27] In diagnosis, it is important to identify potential confounding factors including underlying bone disease such as Paget's as well as history of prior sinus surgery or radiation, which can also induce similar appearing bony changes on CT.

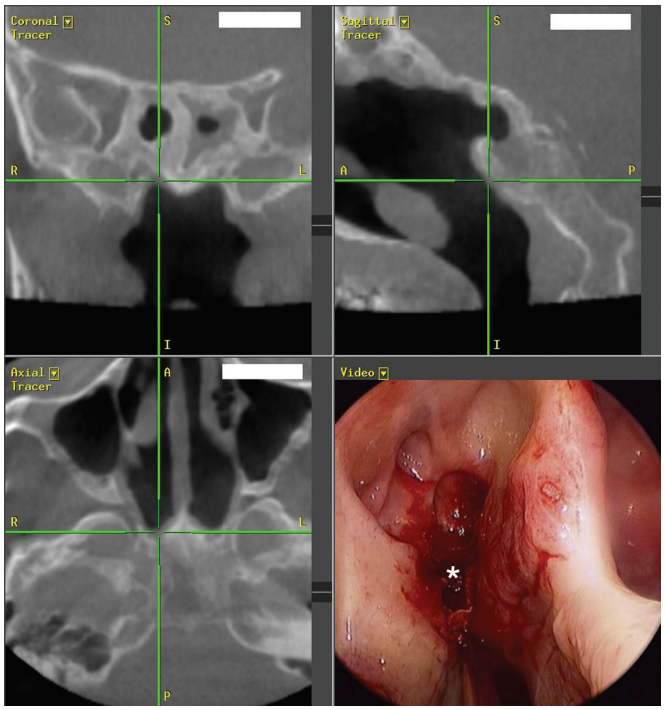

Fig. 38.5: Osteitis of the sphenoid sinuses. Computed tomography images demonstrate the irregular bony thickening that is characteristic of bony osteitis. The overlying mucosal inflammation and narrowing of the sinus cavity as seen on the endoscopic view of the sphenoid sinus are frequently associated with underlying osteitis (asterisk = surgically opened ostium into the sphenoid sinus).

Osteitis as a main etiologic factor in the pathogenesis of CRS has not been established. However, osteitis may play a role as a disease modifier with a potential contribution over time to mucosal scarring and increased potential for bony adhesions. One proposed mechanism for osteitis is the direct bacterial invasion of bone, although as of yet no one has been able to demonstrate presence of bacteria within sinonasal bone in sinusitis. Another proposed mechanism involves overlying biofilms with associated release of inflammatory mediators stimulating bony changes. Speculation for the association between bony remodeling and osteitis comes in part from evidence in the orthopedic literature of biofilm involvement in osteomyelitis of the long bones.[28] Expression of inflammatory cytokines, such as the TGF-b family and the bone morphogenic protein (BMP) family, may be important for bony remodeling seen in CRS.[27]

There is speculation that remodeling processes may become irreversible at some point, possibly leading to recalcitrant CRS.[28] An association between osteitis and worsened baseline CRS has been suggested with an increased prevalence of nasal polyps and revision surgeries in addition to increased severity on CT, endoscopy, and olfactory scores.[29] One study demonstrated pathologically proven osteitis in 6.7% of primary FESS patients versus 58% of revision cases.[27] Osteitis may play a role in medical and surgical treatment failure of CRS and has been associated with reduced improvement in at least some QOL measures postoperatively.[29] Expert opinion recommends surgical removal of osteitic bone when possible, which may lead to the need for more aggressive surgery. Remnants of osteitic bone may provide a nidus for persistent inflammation despite normalization of drainage pathways and re-establishment of more normal airflow through primary FESS. There is little evidence for long-term IV antibiotic management in the treatment of osteitis, especially in the setting of lack of demonstrable bacterial invasion of bone.

SURGICAL THERAPY

Once a patient demonstrates failure of first-line medical therapy for CRS, FESS is recommended with a primary goal of improving paranasal sinus ventilation and mucociliary function through mucosal-sparing techniques. While many patients find significant benefit with primary FESS, a subset of patients will complain of recurrent symptoms prompting discussion of various options for revision surgery. Approximately 10% of patients will require revision surgery within the first 3 years after primary FESS.[30] Persistent symptoms leading to revision surgery may be due to problems such as persistent mucosal thickening and inflammation, polypoid edema, biofilm colonization, and persistent pooling of thick, allergic mucin. Various techniques for revision surgery exist with controversy over the relative effectiveness of surgical strategies emphasizing more targeted approaches versus those emphasizing more aggressive procedures with complete opening and connection of all paranasal sinuses.

Full-House Functional Endoscopic Sinus Surgery

A common revision strategy after primary FESS limited to opening of the maxillary sinuses and anterior ethmoids only is the completion full-house FESS (FHF). Shen et al. define FHF as endoscopic sinus surgery including maxillary antrostomies, complete anterior and posterior ethmoidectomies, wide sphenoidotomies, and Draf IIA frontal sinusotomies.[31] Proponents of FHF argue that more complete removal of sinus tissue prevents unintended obstruction from mucosal edema related to surgery, improves

surveillance of the sinuses in postsurgical follow-up, and provides better access for topical medications and rinses.[30] More limited or incomplete surgery may lead to postoperative obstruction through retained uncinate or remnants of the agger nasi and ethmoid bulla, lateralized middle turbinate, unopened or scarred frontal recess, maxillary antrostomy stenosis or incomplete anterior, and posterior ethmoidectomies.[30] Wide antrostomies are thought to allow for more effective removal of bacterial biofilms through better access of topical medications and irrigations to the affected sinuses. More complete surgical resections also allow for more effective removal of osteitic bone, which has been proposed as a possible nidus for persistent postoperative mucosal inflammation.

In a retrospective review of 21 patients undergoing FHF for recalcitrant CRS, marked improvement in endoscopic mucosal appearance, radiographic Lund–MacKay scores, and patient symptoms determined by the Patient Response Score (PRS) was seen on postsurgical follow-up between 6 and 24 months. There was no significant difference in symptom scores or objective outcomes between patients with and without nasal polyps despite an association of CRSwNP and increased number of revision surgeries in the literature.[31] Definitive conclusions regarding the relative efficacy of FHF to other revision surgery techniques require more studies with direct comparative data.

Radical FESS Procedures

Proponents of radical FESS techniques believe in the complete removal of potential anatomic obstructions in patients who have already failed more limited surgical approaches. Preservation of the middle turbinate and its enveloping mucosa is thought to be important for normal sinonasal function and is part of the mucosa-sparing technique of primary FESS. Although removal of the middle turbinate remains controversial in endoscopic sinus surgery, there may be a role for partial removal of the middle turbinate in revision surgery. This is particularly true in cases where the middle turbinate has lost its functional capacity and is contributing to obstruction. Lateral scarring of the middle turbinate with subsequent middle meatal obstruction and persistent frontal/maxillary sinusitis may represent one example where partial resection improves postsurgical outcome. In patients with more severe disease such as in recalcitrant nasal polyp patients, it has been suggested that middle turbinate reduction may help improve postoperative nasal endoscopy scores and sense of smell.[32]

In comparison to traditional FESS, a more radical "nasalization" procedure combining radical sphenoethmoidectomy with wide maxillary antrostomy, resection of the middle turbinate, and frontotomy has shown improved symptom scores, improved endoscopic findings, and lower recurrence rates for severe nasal polyp patients with recalcitrant disease in a retrospective case series.[33] Patients who are unresponsive to repetitive surgeries have also shown improvement after Denker's procedure, a technique that combines the nasal cavity and the paranasal sinuses into one common cavity (with the exception of the frontal sinuses). More specifically, Denker's procedure involves complete sphenoethmoidectomy in addition to removal of the lateral wall of the nasal cavity and the middle and inferior turbinates.[3] This procedure has been associated with improved QOL scores in recalcitrant CRS patients. A prospective study of 21 patients, all of whom had at least three prior sinus surgeries, demonstrated symptom reduction and improved QOL after undergoing Denker's procedure, which is a nasalization technique that.[3] Outcomes were based on patient responses to the Medical Outcome Study 36-item Short-Form health survey (SF-36), which assesses health-related QOL, and the McGill Pain Questionnaire, which assesses pain. Per report, no patients demonstrated any of the potential significant complications of radical surgery including damage to the nasolacrimal duct with resultant epiphora, empty nose syndrome, or excessive scarring or crusting. These complications are reportedly rare, although extensive nasal crusting must be prevented with an aggressive postoperative nasal irrigation regimen.

Revision Maxillary Sinus Surgery

For revision surgery dedicated to the maxillary sinus, several techniques have been described ranging from more mucosal-sparing endoscopic procedures to more invasive traditional open approaches such as the Caldwell-Luc procedure. Patients with maxillary disease failing primary FESS may benefit from simply widening the maxillary antrostomy. This mucosal-sparing technique focuses on improving mucociliary clearance and drainage from the natural maxillary ostium without significant mucosal stripping (Fig. 38.6). The antrostomy should include complete removal of the uncinate process and any potentially obstructing Haller cells as well as the posterior fontanelle and any accessory ostia. The inferior limit of the antrostomy should reach the insertion of the inferior turbinate.[30]

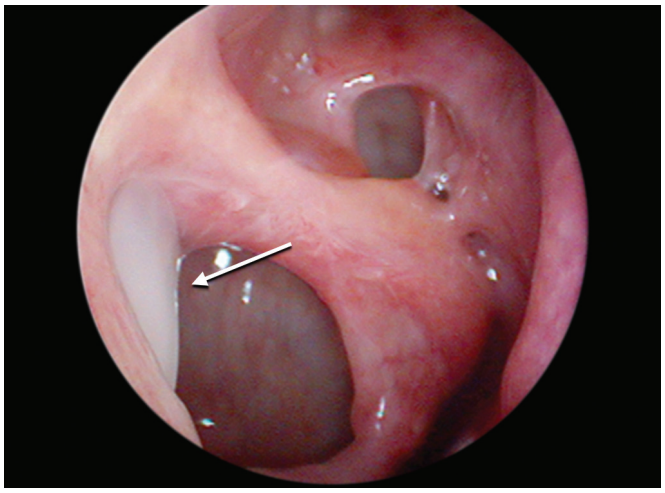

Fig. 38.6: Postsurgical maxillary antrostomy on long-term follow-up. Transnasal endoscopic view of the right nasal cavity demonstrates surgical-widening of the natural maxillary ostium. The neo-ostium is well mucosalized, and despite its significant size, there is preservation of the normal mucociliary transport pattern with mucous directed anteriorly toward the region of natural outflow (arrow). A large maxillary antrostomy further facilitates sinus irrigations, topical drug delivery, and improved visualization and suctioning capabilities during clinic follow-up visits.

Despite widening of the natural ostium and complete uncinate resection, recalcitrant maxillary sinusitis may persist secondary to proposed mechanisms such as long-standing inflammation, scarring from prior surgeries, immunodeficiency, pathogen resistance, or osteitis. In these more severe cases, improvement in mucociliary clearance and more effective delivery of sinus irrigations has been seen with extension of the maxillary antrostomy to the maxillary sinus floor through a "mega-antrostomy" approach. The endoscopic modified mega-antrostomy (EMMA) involves resection of the posterior half of the inferior turbinate with extension of the antrostomy to the floor of the nose.[34] In a retrospective review of 28 patients with surgically recalcitrant maxillary sinusitis undergoing EMMA, authors reported complete or marked symptom resolution in 74% of patients at an average follow-up time of 11 months with no complications and no revision surgeries.[34] Potential complications of the procedure include bleeding from the descending branch of the sphenopalatine artery (SPA), which was addressed by cauterization of the posterior stump of the inferior turbinate. Injury to the nasolacrimal duct (NLD) could occur by extension of the antrostomy too far anteriorly, leading authors to propose avoiding excision of the inferior turbinate beyond the posterior half. A more aggressive alternative to EMMA includes the modified endoscopic medial maxillectomy (MEMM) approach, which includes en bloc resection of the medial maxillectomy wall with subtotal resection of the inferior turbinate. Wang et al. found complete resolution of disease with this procedure in 37 of 46 patients (80%) with recurrent chronic maxillary sinusitis in a retrospective chart review, although resolution of disease was lower in patients with cultures positive for *P. aeruginosa* and *S. aureus*.[35] Proponents of EMMA argue for a more mucosa-preserving approach that may preserve greater function and avoid risk of injury to the NLD, although there is a lack of direct comparative data in the literature. Revision middle meatal antrostomy combined with inferior meatal antrostomy with extension anterior and inferior to Hasner's valve has also been proposed as a method to avoid NLD injury.

All of these various endoscopic techniques for recalcitrant maxillary sinusitis are thought to be less invasive mucosal-sparing alternatives to the more traditional open procedures. While endoscopic techniques have now taken over as the primary surgical method for tackling maxillary sinusitis, there is argument for more traditional open procedures, such as the Caldwell-Luc procedure, for select recalcitrant patients with disease in challenging-to-reach places. Persistent disease in the far anterior and inferior reaches of the maxillary sinus may prove inaccessible even with 70–120 degree telescopes and curved instrumentation. In some severe cases of persistent mucosal inflammation with overlying thick mucin unresponsive to repeated mucosal-sparing endoscopic procedures and medical therapy, some anecdotal evidence exists for radical removal of the diseased mucosa often requiring the more direct access of an open approach. Maxillary sinoscopy, or a sublabial canine fossa puncture, can be performed ideally at the intersection of the midpupillary line and a line extending horizontally from the floor of the nasal vestibule.[32] This allows for visualization of the most anterior and inferior portions of the maxillary sinus. A Caldwell-Luc procedure can be used for further access by expanding the puncture site with a Kerrison rongeur. This approach is common for difficult-to-access benign tumors, such as inverting papilloma, but may be used for CRS as well (Fig. 38.7). Potential complications, cited to be less than 1–3% in the literature, include injury to the maxillary tooth roots and injury to the infraorbital and anterior superior alveolar nerves. Controversy remains in the literature regarding the efficacy of open over endoscopic procedures for CRS with a recent randomized-controlled trial by Lee et al.

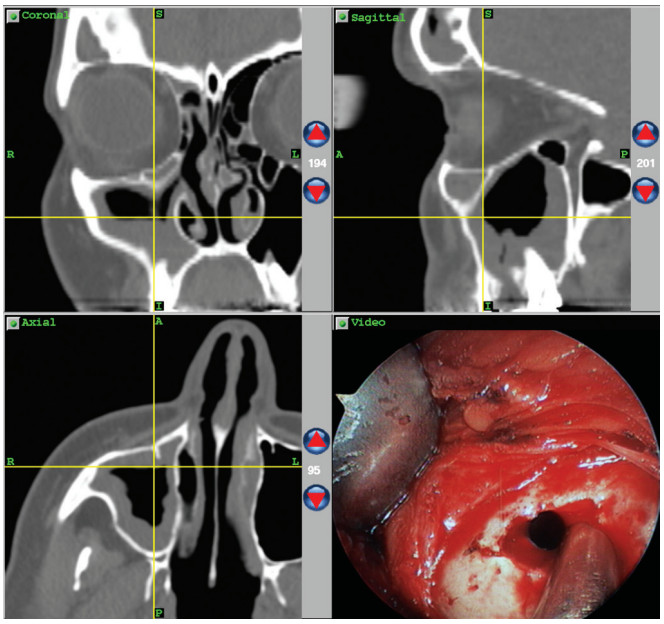

Fig. 38.7: Caldwell-Luc procedure. Computed tomography image guidance demonstrates the location of the tip of the straight suction within the right maxillary sinus during a Caldwell-Luc procedure for recurrent inverting papilloma of the right maxillary sinus floor and lateral wall in the setting of chronic maxillary sinusitis. Endoscopic image shows the intraoral approach with the straight suction inserted through the surgically created defect in the anterior maxillary sinus wall.

showing no difference in outcomes between endoscopic maxillary antrostomy and Caldwell-Luc procedure.[36] Others who have found success with open approaches argue that the variability of disease severity in the literature makes definitive conclusions difficult.[32]

Revision Frontal Sinus Surgery

While standard of care for frontal sinusitis relies on endoscopic mucosal-sparing techniques for opening of the frontal recess, there are several procedures that have been developed for the subset of patients with persistent frontal sinusitis despite first-line surgical and medical therapies. A popular technique for complete frontal sinusotomy is the Draf IIa procedure, which involves removal of the agger nasi cell in addition to any obstructing frontal or supraorbital cells. In a study of 717 patients undergoing frontal sinus surgery, this technique provided effective management in 92% of patients.[30] Persistent or recurrent frontal disease after frontal sinusotomy techniques may be secondary to mucosal stripping with neo-osteogenesis, restenosis, osteitis, retained frontal cells, and difficult to access far lateral disease.[30] For severely recalcitrant patients, the traditional gold standard technique has been frontal sinus obliteration with external osteoplastic flap and abdominal fat harvesting. However, the significant morbidity potentially associated with this procedure including prolonged hospital stays, risk of postsurgical mucocele formation, rare intracranial injury, potential poor cosmesis, risk of supraorbital numbness, persistent frontal headache and difficulties with postoperative monitoring for disease recurrence have led rhinologists to seek alternative therapies.[37]

The endoscopic modified Lothrop procedure or Draf III technique is a transnasal approach for creation of a wide common outflow tract for both frontal sinuses for maximal ventilation and mucociliary clearance. First described in 1981, the Draf III procedure involves the endoscopic removal of a portion of the superior nasal septum, the frontal beak, bilateral frontal sinus floors, and the frontal intersinus septum (Fig. 38.8). The most common reasons for proceeding with the Draf III procedure include mucocele formation and refractory frontal disease. While the significant drilling of bone involved in the Draf III procedure does not follow mucosal-sparing technique, the creation of a large enough common frontal sinus drainage pathway is thought to be sufficient to maintain patency despite inevitable circumferential scarring and granulation tissue formation[37] (Fig. 38.9). Support for the Draf III procedure is widespread with several retrospective studies showing successful outcomes in the majority of patients who have failed prior conservative surgeries.[37,38] A 2009 meta-analysis and systematic review of the literature available for the Draf III procedure showed an overall 82% rate of symptomatic improvement and 95.9% patency rates in refractory patients with a mean follow-up time of 28.5 months.[39] The most common reasons for a Draf III procedure include mucocele formation and persistent frontal disease. Risk of major complications including CSF leak, posterior table dehiscence, and tension pneumocephalus are cited at less than 1% in the literature.[30]

Far lateral disease of the frontal sinuses remains particularly challenging and may not be accessible by even the most complete endoscopic endonasal procedures such as the Draf III procedure. In these cases, an open approach may be necessary. Frontal sinus trephination can provide better access for difficult-to-reach lateral areas and may also be used when significant distortion of anatomy precludes endoscopic identification of the frontal recess. The location for the frontal sinus trephine is

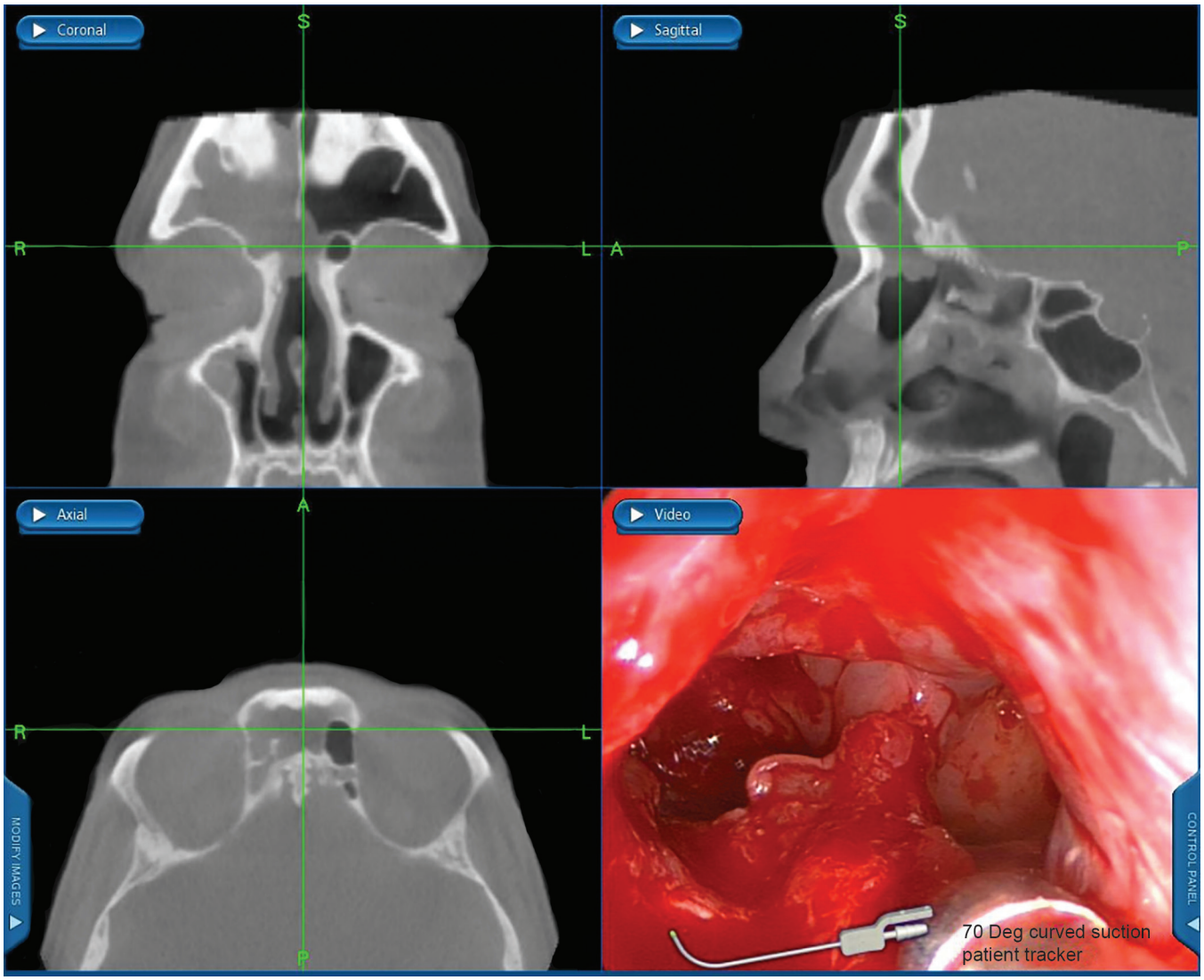

Fig. 38.8: Modified endoscopic Lothrop procedure (Draf III). Computed tomography and endoscopic views demonstrate the creation of a common drainage pathway with drilling away of both frontal sinus floors, removal of the superior nasal septum, and frontal intersinus septum.

traditionally at the point of greatest depth of the frontal sinus, about 1–1.5 cm lateral to midline just below or within the brow, taking care to avoid the supratrochlear and supraorbital neurovascular bundles[32] (Fig. 38.10). Image guidance may be used for more specific disease localization and entry, and endoscopic instruments and irrigations may be introduced through the trephine. Trephination may also be combined with an endoscopic approach. Complications include external scar formation, eyebrow alopecia, wound infection, and more serious complications (although rare) including posterior table penetration, cerebrospinal fluid leak, and injury to the eye.[32]

Surgical Precautions

The benefits of revision surgery should be weighed against the potential increased surgical risk as well as increased risk of treatment failure. While success rates for primary FESS range from 75% to 98%, the rate of success after revision surgery is generally accepted to be lower with a range of 50–92% seen in the literature.[31] Data is lacking regarding the comparative efficacies of various revision ESS techniques with outcomes likely dependent on individual patient factors as well as surgeon experience and comfort with specific techniques. Use of intraoperative CT scanning has been proposed to help ensure surgical

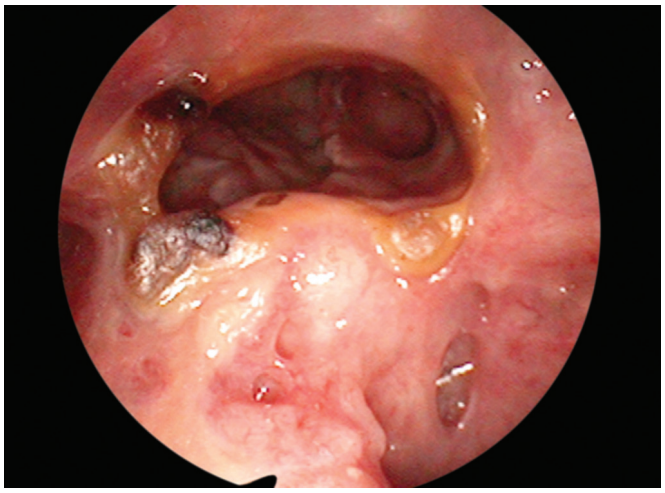

Fig. 38.9: Long-term follow-up after an endoscopic modified Lothrop procedure (Draf III). Transnasal endoscopic view with a 70-degree endoscope shows a persistent, widely patent, well-healed, mucosalized common drainage pathway from the bilateral frontal sinuses on long-term postsurgical follow-up.

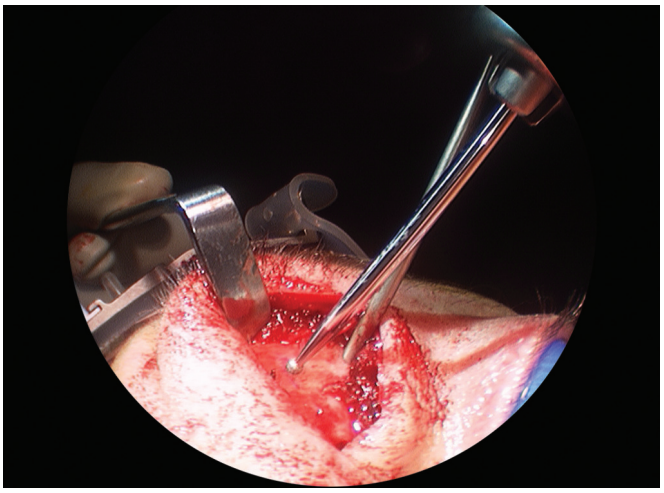

Fig. 38.10: Frontal sinus trephination. Surgical approach begins with a skin incision demonstrated just below the brow line, 1–1.5 cm lateral to midline with care taken to avoid the supratrochlear and supraorbital neurovascular bundles. Opening of the anterior frontal sinus wall may then be performed.

completeness during ESS and continues to be evaluated for its effectiveness in lowering rates of revision surgery.[30] It is important to remember that the goal of surgery in some recalcitrant patients is not always curative and is rather an attempt to improve symptoms through enlarging sinus openings for drainage and aeration and removing diseased mucosa. Sinus surgery often does not directly address mucosal inflammation, which may be the reason for persistence or recurrence of symptoms in patients with recalcitrant disease.[5] The ultimate success of revision surgery often relies on adequate postoperative follow-up with endoscopic debridements as well as patient commitment to a lifelong regimen of nasal irrigations and medical therapy in order to provide maximum benefit.

TOPICAL MEDICAL THERAPY

The current accepted medical management of CRS includes a combination of courses of topical steroids, saline irrigations, courses of antibiotics as well as nasal decongestants, and oral steroids. Failure of these above medications to rid patients of their symptoms then leads to recommendation for endoscopic sinus surgery. However, a subset of patients has persistent symptoms even after revision surgery, leading practitioners to look for additional adjunctive medical therapies in these recalcitrant patients. Topical medical treatments have been studied and applied to improve symptom management in these difficult-to-treat patients. Irrigations have been used in attempts to physically disrupt biofilms, wash out mucous and infectious debris, and deliver medications directly to the sinonasal mucosa. With regard to biofilms, increased concentrations of systemic medications are needed for eradication of biofilms, which can pose an increased risk of systemic toxicities without a guarantee of effectiveness.[40] An appropriate topical antibiotic has the potential to deliver high therapeutic concentrations to the sinonasal mucosa while minimizing the risk of systemic side effects.

Topical Antibiotics

Interest in the use of topical antibiotics to treat CRS has increased in the setting of failure of culture-directed systemic antibiotics to eradicate disease in a subset of patients. Topical antibiotics have the theoretical advantage of increased local concentration at the target site with decreased systemic absorption and related toxicities. They may also play a role in increased penetration in the case of relatively antibiotic-resistant bacterial biofilms with difficult to treat organisms such as *S. aureus* and *P. aeruginosa*. A randomized, double-blinded, placebo-controlled, cross-over study of 14 patients with *S. aureus*-positive refractory CRS looked at the effect of nebulized bacitracin and colimycin versus saline-based placebo on sinus symptoms.[41] While there is still some debate over the importance of *S. aureus* in the underlying pathogenesis of CRS, its predominant presence in the recalcitrant patient population makes it an area of interest for

antibiotic therapies. Frequent colonization of *S. aureus* in the recalcitrant CRS population may contribute to the pathogenesis of resistant disease through biofilm formation and superantigen production.[42] Bacitracin is known to have in vitro activity even against methicillin-resistant *Staphylococcus aureus*.[41] Colimycin is an older antibiotic effective against many multidrug-resistant gram-negative organisms such as *P. aeruginosa*, although its significant systemic toxicity promotes its use more often for topical preparations. While patients in the treatment arm of this study showed improvement in symptoms based on the Visual Analog Score (VAS) and SF-36 responses, the lack of significant difference with the placebo arm suggests no benefit of this topical antibiotic regimen over nebulized saline.

Topical mupirocin has been compared with several other antibiotics for the treatment of refractory CRS with initial data showing potential improved effectiveness over topical vancomycin, ciprofloxacin, and gallium nitrate in the treatment of bacterial biofilms.[11] Mupirocin has strong activity against *S. aureus*, but is rapidly degraded when given systemically, limiting its use to topical applications. Its application has already been established for the eradication of *S. aureus* colonization of the nasal vestibule for prevention of nosocomial infections and has been shown to be effective against biofilms in vitro.[42] Uren et al. performed a prospective study of the efficacy of treatment with topical mupirocin in 16 patients with surgically recalcitrant CRS and cultures positive for *S. aureus*.[42] After 3 weeks of treatment with twice daily nasal lavages with 0.05% mupirocin, 15/16 patients had endoscopic improvement and negative cultures for *S. aureus*, and 12/16 patients had improvement in symptoms. However, major limitations of this study include the short follow-up time and lack of comparison with a control arm. A randomized, double-blinded, placebo-controlled trial from 2012 compared the effects of mupirocin versus saline sinonasal rinses in 25 *S. aureus*-positive patients with recalcitrant CRS.[43] While the study showed more effective eradication of *S. aureus* and initial improvement in endoscopic findings in the treatment group, endoscopic improvements did not persist at follow-up times greater than 1 month, and QOL scores showed no significant improvement over placebo. Symptoms scores were improved in both groups after treatment but were not sustained at delayed follow-up. *S. aureus* has been shown in some studies to have a high reculture rate after mupirocin rinses with more long-term follow-up.[44] Lack of significant patient improvement with topical mupirocin over placebo, despite higher culture-negativity for *S. aureus* (at least initially), supports the proposed multifactorial nature of CRS with the role of *S. aureus* still not fully understood.

Pseudomonas colonization of the sinuses has not only been implicated in refractory CRS but has also been linked to worsened lower airway function particularly in the CF population, where it is a major factor in poor postoperative outcome after lung transplant.[45] Topical aminoglycosides have been used in the CF population with success in decreasing pulmonary complications after lung transplant. In the recalcitrant CRS population, *P. aeruginosa* has been demonstrated to form biofilms that may be resistant to multiple surgeries and high doses of long-term systemic antibiotics. An in vivo study of topical tobramycin against *P. aeruginosa* sinonasal biofilms was conducted to determine the efficacy of biofilm eradication in a rabbit model.[40] While very high concentrations of topical tobramycin were shown to eradicate bacteria in the sinonasal lumen, *P. aeruginosa* attached to the mucosa was still detected on scanning electron microscopy.

With a lack of convincing evidence for the efficacy of topical antibiotics over nasal saline, some authors have looked for alternative antimicrobial agents. NVC-422, a novel broad-spectrum, non-antibiotic antimicrobial has shown some preliminary success with biofilm eradication in a sheep model.[46] Irrigations with manuka honey, which is thought to contain natural antimicrobial agents including hydrogen peroxide and methylglyoxal, have also shown an ability to eradicate biofilms in vitro.[11] What this means for symptom management and improvement of mucosal inflammation in patients with refractory CRS remains uncertain.

Topical antibiotics have been administered via liquid form in saline irrigations and as a nebulized form using a variety of devices (bulb syringe, irrigation bottles, aerosols).[47] Nasal rinses are proposed as a superior method of delivery given the unsatisfactory ability of sprays and ointments to penetrate the sinuses. However, without prior surgery to enlarge the sinus ostia, access to the sinuses is minimal regardless of delivery technique. High-volume positive-pressure nasal lavage has been shown to provide maximal penetration of the sinuses postoperatively.[42,48] The role of maxillary sinus antrostomy tubes (MAST) surgically placed through an inferior meatal antrostomy has been explored as an alternative method to FESS for effective delivery of antibiotic irrigations. While one prospective study showed reduced symptom and endoscopy

scores with antibiotic delivery via MAST, lack of a placebo-controlled arm has again led to the argument that mechanical debridement of saline irrigations may be just as effective as antibiotic irrigations despite changes in delivery technique.[47] No placebo-controlled trial to date has been able to show a benefit to antibiotic irrigations over saline.[7]

Topical Antifungals

While the role for fungus in the pathogenesis of CRS remains controversial, there has been some interest in the presence of fungal elements and resultant inflammation as a source for recalcitrant disease. Some clinicians have employed topical antifungal therapy with amphotericin B despite inconsistent support from the literature with regard to its efficacy as a treatment modality. Amphotericin B is known to have a large side effect profile when taken systemically, but its lack of mucosal absorption has made it a drug of interest for topical therapy. To provide more guidance for the use of topical Amphotericin B in CRS, a systematic review was performed of the literature identifying 6 prospective studies, including 3 placebo-controlled trials, looking at the efficacy of topical amphotericin B in treating patients with CRS.[49] The overall conclusions of the analysis suggested no statistically significant difference in post-treatment CT, endoscopy, and symptom scores between treatment with topical amphotericin B and saline.

Topical and Injectable Steroids

Interest in the use of steroid treatment for recalcitrant CRS stems from the emphasis on mucosal inflammation as a key factor in the pathogenesis of CRS. The use of systemic steroids in CRS has been shown to reduce mucosal inflammation and is frequently used for CRSwNP. The significant side effect profile including but not limited to hyperglycemia, avascular necrosis of the hip, cataracts, elevated intraocular pressure, psychological disturbances, osteoporosis, and hypothalamic-pituitary-adrenal axis dysfunction precludes some patients from being able to take these medications in systemic forms.[50] This has led many practitioners to try topical and locally injectable steroids as a way to decrease systemic side effects while applying medication directly to the sinonasal mucosa. Topical steroid sprays have become a standard first-line therapy in the treatment of CRS. Steroid-eluting stents are also being used now in FESS to help maintain ostia patency and decrease mucosal inflammation. Different forms of steroid applications have been further studied in patients with recalcitrant disease despite first-line medical and surgical therapies.

While two Cochrane systematic reviews have demonstrated steroid spray effectiveness in decreasing polyp size, preventing polyp recurrence, and decreasing sinonasal symptoms in patients with CRSsNP and CRSwNP, these reviews also emphasize the importance of delivery technique and prior surgery for best access of topical steroids to the sinuses.[51,52] Direct delivery of topical steroids to the sinuses has shown more beneficial symptom reductions than simple corticosteroid nasal sprays alone.[51] One placebo-controlled study of medically and surgically recalcitrant CRS patients with comorbid allergic rhinitis showed symptoms improvement and decreased mucosal inflammatory markers and Th2 cytokines when sinuses were directly instilled with budesonide through the MAST technique.[53]

Rhinologists have also turned to steroid irrigations as a noninvasive attempt in recalcitrant patients with surgically opened sinuses to maximize treatment effect and elevate intrasinus steroid concentrations through positive-pressure high-volume delivery devices. Steroid irrigations have been demonstrated to be a safe form of delivery with minimal systemic absorption despite frequent delivery in much greater concentrations than steroid nasal sprays.[50] It has been argued that more effective administration of steroid irrigations to the sinuses allows for better treatment effect while at the same time minimizing dosage to a small fraction of drug delivered since most of the irrigation is washed out. This may be safer than nasal steroid drops, where swallowing of high residual concentrations with resultant GI absorption may be the cause of reports of systemic toxicity with Cushing's syndrome and adrenal suppression.[54] Irrigations have shown to be not only safe but also effective in improving symptoms in the surgically recalcitrant CRS population. Snidvongs et al. showed symptom improvement and decreased endoscopy scores with budesonide or betamethasone irrigations in the postoperative period of refractory CRS patients undergoing endoscopic sinus surgery for the creation of a "common cavity."[54] However, further studies with direct comparison to steroid sprays and saline irrigations will need to be performed to allow for additional conclusions regarding relative treatment efficacy.

Other forms of topical steroid therapy attempted in the recalcitrant CRS population include topical intranasal

mometasone furoate gel, which is thought to provide prolonged adherence to the sinonasal mucosa with gradual release of steroid. A recent retrospective review of in-office endoscopic-guided application of the gel into previously surgically opened sinuses showed only short-term improvement in endoscopic findings and a nonsignificant trend toward decreased need for systemic steroids. Again, the need for larger studies and more randomized-controlled trials looking at the relative efficacies of different forms of topical steroids in comparison to nasal saline will help further define medication effect.

Finally, there are some proponents for intranasal steroid injections for refractory nasal polyp patients. Intranasal steroid injections have been used for allergic rhinitis and nasal polyps for decades although concern has been raised regarding the rare complication of transient and permanent visual loss thought to occur secondary to involvement of the ethmoidal circulation. Schneider et al. argues that in difficult-to-treat nasal polyp patients, injection of steroid directly into nasal polyps has been used effectively to decrease the need for surgery and improve surgical outcomes, with recent studies of thousands of intranasal steroid injections showing no visual or systemic complications.[32]

Surfactants

Chemical and biologic surfactants work as amphipathic molecules that are solvent in both water and organic substrates. This enables surfactants to act as mucolytic agents through disrupting the epithelial adherence of mucous while also decreasing viscosity and surface tension. A second proposed property of chemical surfactant irrigations is its antibacterial effect through a known ability to disrupt bacterial cell membranes and their attachments within biofilms. Chemical surfactant irrigations have shown effective eradication of bacteria from orthopedic wounds in animal models and are now being attempted as an adjunctive therapy in recalcitrant CRS.[55]

Baby shampoo is an inexpensive relatively mild solution of multiple surfactants that has been studied in the CRS population. A small noncomparative study demonstrated efficacy in vitro of eradicating planktonic forms of pseudomonas in addition to inhibiting biofilm formation at an optimal concentration of 1% in normal saline. The second part of this study looking at in vivo irrigations with 1% baby shampoo showed improvement in symptoms (particularly postnasal drainage and thickened mucus), endoscopic findings, and smell testing in over 50% of tested patients with medically and surgically refractory CRS.[55] However, eradication of preformed Pseudomonas biofilms in vitro and in vivo was not seen. This may be secondary to the mild form of surfactants used in baby shampoo with the proposed inability to disrupt the extracellular matrix bonds surrounding bacterial biofilms. The lack of a control arm in this study again begs the question of whether saline irrigations show similar clinical benefit.

Attempts to identify a stronger chemical surfactant for sinonasal irrigations led to the study of citric acid/zwitterionic surfactant (CAZS) in an animal model. Despite promising results with biofilm eradication, a concerning finding was the disruption of sinonasal mucosa with almost 85% temporary loss of cilia after a single treatment compared with saline.[11] An interesting finding in a study comparing the combined use of the hydrodebrider with either CAZS or saline showed a nonsignificant trend toward improved biofilm reduction in the hydrodebrider + saline group over saline flush alone, untreated and CAZS groups. Through the use of confocal scanning laser microscopy, this study again showed significant adverse effects of CAZS on sinonasal cilia, possibly leading to mucociliary transport dysfunction.[56] The hydrodebrider is suggested to be a potentially beneficial topical delivery method through the production of shearing forces that allow for stronger mechanical disruption of mucosal biofilms.

Again, as is the case with other topical therapies described in this section, further placebo-controlled trials evaluating the relative efficacy of surfactants and their comparison to other topical treatments need to be performed. This will allow for additional conclusions regarding comparative treatment effect and the potential benefit of medications beyond simple mechanical washing of sinonasal mucosa as is seen with nasal saline.

SYSTEMIC MEDICAL THERAPY

Systemic medical therapies including antibiotics and oral steroids are frequently used to treat CRS exacerbations. However, potential longer-term management with systemic therapies in the recalcitrant CRS patient has led to increased concern for significant systemic toxicity and microbial resistance. Theoretically safer options for long-term systemic treatments include strategies based on low-dose regimens. This has led to the study of the therapeutic effect of long-term low-dose antimicrobial therapies for recalcitrant CRS. In patients with underlying immune deficiencies, vaccination against pyogenic microbials including *S. pneumoniae* has been suggested to

improve CRS severity. Development of novel monoclonal antibody therapies is also underway in hopes of targeting underlying immune dysfunction thought to be critical in the pathogenesis of CRS. Finally, a recent pilot study on alternative medical therapies in CRS may provide some patients with more choice in treatment options for disease failing more conventional strategies.

Long-Term Low-Dose Antibiotics

Long-term antibiotic regimens of 3 months or greater are often prescribed for difficult-to-treat CRS cases despite limited supporting data in the literature. Disadvantages to long-term systemic treatment include increased risk of systemic toxicity such as ototoxicity or hepatic and renal toxicity, photosensitivity, infusion site infections and embolism with IV delivery, pathogen resistance. Monitoring for systemic side effects often requires additional patient inconvenience with frequent blood testing. To minimize systemic toxicity, long-term low-dose antibiotic regimens have gained increasing interest for the management of recalcitrant CRS.

The macrolide family has been of particular interest in refractory CRS given its anti-staph activity, relatively low side effect profile, and proposed intrinsic anti-inflammatory action. Anti-inflammatory effects on neutrophils in addition to inhibition of a variety of cytokines including IL-8, NF-kB, TGF-β, and GM-CSF have been demonstrated with macrolide therapy. Initial reports also support decreased mucous secretion, possible mucosal reparative effect, anti-biofilm properties and improved sinus-related symptoms with macrolide therapy.[57]

However, the beneficial effects of long-term low-dose macrolide treatment in CRS have not been supported in randomized-controlled trials. The 2011 randomized, double-blinded, placebo-controlled, multicenter macrolides in chronic rhinosinusitis (MACS) trial evaluated the use of long-term low-dose azithromycin in the treatment of recalcitrant CRS. After 3 months of treatment with low-dose azithromycin, there was no statistically significant improvement in symptom scores, QOL, nasal endoscopic findings, smell testing or microbiology in comparison to placebo.[58] While a 2012 retrospective review of long-term low-dose treatment with either trimethoprim-sulfamethoxazole or different macrolides did suggest an improvement in symptoms and nasal endoscopic findings after therapy, conclusions are limited by the lack of comparison with placebo.[59] Furthermore, the treatment doses of macrolide therapy in this study were higher than that used in the MACS trial, with no placebo-controlled studies of this higher dosing regimen available to confirm these results.

Although several small studies have shown no evidence of development of resistant microbial strains in individual patient,[57] the risk of systemic toxicity and pathogen resistance remain real concerns with this method of treatment, especially in the setting of limited clinical evidence for treatment efficacy.

Antifungals

There is some evidence to support an interaction between fungi and the sinonasal mucosal immune response in CRS, namely in the subgroup of allergic fungal rhinosinusitis where an IgE-mediated hypersensitivity reaction to fungus is demonstrated.[7] Theoretically, clearing of fungal elements from the sinuses could disrupt a potential trigger for the underlying abnormal mucosal inflammation seen in CRS. While widespread fungal colonization of the sinuses has been demonstrated in CRS patients, normal individuals are commonly colonized as well, suggesting that the presence of fungi does not equate to a role in the pathogenesis of disease. As discussed previously, topical Amphotericin B has not been shown to be effective in a meta-analysis including several randomized-controlled trials.[49] Studies including systemic antifungals have also failed to show therapeutic benefits in CRS patients. A meta-analysis of the literature for both topical and systemic antifungal treatment in the routine management of CRS demonstrated no benefit of antifungal therapy over placebo.[60] Analysis of subgroups including patients with more recalcitrant disease was not performed. However, adverse events were found to be higher in the antifungal group leading authors to advocate against use of antifungal treatment in the management of most patients with CRS. A 2011 Cochrane review of randomized, double-blinded trials including 5 studies on topical therapy and 1 study on systemic therapy showed no benefit to antifungal therapy and actually found better symptoms scores in patients treated with placebo.[61]

Pneumococcal Vaccine

Subtle immunodeficiencies such as SAD and CVID have been shown to be more prevalent in recalcitrant CRS patients.[18] Low baseline antipneumococcal antibody titers or selective antibody deficiency may contribute to disease severity in CRS as the presence of serotype-specific

antibodies to pneumococcal bacteria is thought to be important against pyogenic mucosal infection.[19] Cross-reactions between pneumococcal capsular polysaccharides and other polysaccharide capsular antigens can provide protective immunity to other pyogenic bacteria. Vaccination with the pneumococcal vaccine is then indicated when antibody titers are found to be low. An inappropriately low immunoglobulin response to immunization with pneumococcal vaccine may diagnose a polysaccharide-specific immunodeficiency and should be evaluated for in patients with recalcitrant CRS.[18,19] IgG2 is particularly important for protection against capsular polysaccharides of pyogenic bacteria such as *S. pneumoniae* and *H. influenzae* (both seen in rhinosinusitis). Administration of the polyvalent pneumococcal vaccine induces specific antibody production particularly from the IgG2 subclass. The pneumococcal vaccine includes an inactive bacterial substance allowing for vaccination in immunodeficient patients without risk of infection. One study showed normalization of serotype-specific antibodies to pneumococcal antigens after vaccination with the pneumococcal vaccine in the majority of patients, with IgG subclass-deficient patients who responded to the vaccine showing no progression in sinusitis episodes.[19] When compared with CVID patients, IgG subclass-deficient patients showed improved response to pneumococcal vaccine with fewer reported episodes of recurrent rhinosinusitis. Treatment with IVIG may have a role in preventing recurrent infections and CRS in patients with CVID.

New Horizons

Monoclonal Antibodies

The Th2 inflammatory cytokine IL-5, which is also an important activator of eosinophils, has been detected in high concentrations in polyp tissue, nasal secretions, and serum of CRSwNP patients. Anti-IL-5 monoclonal antibodies including mepolizumab and reslizumab have been shown to reduce eosinophilia in tissues and blood, suggesting a role in the treatment of selected CRSwNP patients. Two randomized, double-blinded, placebo-controlled clinical trials have been performed with preliminary data supporting treatment with anti-IL-5 antibodies through reduction in endoscopic polyp scores and decreased sinus opacification on CT imaging.[7]

Omalizumab is another monoclonal antibody undergoing active research for the treatment of CRSwNP. This recombinant DNA-derived humanized IgG monoclonal antibody selectively binds to IgE with resultant reduction in free circulating IgE and secondary reductions in immune cell IgE receptors, eosinophils, and Th2 cytokines.[62] This anti-IgE antibody has been used in the past for patients with severe allergic asthma and patients with CRSwNP and atopy, where high levels of IgE are thought to contribute to more severe disease. Patients with CRSwNP and comorbid asthma have also demonstrated high levels of IgE in polyp tissue independent of systemic IgE. In this group of patients, omalizumab is thought to neutralize the IgE produced locally in polyp tissue and perhaps in the peripheral lower respiratory tissues as well.[62]

A recently published 2013 randomized, double-blinded, placebo-controlled phase II trial demonstrated positive effects of treatment with omalizumab in the management of allergic and nonallergic patients with both nasal polyps and asthma.[63] This study showed a reduction in the primary end point of endoscopically graded polyp size as well as improvements in secondary end points including nasal and asthma symptoms and QOL scores. It has been noted that the subset of patients with most severe CRSwNP includes those patients with concurrent asthma. These patients are most likely to exhibit recalcitrant disease to standard treatment options. The above study suggests a potential role for omalizumab in the treatment of CRSwNP patients with asthma, with or without atopy. The fact that atopy did not seem to affect treatment success supports the need for further studies to analyze the role of omalizumab as a treatment option in other recalcitrant CRSwNP patients.[62] Potential side effects of omalizumab include anaphylaxis, cardiovascular events, thrombocytopenia, and cancer.[7]

While treatment with monoclonal antibodies is costly, the expense may be outweighed by the cost of multiple sinus surgeries in some patients with refractory nasal polyps. The question of cost, toxicities, comparison to standard therapy, and long-term benefits are still being addressed and require additional study.

Alternative Medicine

In the setting of failed attempts at conventional therapies for CRS, some patients have turned to complementary and alternative medicine hoping for success in symptom management. An early study of acupuncture in CRS suggested improved sinus-related pain in 60% of patients undergoing acupuncture versus 30% with placebo.[64] A recent prospective nonrandomized pilot study from 2012 looked further into the impact of integrative East-West medicine (IEWM) on sinonasal symptoms and QOL in patients with refractory CRS.[64] Specifically, acupuncture,

acupressure, and counseling on dietary modifications and lifestyle changes were employed. Results of the study showed statistically significant improvements in some QOL measures (based on SF-36 and SNOT-20 responses) including runny nose, reduced ability to concentrate, need to blow the nose, and feelings of frustration, restlessness or irritability. With 73% of study patients having undergone at least one sinus surgery, preliminary data suggest the potential for symptom improvement in the recalcitrant CRS population with no adverse effects. Further randomized-controlled studies should be performed to provide additional evidence for the role of alternative medical therapies in patients with CRS.

SUMMARY

Chronic rhinosinusitis (CRS) places a huge economic burden on the U.S. healthcare system in addition to detrimentally impacting patient QOL. Patients with refractory CRS present a particularly challenging task to the treating physician to develop treatment strategies that will succeed in a setting where universally accepted first-line therapies have failed. In alignment with the proposed multifactorial etiology of CRS, alternative therapeutic strategies have been explored targeting a variety of potential pathogenic factors in order to break the cycle of disease. While the primary underlying mechanism for the development of CRS is not clearly understood, many factors playing a disease-modifying role have been identified.

With regard to the refractory nature of CRS, proposed contributing and predisposing factors discussed in this chapter include underlying systemic diseases and diseases that imitate CRS symptoms, immune defects and deficiencies, bacterial biofilms, and osteitis. Revision surgical therapies for refractory CRS focus on improving drainage and aeration of the sinuses and range from mucosal-sparing minimally invasive techniques to more invasive mucosal-stripping procedures. Another goal of revision surgery is to provide better access to medical therapies including saline irrigations, which are often thought to be critical for maximal treatment benefit in the post-operative patient. Treatment with topical medical therapies including antimicrobials, antifungals, steroids, and surfactants has been employed to target proposed pathogenic processes at the sinonasal mucosal level including biofilms and chronic inflammation. However, data supporting relative therapeutic efficacy of topical therapies over the mechanical effects of normal saline irrigations remains limited. The role of systemic medical therapies including long-term low-dose antibiotics, antifungals, and vaccination against pyogenic bacteria remains controversial in the treatment of refractory disease. Further development and study of novel therapies including monoclonal antibodies and alternative medical practices including acupuncture may provide not only additional insight into the multifactorial nature of disease but also additional weapons for the management of this phenotypically diverse group of patients.

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SECTION 7

Anesthesia

CHAPTER

39

Local Anesthesia

Azeem S Kaka, Subinoy Das

The development and widespread acceptance of endoscopic sinus surgery have been, in large part, predicated on technological advances in instrumentation and visualization. Equally important to the development of endoscopic sinus surgery, however, has been the refinement of local anesthetic techniques. The optimal use of local anesthetics reduces bleeding and pain, and enhances visualization of the surgical field, allowing for safe and precise intranasal surgery. As a result, it is critically important for endoscopic sinus surgeons to possess a mastery of the selection and use of appropriate local anesthetics and awareness of the complication risks that they possess.

INTRODUCTION

Anesthesia and Sinus Surgery

Endoscopic sinus surgery is typically performed via the combined use of general anesthesia and topically applied local anesthetics. However, surgery may also be performed completely via local anesthesia. Local anesthesia with orally or intravenously delivered sedation avoids some of the risks inherent with general anesthesia, allows for the use of in-office surgical techniques, allows for real-time monitoring of vision and pain, and may provide for an additional level of safety. Previous studies have reported that patients undergoing endoscopic sinus surgery under local anesthesia with sedation have decreased operative times and satisfaction levels comparable to that of general anesthesia.

Exclusive use of local anesthetics has a distinct advantage in that inhalational anesthetics are avoided. Volatile agents used in the maintenance phase of anesthesia typically cause vasodilatation, which is particularly harmful to the endoscopic sinus surgical field. Techniques such as controlled hypotension have been developed to assist in the surgical field; however, these are typically accomplished with increased concentrations of these volatile agents that often result in rebound tachycardia and greater vasodilatation, and demonstrate equivocal effects on the quality of the surgical field. Furthermore, controlled hypotension increases the risk of end-organ damage and specifically increases the risk for hypoperfusion-induced strokes.

Propofol, introduced in 1989 by the AstraZeneca Corporation, was the first of a new class of intravenous anesthetics known as alkyl phenols. Propofol is a sedative-hypnotic agent that can be used for induction of general anesthesia as well as the maintenance of anesthesia via a continuous infusion. Propofol is advantageous over inhalational anesthesia during sinus surgery in that it induces arterial hypotension without significant reflex tachycardia, and not does have peripheral vasodilatory effects comparable with those of volatile inhalational anesthetics.

Propofol also causes less postoperative nausea and vomiting compared to volatile anesthetics; however, it causes pain on injection and requires strict aseptic technique since it is delivered as a lipid emulsion and carries a risk of serious bloodstream infections. Propofol has a distribution half-life of 2–4 minutes but readily distributes to peripheral fat and has an elimination half-life of 2–4 hours. Therefore, significant amounts of propofol can build up in a patient's fat stores if propofol is continuously used over several hours. This can adversely increase extubation times from anesthesia.

The advent of fentanyl congeners and target-controlled infusion pumps, which permit delivery of intravenous agents in a manner superior to that of manual injection, has allowed for the advent of total intravenous anesthesia (TIVA). Typically, the combination of propofol with alfentanil can be used without the need for inhalational agents for maintenance. In a prospective, randomized controlled trial Wormwald et al. compared TIVA with traditional anesthesia with sevoflurane and found a significant improvement in a validated grading system of the surgical field independent of heart rate or mean arterial blood pressure. Furthermore, in patients with a high preoperative Lund-Mackay score (> 12), a British study showed there was a significantly decreased amount of intraoperative blood loss using TIVA. While TIVA possesses these many advantages over inhalational anesthesia, there are several barriers that have precluded its widespread adoption.

Variability in patient drug requirements, particularly in obese patients, is significant. The anesthetic plane and depth of anesthesia are limited compared to that of inhalational agents. TIVA combined with muscle relaxants allows for the risk of "awareness" with the inability to move. In addition, TIVA drugs are often significantly much more expensive than traditional agents. Nevertheless, TIVA in combination with topical local anesthetics may prove to be a superior option for many types of intranasal surgery.

Local Anesthetics and Vasoconstrictors

Local anesthetics and vasoconstrictors also play an important role in minimizing postoperative pain and improving the surgical field during endoscopic sinus surgery. There are a myriad of mixtures and protocols used for local anesthesia and vasoconstriction. Two basic classes for local anesthetics exist: the amino esters and the amino amides. Cocaine, a naturally occurring amino ester, was the first anesthetic to be discovered and was introduced into Europe in the 1800s following its isolation from coca beans. William Halsted, an American surgeon who was one of the founding four members of Johns Hopkins hospital, became an early champion of cocaine and unfortunately became addicted to the substance through self-experimentation. Procaine, the first synthetic derivative of cocaine, was developed in 1904. Lofgren later developed lidocaine in 1943 during World War II. Lidocaine, an amino amide, has become the most widely used cocaine derivative and is ubiquitously used during surgical procedures.

Cocaine and its derivatives produce anesthesia by inhibiting excitation of nerve endings and/or blocking conduction in peripheral nerves by reversibly binding and inactivating sodium channels. This prevents depolarization of nerve cells and thus causes a loss of sensation in the local area innervated by the sensory nerve. The mechanism for differential block of pain perception as compared to motor function is still poorly understood.

Cocaine-derived anesthetics contain a chemical structure that possesses an intermediate chain with a hydrophilic amine on one end connected to an aromatic ring on the other end. There are two classes of local anesthetics: amino esters and amino amides. Amino esters have an ester link between their intermediate chain and their aromatic ring, and amino amides have an amide link. Common esters include cocaine, procaine, tetracaine, and benzocaine. Common amides include lidocaine, mepivacaine, prilocaine, bupivacaine, and ropivacaine.

Amino esters and amino amides differ in several important aspects. Esters are metabolized in plasma via pseudocholinesterases, whereas amides are metabolized in the liver. Esters are unstable in solution, whereas amides are very stable. Esters are more likely to cause true allergic reactions. All esters and amides are vasodilators with the exception of cocaine, which is a vasoconstrictor. Thus, the combination of anesthesia and vasoconstriction makes cocaine an ideal anesthetic for intranasal surgery. However, the euphoria and highly addictive nature of cocaine have made it one of the most widely abused recreational drugs and thus made it illegal in most countries. As a result, cocaine is more difficult to use for legitimate medical purposes. Cocaine is also known to cause cardiac arrhythmias and many have recommended its abandonment[8] with the use of safer mixtures.

Epinephrine, a human adrenergic catecholamine, is a potent vasoconstrictor commonly added to local anesthetics at a variety of concentrations. Epinephrine acts peripherally by inducing alpha-receptor contraction of myoepithelium to produce vasoconstriction. Concentrations vary from 1 in 1,000 parts epinephrine to 1 in 200,000 parts epinephrine. As a result, care must be taken to prevent syringe mislabeling so as to not inject more potent concentrations of epinephrine meant for topical use directly into the bloodstream.

Oxymetazoline is a selective alpha-1 agonist and partial alpha-2 agonist that are often used as a topical decongestant. Developed by Merck, Inc., oxymetazoline, given the trade name Afrin, was first sold as a prescription

medicine in 1966 and became an over-the-counter medication in 1975. Oxymetazoline acts by activating alpha-1 receptors and endothelial postsynaptic alpha-2 receptors primarily within the inferior turbinates, which temporarily increases the diameter of the nasal airway lumen and minimizes fluid exudation from postcapillary venules within septal and turbinate mucosa. While persistent use of oxymetazoline leads to rhinitis medicamentosa and possible permanent turbinate hyperplasia, the perioperative use of oxymetazoline is very effective for improving visualization of nasal and sinus anatomy and minimizing bleeding.

Phenylephrine, commonly marketed as Neo-Synephrine, is also a selective alpha-1 receptor agonist and is used as a vasoconstrictor during intranasal surgery, though its effectiveness as a vasoconstrictor has been brought into question through multiple placebo-controlled trials.

INJECTION LOCATIONS

Greater Palatine Block

The authors utilize bilateral greater palatine blocks in most cases, particularly when total ethmoidectomies and/or sphenoidotomies are being performed (Fig. 39.1). Three milliliters of 1% lidocaine with 1:100,000 epinephrine are delivered into a 5 mL Luer lock syringe. The expiration date and the proper concentration and labeling of the lidocaine and epinephrine on the stock container are confirmed by the surgeon and drawn directly from the bottle into the syringe by the surgeon. This minimizes the risk of accidental injection of a different concentration. A 1 and a ½ inch 25 gauge needle is measured with a ruler and bent at 60° at a length of 25 mm for all adults. After the patient has been intubated and the bed turned, two tongue blades are placed in the mouth and used to palpate the hard palate/soft palate junction. The greater palatine foramen is typically located just anterior to the border of this junction. It can often be seen as a subtle depression in the hard palate mucosa and/or palpated with a glove finger. Although historically described as next to the second maxillary molar, the foramen is next to the third molar approximately 50% of the time. The needle is placed into the greater palatine foramen and advanced to the bend of the needle. Occasionally, the needle is marched anteriorly from the hard palate border when the greater palatine foramen is difficult to find. The needle is then aspirated for blood to prevent an intravascular injection. If no blood is obtained, then 1.5 mL of the anesthetic is delivered slowly to the canal. If the needle is properly placed, then there will be moderate resistance to the fluid being delivered into the canal. If there is very minimal resistance, it is likely that the needle went through the soft palate into the nasopharynx, and is not correctly placed in the canal. The same procedure is repeated for the contralateral canal.

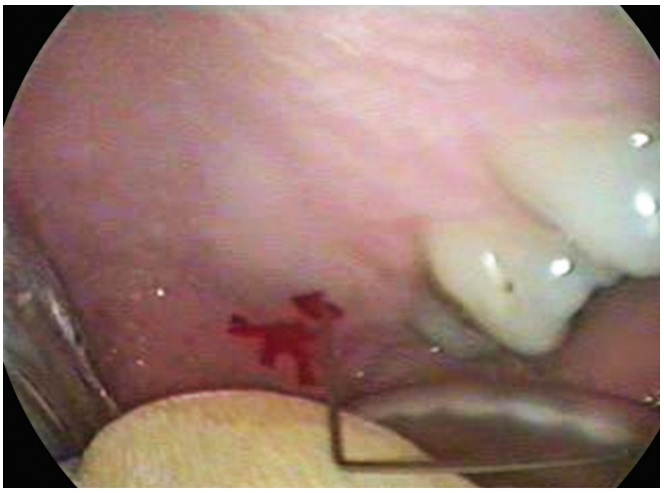

Fig. 39.1: Intraoral greater palatine injection.

Sphenopalatine Block

The sphenopalatine foramen is injected transnasally posterior and superior to the horizontal portion of the basal lamella at the posterior aspect of the middle turbinate. One percent of lidocaine with 1:100,000 epinephrine is used. This is a technically difficult injection that is performed by placing a 30° bend in the first centimeter of a spinal needle or by using an angled tonsil needle. The tip of the needle is used to palpate the foramen. The needle is placed in an upward and lateral direction and used to bleb up the mucosa adjacent to the sphenopalatine foramen. Typically, blanching is already seen by a properly injected greater palatine foramen block, and the sphenopalatine injection augments this blanching (Fig. 39.2). If the foramen is unable to be reached, then a bleb near the foramen will diffuse to the foramen and cause vasospasm of the sphenopalatine branches. Alternatively, the injection can be placed medially at the rostrum of the septum between the middle turbinate and the inferior turbinate to minimize bleeding from the posterior nasal artery. As always, care should be taken to aspirate before injecting to prevent an intravascular injection.

Lateral nasal wall injections: The lateral nasal wall is injected with 1% lidocaine with 1:100,000 epinephrine

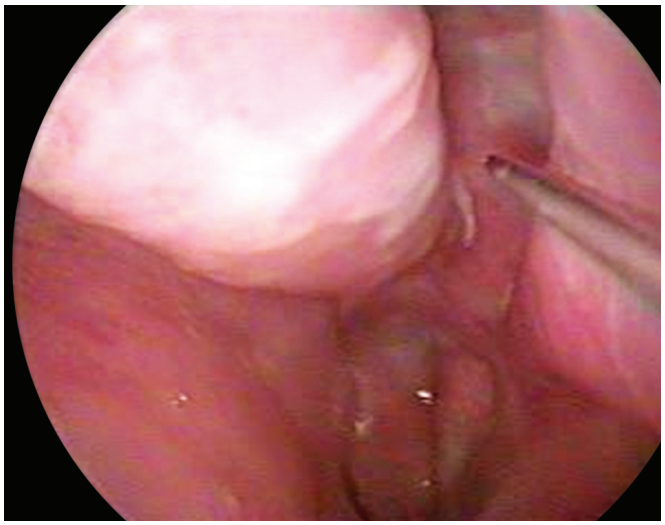

Fig. 39.2: Transnasal sphenopalatine injection.

via a 25-gauge needle typically with a slight bend at the tip. The optimal injection is superior and anterior to the anterior attachment of the middle turbinate. The inferior portion of the uncinate process, the inferior border of the middle turbinate, the septum, the superior turbinate, and other supplemental injections are utilized depending on the disease process and type of operation. The benefits of this injection must be weighed against the nuisance bleeding that can occur from these injection sites that can interfere with the performance of the operation.

Recent randomized controlled trials have shown that there is a statistically significant improved surgical field, reduced blood loss, and reduced postoperative pain in using a bilateral greater palatine block or an endoscopic sphenopalatine block in sinus surgery. The authors suggest that either of these techniques are used in all cases.

APPLICATION TECHNIQUES FOR IN-OFFICE SINUS SURGERY

Optimal local anesthesia is essential for the performance of in-office sinus surgery such as balloon sinuplasty. Many techniques are used. The authors prefer premedicating patients with 5 mg of valium. Next, patients are given aerosolized sprays of a lidocaine/oxymetazoline mixture. Pledgets containing tetracaine are then applied to the middle meatus for a minimum of 5 minutes, and then reapplied deeper in the middle meatus on the face of the ethmoid bulla. Despite these applications, the procedure can be painful, particularly during inflation of the balloon.

Table 39.1: Toxicity of commonly used local anesthetics

Local anesthetic	*Class*	*Toxic plasma concentration*
Lidocaine	Amino amide	4 mg/kg (without epinephrine) 7 mg/kg (with 1:100,000 epinephrine)
Bupivacaine	Amino amide	2.5 mg/kg (without epinephrine) 3.0 mg/kg (with 1:100,000 epinephrine)
Prilocaine	Amino amide	7 mg/kg (without epinephrine) 8 mg/kg (with 1:100,000 epinephrine)
Cocaine	Amino ester	3 mg/kg

Complications

Lidocaine toxicity is a result of excessive blood concentrations that cause central nervous system or cardiovascular reactions (Table 39.1). Excessive blood concentrations can result from direct intravascular injection or, less commonly, from vascular absorption. Lidocaine toxicity on the central nervous system is biphasic; first, inhibitory fibers are blocked resulting in stimulation with tingling, numbness, mental status changes, and eventually seizures. Eventually, excitatory pathways are also blocked that can cause unconsciousness, respiratory depression, and arrest. Cardiovascular effects are from effects on sodium channels in the heart that lead to arrhythmias. The first sign of toxicity is central nervous system symptoms akin to alcoholic inebriation with lightheadedness, vertigo, and possible perioral tingling. Patients are treated by securing an airway, mechanical ventilation, and circulatory support. Seizures are controlled with benzodiazepines and succinylcholine. Arrhythmias are best treated with bretylium. The maximal dosage of lidocaine (without intravascular injection) is between 2 mg/kg and 4 mg/kg, with many individual factors affecting serum concentrations. Epinephrine limits lidocaine absorption due to vasoconstriction. Maximal dosage with epinephrine is typically 7 mg/kg. Patients may rarely develop anaphylaxis to local anesthetics, though this is more common with esters.

Cocaine toxicity results primarily from its vasoconstrictive property and its effect to stimulate the sympathetic nervous system. Cocaine administration will lead to increased concentrations of catecholamines (norepinephrine and dopamine) in the synaptic cleft, which then leads to increased sympathetic tone. These properties have been shown to lead to increased coronary vasospasm, myocardial ischemia, arrhythmias, hypertension, and tachycardia. This effect of myocardial ischemia may be seen as

late as 6 weeks after the last administered cocaine dose. Given these potential disastrous complications and the rising rates of premorbid cardiac conditions, cocaine use has been largely abandoned in sinus surgery.

CONCLUSION

The proper use of local anesthetics and injection techniques is an essential aspect of performing surgery safely and effectively. A comprehensive working knowledge of local anesthetics including their pharmacodynamics, risks, and benefits is mandatory for otolaryngologists.

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CHAPTER

40

Anesthesiology

Jerry Chao, Philip Lebowitz

HISTORICAL PERSPECTIVE OF CURRENT PRACTICE

Although botanicals like opium and cocaine, as well as alcohol, have been used since antiquity to relieve pain and provide a disordered sensorium, the modern era for anesthesia began in the 19th century when a highly publicized search for an inhaled substance that could transiently produce a state of unawareness and analgesia led to the near-simultaneous discovery of nitrous oxide, diethyl ether, and chloroform as anesthetics.[1] Although a number of individuals had earlier experimented with nitrous oxide, it fell to Horace Wells, a dentist, to demonstrate the utility of this gas for his own dental extraction. William TG Morton, another dentist, happened upon sulfuric ether, which he used with success in his dental practice. On October 16, 1846, Morton was allowed to give his "Letheon" to a young man whose vascular neck tumor was to be excised by the chief surgeon at the Massachusetts General Hospital in Boston, John Collins Warren. The procedure was a success and Morton's "discovery" was immediately hailed by Warren, saying "This is no humbug". The event was quickly celebrated in the *Boston Medical and Surgical Journal* (antecedent of the *New England Journal of Medicine*), and ether inhalation for surgery was established as the standard of its time. Oliver Wendell Holmes gave it the name anesthesia: Greek for *an*, without, and *esthesia*, feeling.

Wells, Morton, and Charles Jackson (who had suggested sulfuric ether to Morton) all vied for the prestige (and hoped-for wealth) that attended the discoverer of this "boon to mankind". To complicate the picture, Crawford Long had used ether for surgical pain relief as early as 1842, but he did it in the state of Georgia, which did not attract the attention of the Western medical establishment as had Morton in Boston.

Spontaneous ventilation and support of the circulation were well maintained with ether, though it was flammable and frequently caused postoperative nausea and vomiting. The continued search for a better inhalational agent led to James Simpson's use of chloroform in England within the year. Chloroform became the mainstay in England for surgical and obstetrical pain relief, but was eventually removed from use because of hepatotoxicity and the tendency to cause ventricular fibrillation. Nitrous oxide regained popularity in the 1860s and, despite the controversy over its side effects, remains in use to this day. Diethyl ether, the eventual successor to Morton's version, lost its popularity as nonflammable inhalational agents were introduced into anesthetic practice.

Halothane, introduced clinically in 1956, was nonflammable, less emetic, and more potent; it quickly replaced ether and other flammable agents like cyclopropane. Unfortunately, some patients who had been anesthetized with halothane developed hepatic injury, occasionally to the point of fatal hepatic necrosis. The prototype of the clinically utilized methyl–ethyl ethers was methoxyflurane, but that was found to be nephrotoxic in dose-dependent fashion. Subsequent variants, enflurane and isoflurane, were progressively less likely to injure the kidneys, and isoflurane continues to be used today. More recently, sevoflurane and desflurane—volatile liquids that, as gases, are inhaled via anesthesia machine breathing circuits—have come to dominate modern practice. In contrast to

nitrous oxide, which is analgesic but only a partial anesthetic under normal conditions, the other named agents are full anesthetics.

The characteristics of potent inhaled anesthetics include analgesia (the absence of pain), amnesia (the absence of awareness), and immobility (the absence of movement). At an appropriate, individualized brain concentration, each of the potent inhalational anesthetics produces anesthesia under which is subsumed the aforementioned characteristics. Aside from opioids like morphine, intravenous (IV) hypnotic/sedatives did not regularly enter the clinical sphere until hexobarbital was introduced in 1932. Sodium thiopental followed in 1934 and constituted a building block in balanced anesthesia, where general anesthesia was allegedly more safely produced by using smaller doses of several drugs. In expert hands, thiopental became the predominant, safe IV anesthetic induction agent and was ubiquitous until propofol's ascendancy in the 1990s.

The other class of drugs, besides hypnotic/sedatives, opioids, and nitrous oxide, that constituted balanced anesthesia was the muscle relaxants or, more properly, neuromuscular blocking drugs. The first clinically useful compound was d-tubocurarine or curare, which was introduced in 1940 and served to relax patients' muscles to improve surgical exposure and wound closure. Succinylcholine, a depolarizing drug, and the nondepolarizing triad of vecuronium, rocuronium, and cisatracurium constitute the array of neuromuscular blocking drugs in today's practice. The use of these drugs facilitates endotracheal intubation and produces a state of surgical relaxation at lower concentrations of inhaled anesthetic than would be required if the inhaled anesthetic was given alone.

Regional anesthesia—the use of local anesthetics to transiently defunctionalize the spinal cord, nerve bundles, individual nerves, or a localized distribution of dendritic nerve terminals—is a discipline that harkens back to the late 19th century and the isolation of cocaine from the dried leaves of the coca plant in 1856. Sigmund Freud gave some cocaine to Carl Koller, who applied the drug topically to a patient's eye and was able to perform superficial surgery. Following this demonstration in 1884, William Halsted investigated the use of cocaine solution to block a variety of nerves or nerve distributions with good results. Procaine (Novocaine) was synthesized in 1905, followed by tetracaine in 1932, lidocaine in 1948, and bupivacaine in 1963, among others. Advances in radiological guidance and now ultrasonic guidance have fostered an abundance of nerve blocks for chronic pain as well as for regional anesthesia as the sole or the adjunctive mode of surgical anesthesia.

Modern anesthetic practice generally involves an IV infusion with ports for administering IV medications, an anesthesia delivery system, and electronic patient monitoring. The principal breathing circuit is termed a semiclosed circle system and includes separate inspiratory and expiratory flow valves, a carbon dioxide absorption system, an excess gas relief and scavenger, a reservoir bag, a ventilator, a valve to separate the reservoir bag from the ventilator, and an attachment to the common gas outlet of the anesthesia machine itself. The anesthesia machine includes a dual oxygen supply (wall/ceiling and tanks—also called cylinders), pressure-reducing valves from the oxygen tanks, oxygen (and often air and/or nitrous oxide) flowmeters, oxygen analyzers, fresh gas apportioners, vaporizers, and an auxiliary oxygen outlet. The newest version of anesthesia machine incorporates microprocessors that obviate the need for older, mechanical safety devices. Standard monitoring in current practice includes continuous electrocardiography, intermittent noninvasive blood pressure, continuous pulse oximetry, continuous capnography/capnometry, and temperature. Today's monitors also include the capability of invasive pressure measurements, such as continuous intra-arterial and central venous pressure determinations. Increasingly, automated electronic anesthesia record-keepers are replacing the conventional pen-and paper graphic forms.

MECHANISMS OF ANESTHETIC ACTION

Despite the span of time since Morton's ether demonstration, the precise explanation for how anesthetics affect the central nervous system to eliminate awareness/consciousness, prevent pain perception and blunt the autonomic responses to stressful surgical stimuli, produce immobility in the face of those noxious stimuli—in essence reduce the patient to a comatose state—then return the patient to the sentient person he or she was before the anesthetic, remains elusive.[2] In general, drugs act by attaching to cellular receptors that, in turn, initiate signal transduction mechanisms in the cell. The merged effects on cells, organs, and the whole body by drugs are complex and involve the regulation of many receptors and channels. Anesthetic drugs, in particular, affect numerous receptors. Principal among them are G protein-coupled

receptors on the extracellular surface of the cell that couple to intracellular effector systems via intermediary guanine nucleotide proteins (G proteins). G protein systems include the adrenergic, muscarinic cholinergic, opioid, serotonin, histamine, cannabinoid, cholecystokinin, endothelin, and substance P receptors.

Additionally, anesthetics can affect ion channels that are specialized for gating ion movement and generating electrical signals in response to specific chemical neurotransmitters, such as acetylcholine (ACh), glutamate, glycine, and gamma-aminobutyric acid (GABA). Initiators of ion channel gating include the nicotinic cholinergic receptor, inhibitory amino acid ($GABA_A$) receptors (which bind benzodiazepines, barbiturates, and ethanol), and excitatory synaptic (N-methyl-d-aspartate or NMDA) receptors (which bind phencyclidine, ketamine, and glycine).

Voltage-gated ion channels underlie the physiology of nerve and muscle, among others. Growth factor receptors, transmembrane guanylate cyclase-type receptors, and the nitric oxide system also contribute to the complex molecular pharmacology of receptor channels and signal transduction. The interaction of anesthetics with these systems continues to be elaborated, but, in summary, inhalational anesthetics appear to affect all of these systems to greater or lesser degrees.

Even the essential question of where in the body anesthetics exert their effects remains uncertain. Although one might presume that the principal site is the brain, evidence suggests that anesthetizing the cerebrum can produce amnesia and unconsciousness, but surgical immobility derives from anesthetic effects on the spinal cord. Analgesia, on the other hand, has been far better elucidated. Opioid receptors (principally mu-type) are located in both the brain and in the dorsal horn of the spinal cord. It is likely that G protein-coupled receptors play a role in mediating the stimulation of mu receptors by morphine-type medications, as well as endogenous enkephalins and endorphins. In this fashion, opioids produce analgesia by inhibiting directly the ascending transmission of nociceptive impulses from spinal cord and by activating pain control circuits that descend from the midbrain via the rostral ventromedial medulla to the spinal cord dorsal horns.

Local anesthetics, in contrast, exert their effects by diffusing through axonal nerve membranes and interfering with impulse transmission along the nerve. Local anesthetics prevent impulse-associated depolarization at the point(s) where they have penetrated the nerve membrane. Their likely binding site is the Na^+ channel, which is the locus for propagation of the electrochemical stimulus that, in turn, initiates depolarization. The result is a stabilized nerve that is transiently incapable of being stimulated. Sensory, motor, and autonomic effects, depending upon the particular nerve, are thus blunted until the local anesthetic molecules sufficiently diffuse away from the nerve.

PRINCIPLES OF ANESTHETIC MANAGEMENT

Patients undergoing surgery are subjected by definition to nonphysiological trespass that threatens to destabilize their homeostasis.[3] Consequently, the anesthesiologist needs to take an active role in the process from the outset and must work closely with the surgical team in order to bring the patient through the operation without adverse outcome. This coordinated effort involves preoperative patient evaluation, optimization of the patient's composite organ function or dysfunction, provision of an appropriate anesthetic with appropriate physiological monitoring, careful patient positioning, preservation of cardiovascular stability, maintenance of oxygenation and ventilation, and smooth emergence from the anesthetized state to the recovering state.

Anesthetic Agents, Adjuvants, and Drug Interactions

There are many pharmacologic agents available in the armamentarium of the anesthesiologist to provide surgical anesthesia to the patient and enable optimal operating conditions. These include the inhaled anesthetics, IV agents that produce a hypnotic and amnestic state, anxiolytic medications such as benzodiazepines, opioids, and local anesthetics. There is no single ideal anesthetic drug that accomplishes complete surgical anesthesia. Successful anesthetic management therefore depends on a balanced approach utilizing multiple agents from different drug classes.

Inhaled Anesthetics

The inhalational agents most commonly employed in modern anesthetic practice include nitrous oxide and the potent halogenated ethers: isoflurane, sevoflurane, and desflurane. The inhaled agents are utilized in both the induction and maintenance phases of anesthesia. Induction with inhaled agents, termed an inhalational

induction (as opposed to an IV induction), is a technique used mostly for pediatric and neonatal patients in whom IV access has not been established. Adult patients with a phobia of needles who request an inhalational induction are rare exceptions. Inhalational agents possess the properties of being able to generate an unconscious state in which the patient spontaneously breathes but is insensate and possibly immobile; they also possess mild analgesic properties as well. The pharmacologic principle of minimal alveolar concentration (MAC) is defined as the inhaled concentration of anesthetic at which 50% of subjects do not move in response to a surgical stimulus. Nitrous oxide is a weak inhalational anesthetic and has a MAC of 105%. The potent volatile anesthetics have MAC values of 1.2%, 2%, and 6% for isoflurane, sevoflurane, and desflurane, respectively. Another pharmacologic principle of inhaled anesthetics is the blood/gas solubility or blood/gas partition coefficient. This property determines the propensity of the gas to dissolve in blood and has important clinical implications for the speed of inhalational anesthetic induction and speed of emergence from general anesthesia. Nitrous oxide has the lowest blood/gas partition coefficient followed by desflurane, sevoflurane, and finally isoflurane. The lower the coefficient, the less the particular agent tends to dissolve in blood and the faster the induction and emergence from anesthesia. Conversely, the higher the blood/gas coefficient, the slower the induction and emergence.

Nitrous oxide is a weak inhalational agent and is used most commonly as an adjunct agent to decrease the amount of potent volatile agent needed. It also has a long history of use for sedation in dental anesthesia. Many practitioners choose to utilize nitrous oxide in tonsillectomy and adenoidectomy surgery because it enables the maintenance of general anesthesia while helping to speed emergence at the end of surgery. Nitrous oxide dissolves into air-filled spaces at a rate many times faster than oxygen. Therefore, it may be prudent to avoid nitrous oxide in any clinical scenario where the surgery may create or involve hollow cavities. Classically, bowel surgeries, ophthalmologic surgeries, otologic surgery, and trauma situations (possible pneumothorax) would be examples of surgeries in which avoidance of nitrous oxide may be prudent. Nitrous oxide is emetogenic, and patients administered this agent may develop nausea and vomiting. Prophylactic treatment with 5-HT receptor blockers (e.g. ondansetron) and dexamethasone may prevent this adverse response.

The potent volatile agents such as isoflurane, sevoflurane, and desflurane are all structurally related ethers with fluorinated side groups. They possess the properties of being potent with low MAC values and are all cardiopulmonary depressants. They are potent vasodilators and cause a decrease in systemic vascular resistance. Isoflurane is the oldest of the three anesthetics, followed by sevoflurane and finally desflurane. Sevoflurane has the property of smelling less pungent (it is described as possessing a sweeter smell) and is the most often used volatile anesthetic agent for inhalational inductions in modern anesthetic practice. Desflurane is the anesthetic agent with the lowest blood/gas partition coefficient and can be used for faster wake-up times.

Intravenous Anesthetics

Propofol is a commonly used anesthetic agent for IV sedation and induction of general anesthesia. Its chemical structure consists of a phenol ring with two isopropyl groups (2,6-diisopropylphenol) prepared in an emulsion of egg lecithin, soybean oil, and glycerol. When administered, it causes a variably severe burning sensation at the injection site. At low doses, it provides sedation and unconsciousness with spontaneous respiration and, at higher (induction) doses, it causes apnea and hypotension from vasodilation.

Ketamine is a phencyclidine derivative that can be administered intravenously or intramuscularly for the purposes of sedation or general anesthesia. It has the properties of being a sympathomimetic, i.e. it potentiates the sympathetic nervous system and produces tachycardia and hypertension. It is less of a respiratory depressant and has the added benefit of being a potent bronchodilator, which is useful in patients with reactive airway disease. Ketamine can cause excessive salivation as well as hallucinations and other psychological side effects such as dysphoria when not coadministered with a benzodiazepine. Patients administered ketamine by itself develop a dissociated, catatonic state of being. Because it is not as potent of a cardiopulmonary depressant, ketamine is unique in its use for the care of unstable patients in shock or cardiac tamponade. In uncooperative patients unable to receive either an IV or mask induction, ketamine can be delivered intramuscularly to induce a sedated and anesthetized state.

Etomidate is a carboxylated imidazole dissolved in propylene glycol. It is used primarily to induce general anesthesia in patients who are hemodynamically unstable

because it holds the distinction of being the least cardiovascularly depressing of the IV anesthetics. However, it can produce masseter muscle spasticity and also causes adrenocortical suppression in a transient, dose-dependent manner.

Opioids

Opioids bind to receptors located throughout the central nervous system and are potent analgesics as well as possessing a mild-to-moderate sedating effect. Endorphins, enkephalins, and dynorphins are examples of endogenous peptides that produce a similar effect by binding to the same receptors. By blocking nociceptive neuronal transmission, the opioids attenuate the pain response to surgical stimulus. In anesthetic doses, all opioids depress ventilation and raise the apneic threshold, i.e. the highest $PaCO_2$ at which a patient remains apneic. They also all slow gastric motility and prolong gastric emptying time.

Fentanyl is highly lipid soluble and can be administered intravenously, transmucosally, as well as transdermally. It has a rapid onset of action and a short duration of action because it is quickly redistributed to other tissue compartments. Morphine is poorly lipid soluble and therefore slow to cross the blood–brain barrier. This explains morphine's slower onset of action and prolonged duration of action. It is biotransformed in the liver to form morphine 3-glucuronide and morphine 6-glucuronide that are renally cleared. These metabolites may cause prolonged sedation and increased respiratory depression in the setting of end-stage renal disease.

Remifentanil is unique by virtue of its metabolism by nonspecific esterases in blood. The effective half-life is approximately 5–10 minutes. Therefore, remifentanil is extremely useful in producing a deep analgesic state, but its effects cease soon after discontinuation of drug administration. This distinction makes remifentanil a superior drug for use in cases in which a deep analgesic state is required with rapid awakening and return of spontaneous ventilation [i.e. direct laryngoscopy and endoscopic sinus surgery (ESS)].

Neuromuscular Blocking Agents

Neuromuscular blocking agents bind to the nicotinic ACh receptor at the neuromuscular junction and produce a state of muscle relaxation. Two mechanistically distinct groups of neuromuscular blocking agents exist: the depolarizing relaxants (succinylcholine) and the nondepolarizing relaxants.

As the name implies, the depolarizing relaxants induce a strong depolarization and lead to the deactivated state of the ACh receptor, termed phase I blockade. The onset of neuromuscular blockade is rapid (30–60 seconds) and duration of action is short (less than 10 minutes after a 1 mg/kg dose). Succinylcholine is the only depolarizing agent used in clinical practice. Clinically, succinylcholine is used in settings where rapid muscle relaxation and intubation are required in patients at high risk of aspiration of gastric contents.

The nondepolarizing neuromuscular relaxants produce competitive antagonism at the ACh receptor and prevent normal muscle contraction. There are a variety of nondepolarizers and they are grouped into two structurally distinct groups: the benzylisoquinolines and the steroidal compounds. Steroidal compounds tend not to affect heart rate, while the benzylisoquinolines tend to release histamine. Examples of steroidal muscle relaxants include pancuronium, vecuronium, and rocuronium. Vecuronium and rocuronium are the two most commonly used nondepolarizing neuromuscular blocking drugs in modern anesthetic practice. Benzylisoquinoline relaxants include atracurium and cisatracurium.

Local Anesthetics

Local anesthetics are of particular interest to the otorhinolaryngologist because of the drugs' myriad uses in ambulatory and inpatient surgery. Mechanistically, the local anesthetics work by blocking voltage-gated sodium channels and nociceptive neuronal transmission. Sensitivity to nerve blockade is inversely related to axonal diameter and degree of myelination. The potency of a local anesthetic correlates with lipid solubility where the more lipid soluble an agent is, the greater the degree of penetration through the lipid nerve membrane. Local anesthetics are all weak bases. The p*K*a is a biochemical property of a drug that determines the relative concentration of the nonionized lipid-soluble form of the anesthetic to the ionized water-soluble form in tissues. The closer the p*K*a of an agent is to physiologic pH, the higher the concentration in tissue of the nonionized base and the greater the ability of the drug to diffuse through the lipid neuronal membrane, hence the faster the onset of action. Duration of action of an agent is also correlated with lipid solubility, where the higher the lipid solubility, the longer the duration of action. Toxicity of local anesthetics relates to systemic absorption and action at undesired end-organs, most notably the brain and the heart. The rate

Table 40.1: ASA physical status classification

I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes
E	Emergency operation (appended to the foregoing, e.g. III E)

of systemic absorption is proportional to the vascularity of the injection site with an IV site obviously having the highest rate of absorption. This is followed by tracheal, intercostals, caudal, paracervical, epidural, brachial plexus, and subcutaneous sites.

Local anesthetics can be classified structurally into the amino-esters and the amino-amides. Ester local anesthetics are the older of the two classes with cocaine being a classic example as well as chloroprocaine, procaine, and tetracaine. Ester local anesthetics are metabolized predominantly by pseudocholinesterase and undergo ester hydrolysis. Amide local anesthetics include lidocaine, bupivacaine, mepivacaine, and ropivacaine. They undergo hepatic metabolism by microsomal P-450 enzymes. Conditions of hepatic dysfunction or failure will reduce the metabolism of these drugs and place the patient at risk of toxicity. Lidocaine and bupivacaine (Marcaine) are the two most commonly used local anesthetics in clinical practice. Lidocaine is a medium-potency local anesthetic with fast onset and a moderate duration of action. Bupivacaine has a slow onset of action and a long duration of action. Bupivacaine possesses the undesirable distinction of being the most cardiotoxic local anesthetic and may cause life-threatening arrhythmias such as ventricular tachycardia and ventricular fibrillation when toxic limits are reached. It is therefore always important to exercise good technique when injecting bupivacaine (and all local anesthetics in general) by first aspirating back on the syringe and ruling out blood return. Signs and symptoms of local anesthetic toxicity include circumoral numbness, a metallic taste, and dizziness; tinnitus and blurred vision may also occur. Awake patients may describe restlessness, paranoia, agitation, and a sense of unwellness. Severe CNS toxicity may lead to generalized tonic-clonic seizures.

DRUG INTERACTIONS

Anesthetic agents tend to be synergistic in terms of their effects; i.e. the use of any one agent will decrease the dose needed of another anesthetic agent. Intravenously administered local anesthetics decrease the MAC requirements of volatile anesthetics by up to 40%. Similarly, opioids also decrease MAC requirements. Neuromuscular agents, while not strictly speaking a type of anesthetic, decrease the requirement for anesthetic agents in order to provide good operating conditions.[4]

PREOPERATIVE EVALUATION AND PREPARATION

The most basic stratification of preoperative patient health is the American Society of Anesthesiologists' (ASA) physical status classification system[5] that dates back to 1941. Although relatively uncomplicated, it offers a time-honored method of categorizing the level of concern that an anesthesiologist should apply in considering a given patient's anesthetic (Table 40.1). Although anesthesiologists have debated for decades precisely which patients fall into which categories, the ASA has declared that "there is no additional information that will help you further define these categories." Just the same, the Cleveland Clinic has publicized on its web site the following examples[6] listed in Table 40.2.

This system was not conceived as a means of stratifying risk, but rather a means of getting anesthesiologists to think about their patients' preoperative condition with an eye toward modifying the anesthetic that they would be administering. Just the same, the ASA physical status classification appears to be as good a prognosticator of postoperative complications as more recent and complex methodologies such as the well-known Cardiac Risk Index published by Goldman et al. in 1977.[7]

In order to classify a patient's preoperative physical state, it is necessary to obtain a detailed history, perform a physical examination, and consider relevant laboratory test results. As Roizen describes[8] for tests reported over a continuous range of results, the distribution in a population is Gaussian, i.e. a normal distribution. Arbitrarily, 2.5% of lab test results for healthy patients will fall above the "normal" range and another 2.5% of the same test results for healthy patients will fall below the "normal" range. Furthermore, ordering multiple tests increases the probability of an "abnormal" finding in a healthy patient.

Table 40.2: Illustrations of ASA physical status categories

I	No organic, physiologic, or psychiatric disturbance; excludes the very young (< 2 years) and very old (> 70 years); healthy with good exercise tolerance
II	No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy
III	Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms
IV	Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
V	Not expected to survive > 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy

From The Cleveland Clinic Foundation.[6]

There is no established standard among anesthesiologists as to what testing needs to be done preoperatively. Rather, it is more logical to obtain laboratory information on the basis of the patient's underlying conditions and medications. While healthy patients undergoing minor, noninvasive procedures need not have any laboratory testing whatsoever, a patient with multisystem disease undergoing major surgery needs extensive evaluation.

Even so, many surgeons have had the unfortunate experience of having evaluated (or having had evaluated for them by an internist or an anesthesiologist) a patient some days prior to surgery, only to have a different anesthesiologist on the day of surgery hold up the surgery by requiring additional testing. It goes without saying that it is insufficient simply to have had an internist "clear" the patient without understanding the implications of that patient's medical condition on the conduct of the anesthetic and surgery. In effect, only the anesthesiologist on the day of surgery can "clear" the patient. Good anesthesiologists, however, do look to a good internist's or a colleague's evaluation of a patient's physical status, particularly from the beneficial viewpoint of a relevant longitudinal history, as an important means of assessing that patient's optimization for surgery.

The best way to avoid having a patient's surgery delayed (or worse, having the patient unsafely undergo the procedure) is to apply consistently an appreciation of the interactions of a patient's medical condition with anesthesia and surgery. A group of anesthesiologists should ideally gravitate to a consistent approach over time, particularly with regard to required laboratory testing. Having already stated that there is no standard among anesthesiologists in this regard, we might suggest the following schema (modified from Roizen[8]) for adult patients undergoing rhinological surgery under general anesthesia:

- CBC, including platelet count
- Electrolytes (Na^+, Cl^-, K^+, HCO_3^-), BUN, creatinine, glucose
- INR, PTT
- Liver function tests
- ECG for age more than 50 or symptomatic
- Chest X-ray only for patients with worsening pulmonary symptoms.

This list is not exhaustive nor does it preclude other testing as indicated by the patient's history or physical examination. Likewise, it includes testing where the yield is likely to be low. Its purported value is its sharing a common ground for most anesthesiologists in order to minimize delays or cancellations on the day of surgery. This discussion may be moot if hospital policies have been elaborated that dictate the extent and timing of the preoperative evaluation and laboratory testing.

To that last point, there is no standard among anesthesiologists regarding how recently the history, physical examination, and laboratory testing need to have been done in order to be considered useful. In the absence of new symptoms and to the degree that a given patient is known to have been stable in terms of medical conditions and medications, repeated testing becomes less important. Conversely, new or interval change in symptoms, medical instability, and/or changed medication regimens all heighten the need for testing close to the day of surgery.

The preceding general discussion of preoperative evaluation and preparation can be more definitively refined for adult patients with cardiac disease undergoing noncardiac surgery. The American College of Cardiology (ACC) and the American Heart Association (AHA) jointly published[9] their most recently revised set of practice guidelines for this subgroup of patients in 2007. This algorithm, based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients

50 years of age or greater, provides a stepwise description of the types of further cardiac investigation that are recommended for patients with cardiac disease relative to the type of surgery planned. A summary of the algorithm follows:

- Emergency noncardiac surgery requires no further workup. The procedure needs to be performed, so perioperative surveillance and treatment are implemented both in the operating room and during recovery.
- Nonemergency surgery allows greater discretion on the parts of the caregivers to assess the patient's cardiac status and, if needed, define the extent of disease and treat it accordingly.
- Active cardiac disease encompasses unstable or severe angina, recent myocardial infarction, decompensated heart failure (i.e. New York Heart Association Class IV patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest), significant arrhythmias, and severe valvular disease.
- Low-risk surgery (risk of cardiac death and nonfatal myocardial infarction < 1%) includes endoscopic and superficial procedures, while intermediate-risk surgery (cardiac risk 1–5%) includes prostate surgery and intraperitoneal surgery. High-risk surgery (cardiac risk > 5%) relates to vascular surgery.
- A person with an exercise tolerance of four metabolic equivalents (METs) can climb a flight of stairs or walk up a hill, walk on level ground at 4 mph (6.4 km per hour), run a short distance, do heavy work around the house like scrubbing floors or lifting or moving heavy furniture, participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football.
- A patient without active cardiac disease having low-risk surgery or exhibiting functional capacity equivalent of greater than or equal to four METs without symptoms can proceed to surgery without further workup.
- A patient with active cardiac disease undergoing low-risk surgery can proceed directly to surgery.
- A patient with active cardiac disease with a functional capacity equal to or greater than four METs without symptoms undergoing intermediate- or high-risk surgery can proceed to surgery if noninvasive testing will not alter treatment.
- A patient with active cardiac disease undergoing intermediate- or high-risk surgery with less than four METs exercise tolerance needs an evaluation of his/her clinical risk factors. These include ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease.
- If the person does not have any of these clinical risk factors, the planned surgery should proceed. Otherwise, it is recommended to proceed with surgery in patients with one to three clinical risk factors unless noninvasive testing will change management.
- Patients with three or more clinical risk factors requiring vascular surgery need further testing if it will change anesthetic management.
- Assessment for coronary artery disease risk and functional capacity includes a 12-lead electrocardiogram, exercise stress testing, and pharmacological stress testing.
- Supplemental preoperative cardiac evaluation consists of left ventricular function by radionuclide angiography, echocardiography, and contrast ventriculography.

While the foregoing algorithm is complicated, its application, in brief, is that patients undergoing intermediate-risk surgery who do not have functional capacity greater than four METs or who do have cardiac symptoms need to be evaluated by a cardiologist or internist. If that patient is appraised as having no clinical risk factors (listed above), one may proceed with the planned surgery. Patients with 1, 2, or 3 clinical risk factors may proceed to surgery, particularly with heart rate control, if management will not likely be affected. Alternatively, these patients should undergo noninvasive testing if it will likely change the patient's perioperative management. The nebulous nature of these last two statements suggests that the surgeon, anesthesiologist, and cardiologist or internist confer prior to the day of surgery in order to arrive at common ground.

A patient's integrated cardiopulmonary performance can be limited by lung disease in the absence of heart problems. Auscultation of the lungs with a stethoscope can quickly determine the presence or absence of rhonchi, wheezes, or rales. A chest X-ray in the absence of history or physical examination findings suggestive of cardiopulmonary disease is unlikely to add any useful information and is an unnecessary screening test. In the presence of positive historical or physical evidence, however, a chest X-ray can serve as a valuable basis for postoperative comparison.

Pulmonary function testing (PFT) is an objective means by which to quantify a patient's respiratory dysfunction

beyond that achieved after obtaining a medical history and performing a physical examination. PFTs are done to predict how well a patient with lung disease will deal with the stressors of surgery and anesthesia so as to avoid perioperative pulmonary complications (PPCs), such as atelectasis, pneumonia, respiratory failure, and exacerbation of long-standing lung disease.

Useful PFTs include arterial blood gas measurement and spirometry. The latter includes forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), the FEV1/FVC ratio, peak flow, and forced expiratory flow between 25% and 75% of lung volume (FEF 25–75%)—before and after bronchodilator treatment. Examination of the flow-volume loop configuration, in addition to providing the aforementioned data, can be informative about the location of fixed or variable airway obstruction. Essentially, PFTs, including arterial blood gas analysis, offer information about whether a patient's pulmonary disease is obstructive versus restrictive, whether the patient has a propensity to retain carbon dioxide, and whether the patient's pulmonary disease has a reversible component.

Asthmatic patients will tell you specifically what makes them better and what makes them worse. Continuing their established treatment or prevention regimen through the day of surgery and prophylactically by administering an inhalable bronchodilator before induction of anesthesia will, along with a smoothly conducted anesthetic, serve to minimize perioperative bronchospasm.

In 2006, the American College of Physicians[10] elaborated a set of guidelines for risk assessment and reduction of PPCs. They stated that significant preoperative risk factors for PPCs are chronic obstructive pulmonary disease, age more than 60 years, ASA physical status class II or higher, serum albumin levels less than 3.5 g/dL, functional dependence, and recumbent congestive heart failure. They also determined that surgery more than 3 hours duration, abdominal surgery, and general anesthesia were significant risk factors for PPCs in these patient populations. The guidelines concluded that these patients at risk should receive preoperative PFTs and postoperative incentive spirometry.

Preoperative measures to improve lung function include smoking cessation, mobilization of secretions, bronchodilator treatment, and improved stamina. Although smoking-induced destruction of lung architecture cannot be reversed, smoking cessation results in decreased airway secretions, decreased airway reactivity, and improved mucociliary transport. Just the same, these benefits may not be realized for 2–4 weeks. Smoking cessation on the day prior to surgery will only improve the picture by decreasing the carbon monoxide carried by blood. Reducing the percentage of circulating carboxyhemoglobin will, however, improve the amount of oxygen carriage by the blood. A related and, given the current obesity epidemic, an increasingly important issue is that of obstructive sleep apnea (OSA).[11]

The reason why OSA has interested anesthesiologists and for which the ASA has issued a set of guidelines is that OSA patients risk airway obstruction during induction of anesthesia and upon emergence from anesthesia. Coupled with their increased sensitivity to anesthetics, manifested as respiratory depression, OSA patients in the supine position tend more than other patients to have their tongue, tonsils, and soft palate come to rest against their hypopharynx, thus obstructing airflow above the level of the larynx. The insertion of an endotracheal tube effectively stents the upper airway, allowing free passage of air or anesthetic gases to the lungs. Even if tracheal intubation has been performed successfully (though not necessarily easily), removal of the endotracheal tube at the end of surgery can result in life-threatening airway obstruction.

Consequently, the ASA guideline urges that extubation be performed in the semi-upright, upright, or nonsupine position after full neuromuscular recovery has been verified and the patient has fully awakened. Problems arise in these patients when the patient struggles against the presence of the endotracheal tube but has not sufficiently regained consciousness so as to maintain airway patency. Deep extubation is clearly contraindicated. The principle of avoiding extubation while the patient is excitedly emerging from anesthesia but has not yet achieved sufficient recovery so as to protect the airway needs to be followed in these patients scrupulously.

In performing a preoperative evaluation, the anesthesiologist should always examine the patient's airway anatomy to determine whether ventilation of the patient's lungs by anesthesia facemask or direct laryngoscopy and intubation of the patient's trachea might prove to be difficult.[12] The airway examination consists of assessing the patient's cervical range of motion (particularly active neck extension), maxillary–mandibular alignment (otherwise referred to as the thyromental distance), mouth opening, state of dentition, and the patient's Mallampati Airway Classification.[11]

Although the Mallampati Airway Classification does not by itself provide an infallible correlation between class

score and ease of laryngoscopy, its simplicity has earned it widespread application. The examiner directs the patient to sit up straight, open the mouth, stick out the tongue, but not phonate. The classification is as follows: Class 1: visualization of soft palate, fauces, uvular, and tonsillar pillars; Class 2: visualization of soft palate, fauces, and uvula; Class 3: visualization of soft palate and uvular base; Class 4: visualization of the hard palate only.

The guiding principle holds that alignment of the oral, pharyngeal, and laryngeal axes for direct visualization of the larynx is most easily accomplished in patients with full neck extension at the atlanto-occipital joint, matched maxillary–mandibular alignment, BMI less than 25 kg/m^2, neck circumference less than 40 cm, normal mouth opening, and Mallampati 1 classification, aided by the absence of maxillary dentition. Conversely, limited neck extension, retrognathia, BMI more than 30 kg/m^2, neck circumference more than 40 cm, limited mouth opening, and Mallampati 4 classification, made more difficult by full maxillary dentition, separately, or in combination, can lead to poor alignment of the oral, pharyngeal, and laryngeal axes and an inability to visualize the larynx directly. Other airway features such as a large or immobile tongue, radiation fibrosis of airway structures, or tumors of the head and neck can likewise complicate the ease of lung ventilation by anesthesia facemask and/or tracheal intubation.

The anesthesiologist, in planning for a general endotracheal anesthetic, must decide whether, given the constellation of physical findings, he or she believes that ventilation of the patient's lungs by anesthesia facemask and direct laryngoscopic visualization of the patient's larynx can be accomplished without inordinate difficulty, once anesthesia induction has commenced. When difficult ventilation and/or difficult tracheal intubation are contemplated, the anesthesiologist must make provision for these potential difficulties by arranging for the availability and usability of auxiliary airway management devices and, if possible, the assistance of a second anesthesiologist. The anesthesiologist, furthermore, has to decide whether these auxiliary devices can be safely employed after the patient has been anesthetized or, if not, whether the airway needs to be secured prior to the patient's having received an anesthetic. The commonest approach in such patients is awake/sedated fiberoptic laryngoscopy and tracheal intubation. Even so, despite careful evaluation and sound clinical judgment, the anesthesiologist will occasionally encounter a patient whom he or she believed to be safely intubatable but whose larynx eludes visualization and whose trachea eludes intubation. In such situations, the anesthesiologist should apply the principles of the ASA Difficult Airway Algorithm,[13] a stepwise sequence of branched decision making, the goal of which is an unharmed patient.

If, for example, initial intubation attempts have proved unsuccessful, the anesthesiologist must ventilate the patient's lungs by anesthesia facemask. If ventilation is adequate, a nonemergency pathway can be followed where alternative approaches to intubation can be tried, including allowing the patient to awaken. If, however, facemask ventilation is not adequate, a laryngeal mask airway (LMA) should be inserted, if feasible. If LMA ventilation proves adequate, the anesthesiologist can return to the nonemergency pathway. If LMA ventilation is not adequate, the anesthesiologist must follow the emergency pathway that leads either to the patient's awakening or to the insertion of an emergency invasive airway access device, i.e. a tracheostomy or a cricothyroidotomy.

Another issue that unites (but sometimes divides) surgeon and anesthesiologist is NPO (Latin: *nil per os* = nothing by mouth) status. The consequence of aspiration of solids or liquids into the trachea can range from obstruction of the airway to soilage of the pulmonary parenchyma and, potentially, pneumonitis and even death. Pulmonary aspiration of acidic gastric contents is particularly problematic: pulmonary morbidity from aspiration is proportional to the volume of aspirate and inversely proportional to the pH of the aspirated material. Risk factors for pulmonary aspiration include a "full stomach", pregnancy, obesity, gastroesophageal dysfunction (including prior esophageal surgery, symptomatic hiatal hernia, and dysphagia), functional or mechanical obstruction to digestion, and vocal cord malfunction. Gastroparesis, idiopathic or associated with diabetes mellitus, compounds the problem. Alkalinizing the gastric contents with proton pump inhibitors, histamine-2 antagonists, and/or a nonparticulate antacid like sodium citrate by mouth can ameliorate the potential injury to the lungs by eliminating the acid component of the aspirate.

In these situations, the anesthesiologist modifies routine practice by performing a rapid sequence induction, doing an awake fiberoptic intubation, or entirely avoiding general anesthesia, where possible. A rapid sequence induction involves preoxygenation, the administration of a rapidly acting induction drug and the near-simultaneous administration of a rapidly acting muscle relaxant, usually while an assistant applies cricoid pressure to compress the esophagus between the cricoid cartilage and the vertebral column. Although the utility of cricoid pressure has lately

been criticized as ineffectual and, what's worse, distorting to the intubator's laryngoscopic view, the cardinal principle is that the trachea be protected by a cuffed endotracheal tube in as short a time period as possible after loss of consciousness (with the attendant loss of protective airway reflexes).

The best way to avoid such risks is to keep the patient's stomach empty. Hence, the traditional NPO dictum that elective patients have nothing to eat or drink after midnight. The ASA, having examined the literature on this subject, helpfully offers some guidelines to consider in making go/no-go decisions.[14] In summary, a patient may consume clear liquids (liquids through which one can see, e.g. water, nonpulp fruit juice, carbonated beverages, clear tea, black coffee) up to 2 hours prior to anesthetic induction. There is some evidence that ingestion of clear liquids actually aids gastric emptying. The guidelines state that breast milk requires 4 hours for gastric emptying. More directly applicable to adults, the guidelines suggest 6 hours for a modest amount of nonhuman milk, infant formula or a light meal, such as toast and clear liquids. The guidelines get less prescriptive after that: "Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period."

Our version of today's best practice requires patients to be NPO after midnight, discouraged from having pizza and beer at 11:59, allowed—even encouraged—to have clear liquids up to 2 hours preoperatively, and considered to have a "full stomach" the entire calendar day after ingesting a full meal. Establishing an agreement on principles among a hospital's surgeons and anesthesiologists can prevent confusion and conflict when patients fail to do what they are asked to do.

ANESTHETIC MANAGEMENT FOR RHINOLOGICAL SURGERY

Standard Monitoring Techniques

Upon completion of the preoperative assessment and when the patient is deemed a suitable candidate for general anesthesia, the patient is brought into the operating room and placed on the OR table, at which point standard monitoring is placed on the patient in order to enable continuous observation of vital signs during surgery. These monitors include 5-lead electrocardiography, pulse oximetry, and blood pressure. Additional monitors are capnography (tidal CO_2) and temperature. Once these continuous monitors are applied to the patient, IV access is achieved. Administration of 100% oxygen to the patient by facemask is begun with the goal of preoxygenating or denitrogenating the patient; i.e. the functional residual capacity of the patient is filled with 100% oxygen instead of the 21% FiO_2 of room air. During this time, the anesthesiologist may choose to administer an IV benzodiazepine or opioid with the goal of alleviating anxiety and beginning to sedate the patient. A good seal of the facemask enables determination of the gases that the patient is inhaling and exhaling, including oxygen, carbon dioxide, and any inhalational anesthetics chosen by the anesthesiologist to administer to the patient. Once the end-tidal oxygen approaches 100%, the anesthesiologist administers IV induction agents to achieve a state of general anesthesia.

Airway Management

Proper airway management begins in the preoperative assessment as detailed above with the determination of the relative difficulty or ease of delivering positive-pressure ventilation to the patient's lungs and potential endotracheal intubation. Prior to inducing general anesthesia, the otolaryngologist and anesthesiologist should decide what type of airway is most appropriate for the case. Is an LMA acceptable or an endotracheal tube preferred? A standard endotracheal tube may be sufficient but the otolaryngologist may prefer to have an oral or nasal right-angle endotracheal tube, reinforced tube, or armored tube.

Upon achieving an apneic state after induction, the anesthesiologist will attempt to deliver a positive pressure breath and determine the adequacy of ventilation and oxygenation. Clinical signs of successful ventilation include chest rise, fogging in the mask and transparent anesthesia right-angle elbow piece, the tactile feel of lung compliance in the manual ventilation bag, as well as the appearance of tidal CO_2 on the anesthesia machine monitor. Ventilation is the single most important clinical maneuver to achieve and verify after induction of general anesthesia, and it is a synthesis of different clinical data. If the anesthesiologist is unable to adequately mask ventilate the patient, a quick escalation of care must occur in order to ensure that the patient's airway be secured, or hypoxia and the sequelae of hypoxia may ensue, ultimately leading to ischemic injury of vital organs. Typical maneuvers include increasing the positive pressure administered by dialing up the adjustable pressure limiting valve of the

anesthesia machine. Simultaneous maneuvers to alleviate and overcome upper airway obstruction can be carried out including a chin lift, jaw thrust (one-handed or two-handed), and oropharyngeal and/or nasopharyngeal airway placement. If the patient has not already been optimally positioned in the "sniffing position," this can be carried out by placing a roll under the shoulders and by elevating and extending the head. If these maneuvers continue to be unsuccessful, the anesthesiologist should activate the ASA difficult airway algorithm by calling for help and either attempting direct laryngoscopy or placing a LMA. A variety of advanced airway equipment can be used to help achieve endotracheal intubation including video laryngoscopes, intubating LMAs, flexible fiberoptic bronchoscopes, and a Combitube. If all efforts to noninvasively secure the airway fail, a surgical airway may need to be achieved via cricothyroidotomy or tracheostomy.

INDUCTION AND MAINTENANCE OF ANESTHESIA

Unless there is an underlying airway or cardiopulmonary issue, induction of anesthesia for rhinological surgery often commences with an IV dose of midazolam for anxiolysis, followed, after oxygenation/denitrogenation of the lungs, by IV propofol in a dose sufficient to produce unconsciousness and apnea. After assuring the ability to ventilate the patient's lungs by mask, the anesthesiologist will usually administer a neuromuscular blocking drug intravenously in order to provide ideal conditions for tracheal intubation. As described above, succinylcholine is used for a rapid sequence induction, when the procedure is too short to accommodate a longer-acting relaxant, or when the surgeon intends to use a nerve stimulator. In other situations, the anesthesiologist may give a nondepolarizing relaxant, which has fewer side effects than succinylcholine but whose muscle weakness will need to be antagonized by an anticholinesterase coupled with an anticholinergic at the conclusion of surgery. Because of succinylcholine's tendency to produce bradycardia in children and because succinylcholine may trigger malignant hyperthermia, anesthesiologists tend to avoid this drug in children and will often intubate a child's trachea under deep anesthesia without benefit of any relaxant.

The decision to use an LMA for airway management instead of an endotracheal tube for rhinological procedures is controversial. On the one hand, LMA insertion is generally easier than an endotracheal tube, does not require muscle relaxant use, and avoids potential trauma to the larynx. On the other hand, because of its superglottic position, an LMA is not protective against laryngospasm and its consequences or against pulmonary aspiration of gastric contents. In the specific situation of rhinological surgery, blood trickling from the nose into the hypopharynx may escape suctioning above the LMA, stimulate the vocal cords and induce laryngospasm, and/or be aspirated causing hypoxemia.

Surgical preparation of the nose for surgery by injection of local anesthetic with epinephrine, as well as by the topical application of vasoconstrictor-soaked pledgets, frequently leads to a transient tachycardia from absorbed catecholamine. The combination of epinephrine and cocaine, when used as a nasal vasoconstrictor, is particularly worrisome. Injection and absorption of a sufficient quantity of both together can result in malignant hypertension, severe tachycardia, multifocal PVCs, ventricular tachycardia, and even ventricular fibrillation. Cocaine, by preventing the reuptake of norepinephrine at nerve endings, enhances the cardiovascular sequelae of the injected epinephrine. Oxymetazoline, for example, does not share cocaine's systemic pharmacological effects and is safer.

Once the procedure is under way, the anesthesiologist can contribute to the surgeon's ease and efficiency by keeping the blood pressure low in order to limit nasal bleeding. The readily available strategy of employing higher than usual concentrations of the inhaled anesthetic is often sufficient to maintain the patient's systolic pressure below 100 mm Hg. Alternative or adjunctive measures to reduce vascularity include the use of a 15° head-up position to decrease venous pressure, IV beta blockers like labetalol or metoprolol, and direct vasodilators like IV hydralazine.

The anesthesiologist has to balance the advantage to the surgeon of producing deliberate or intentional hypotension with the patient's need for adequate organ perfusion. Inhaled anesthetics interfere with autoregulation—the maintenance of blood flow over a wide range of systemic blood pressures—with the consequence that a lower blood pressure may put organs like heart, brain, and kidney at risk. Maintaining adequate hydration can minimize the reduction in blood flow to these organs, but there is no question that their blood flow is decreased under these circumstances.

STRATEGIES FOR EMERGENCE FROM ANESTHESIA

In considering emergence from anesthesia, the anesthetics used for maintenance, their dosing intervals, and their functional half-lives must be reckoned, as these are crucial for the discontinuation of effect in preparation for wake-up. Neuromuscular blockade, if employed, must be reversed, and maintenance anesthetics must be discontinued. As the patient is waking up, the anesthesiologist may decide if he wishes to perform a deep or an awake extubation. An awake extubation is the most common strategy and, as its name implies, involves removal of the airway device when the patient is fully awake and has regained full airway reflexes. In a deep extubation, the anesthesiologist is making a judgment that the patient, despite still being deeply anesthetized, will be able to oxygenate and ventilate (exhale CO_2) without an endotracheal tube or LMA, and that the risk/benefit analysis justifies his/her action. Benefits of a deep extubation include possible avoidance of bucking and straining on the airway and prevention of a Valsalva-type reaction in which intracranial, intrathoracic, and airway pressures become elevated, thereby jeopardizing underlying coagulated tissues and suture lines. Once a deep extubation has been performed, the patient should be monitored closely for maintenance of adequate ventilation and oxygenation either in the OR or, when the anesthesiologist deems it safe to transport the patient, in the PACU. During transport and in the PACU, the patient should continue to be monitored closely without being disturbed until recovery of consciousness. Contraindications to a deep extubation may include difficult airway management (i.e. ventilation, intubation), rapid sequence indication, OSA syndrome, obesity, as well as blood emanating from the nose into the oropharynx.

Since deep extubation is problematic in many rhinological procedures, anesthesiologists have devised diverse strategies for maintaining a suitable anesthetic depth while surgery is proceeding yet achieving a smooth but prompt recovery from anesthesia once surgery has ended. These strategies include the use of droperidol (along with an opioid) to create in the patient a partial neuroleptic state, i.e. a level of consciousness where the patient is aware of his/her environment but lacks the affective or emotional component of the usual wakeful state. Droperidol is a butyrophenone, similar to phenothiazines, that is also antiemetic, slightly vasodilatory, and sedative. Its use has been limited by an FDA "black box warning" that alerts practitioners to droperidol's tendency to prolong patients' electrocardiographic QT interval. The warning limits the drug's use to 2.5 mg IV in patients without preexisting QT prolongation unless special precautions are taken. Patients given higher doses and/or having preexisting QT prolongation stand at higher-than-normal risk of developing torsades de pointes, a form of ventricular fibrillation.

Alternatively, a dexmedetomidine (Precedex) infusion can be used to bridge the gap between surgical anesthesia and wakefulness. Dexmedetomidine is an alpha$_2$ agonist that is sedating while preserving spontaneous ventilation. Every drug has its side effects, and this drug can produce treatment-refractory hypotension, as well as bradycardia and even hypertension, particularly if given as a bolus. Infusions given without a loading dose are better tolerated.

POST-ANESTHESIA RECOVERY

Goals during post-anesthesia recovery include monitoring for adequate ventilation and oxygenation, stable vital signs, pain control, and careful observation for the appearance of any surgical complications. Patients who have undergone rhinological procedures under general anesthesia have usually also received intranasal local anesthetic injections (with epinephrine) and/or instillation of vasoconstrictors (including cocaine). The residual local anesthetic effects reduce the postoperative requirement for IV or PO analgesics. Nausea and vomiting are, however, enhanced by the swallowing of nasopharyngeal blood and subsequent gastric irritation. Typical antiemetics for rhinological surgery include ondansetron, dexamethasone, and droperidol, though there are many alternatives. Individual anesthesiologists and ORL surgeons may use their personal preference, though the use of some antiemetic regimen is recommended. The combination of several antiemetics that function at different sites at the chemoreceptor trigger zone in the medulla is more effective in preventing or mitigating postoperative nausea and vomiting than any single drug used alone.

REGIONAL ANESTHESIA FOR RHINOLOGICAL SURGERY

Regional nerve blockade in the head and face can be a useful adjunct in providing both intraoperative anesthesia and postoperative pain control. Nerve blockade entails drug injection (usually local anesthetic) into the extraneural or paraneural spaces, providing complete

anesthesia in the region supplied by that nerve distal to the site of injection.[15,16] Specific nerve blocks are described in detail in other chapters of this book.

Patient Positioning and Related Injuries

The most common position for patients undergoing rhinological surgery is supine or supine-back elevated. Regardless of position, an immobile, insensate patient who stays in the same position for hours on end may experience pressure injury to subcutaneous tissue and skin. Patients in the supine position are at particular risk for ulnar nerve compression and neuropathy, pressure injury to the dependent parts of the head (occiput), feet (heels), and back. Ulnar nerve compression and neuropathy can be avoided by carefully supinating the hands and by padding the ulnar groove. The patient's face is also at risk for injury during rhinological surgery from pressure or puncture by misdirected instruments.

Monitored Anesthesia Care

Monitored anesthesia care refers to a plane of sedation less than that provided by general anesthesia. The patient is allowed to breathe spontaneously and is provided supplemental oxygen via nasal cannulae. Monitored anesthesia care can quickly escalate to levels approaching general anesthesia as the patient is deepened to provide optimal operating conditions. Obese patients or those with OSA may develop unacceptable upper airway obstruction and hypoxemia as the anesthetic is escalated. Thus, the anesthesiologist may have to provide additional airway support and convert to a general anesthetic if needed. A case booked as "MAC only" should therefore never be underestimated, and the anesthesiologist should always be prepared for general anesthesia. The anesthesiologist should always carefully screen a patient for MAC as though general anesthesia was planned.

Despite its implied simplicity, monitored anesthesia care (or as it formerly was termed—"local-sedation") is in many ways more difficult than providing general anesthesia. The anesthesiologist has to balance the drug effects that produce anxiolysis, sedation, and even unawareness against the accompanying loss of muscle tone and respiratory depression. The reduced muscle tone allows the patient's tongue to fall backward and partially or completely block gas movement through the oropharynx and, potentially, the nasopharynx. This is a particular problem in rhinological surgery since the nasal passageways may themselves be blocked by pathology, instruments, packs, and blood. Lifting the patient's chin and/or the angles of the jaw may lift the patient's tongue up from the hypopharynx but is itself stimulating and may awaken the patient. Nearly all sedative drugs are central respiratory depressants that decrease minute ventilation and, consequently, raise end-tidal CO_2. Proper patient selection and thorough local anesthetization of the nose promote the procedure's being successfully accomplished with less sedative medication.

TOTAL INTRAVENOUS ANESTHESIA

Total intravenous anesthesia (TIVA) has been shown in some studies to optimize cardiovascular parameters, reduce blood loss, promote hemostasis, and improve surgical field visualization during functional endoscopic sinus surgery compared with a balanced technique incorporating inhalational anesthesia.[17,18] The ability to precisely titrate TIVA to specific hemodynamic values and create controlled conditions of hypotension may reduce blood loss and improve surgical conditions. Even though a balanced technique involving inhalational anesthesia can provide the same degree of hypotension, there may be effects specific to TIVA (and especially remifentanil) that provide superior operating conditions. Recent meta-analyses of the available clinical trials, however, have challenged the validity of these studies and have placed into doubt the purported benefits of TIVA.[19,20] Another recently published prospective randomized trial consisting of 33 patients undergoing ESS found there was no significant difference in blood loss and surgical conditions with TIVA versus inhalation anesthesia.[21] The limited number of controlled trials, insufficient powering, variability among inhalation anesthetics without detailed reporting of the concentrations used, and lack of standardization of grading of visibility scores and perioperative characteristics prevent definitive demonstration of the superiority of TIVA. More high-quality studies are needed before declaring the superiority of TIVA over inhalational anesthesia.

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SECTION 8

Functional Surgery of the Nasal Airway

CHAPTER

41

Surgery of the Nasal Septum

Waleed M Abuzeid, Sam P Most, Peter H Hwang

INTRODUCTION

Within the human body, there are few anatomic structures that have been operated on with greater frequency or using a wider array of techniques than the nasal septum.[1] Abnormalities of the nasal septum have been documented for centuries. Indeed, in 1657, MacKenzie analyzed 2152 skulls and noted that 75% of these demonstrated a nasal septal deformity. Later, these deformities were associated with nasal obstruction, as well as less likely maladies including psychosis and emphysema.[1,2] An increased understanding of the functional role of the nasal septum has better defined the disease states that result from septal deformity, and has allowed for the development of various techniques that aim to re-establish normal function. This chapter will cover the surgical anatomy of the nasal septum, and the indications, techniques, and outcomes of surgery for nasal septal deviation and perforation.

SURGICAL ANATOMY

The nasal septum is the central support structure of the nose, and consists of an anterior membranous component, a posterior osseous segment, and an intervening cartilaginous segment[2,3] (Fig. 41.1). The membranous septum is located between the medial crura of the lower lateral cartilage and the quadrangular cartilage, the latter of which constitutes the cartilaginous portion of the septum. As a result, the quadrangular cartilage is often termed the septal cartilage. The quadrangular cartilage provides

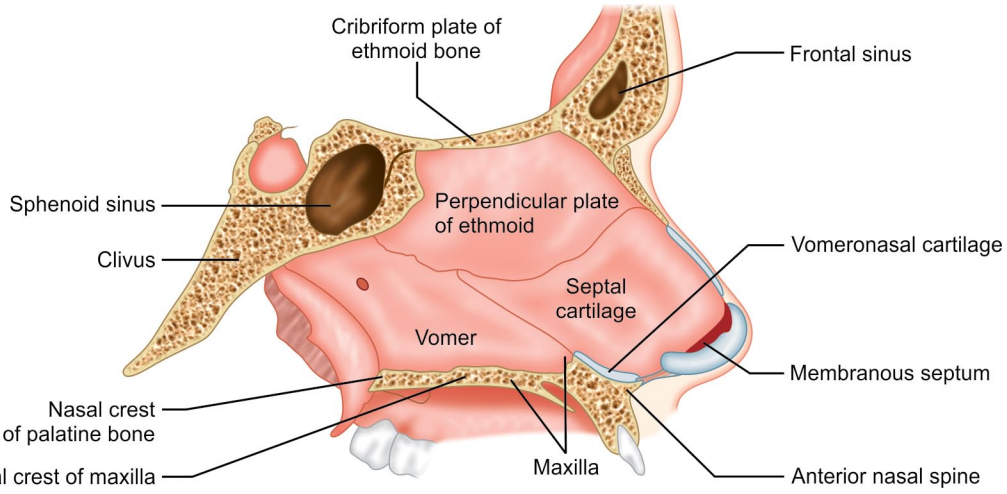


Fig. 41.1: Anatomy of the nasal septum.

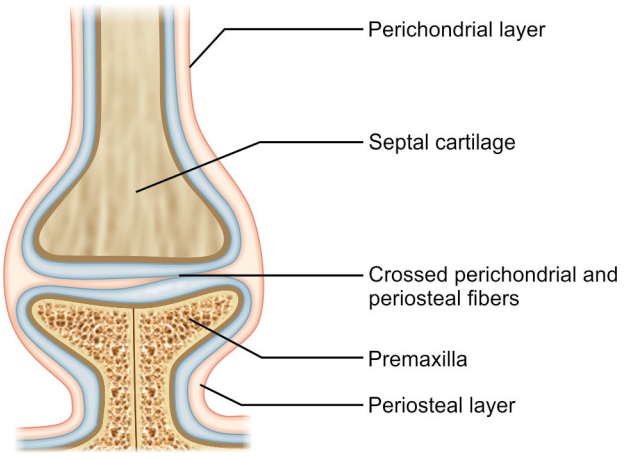


Fig. 41.2: Coronal view of the articulation of the septal cartilage with the maxillary crest. Note the decussation of the perichondrial and periosteal fibers.

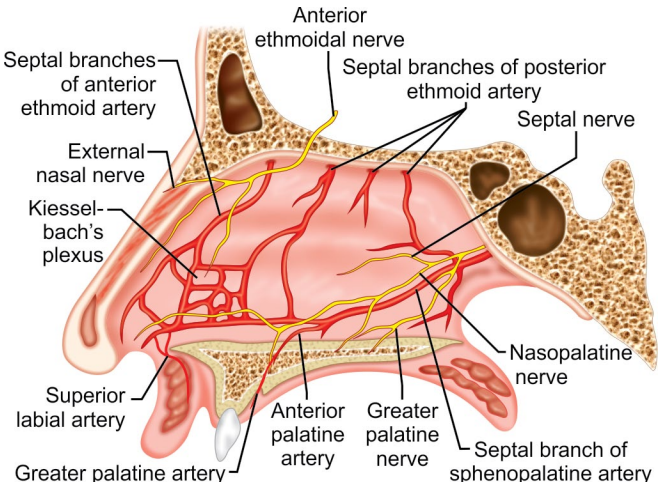


Fig. 41.3: Neurovascular supply of the nasal septum.

structural integrity to the nasal dorsum from the rhinion to the supratip region.[4] Immediately posterior to the quadrangular cartilage is the osseous septum consisting of the perpendicular plate of the ethmoid bone, the nasal crest of the palatine and maxillary bones, and the vomer.[3] The anterior edge of the perpendicular plate of the ethmoid articulates with the posterior edge of the quadrangular cartilage. Inferiorly, both structures articulate with the wedge-shaped vomer.[2]

The premaxillary crests of the maxilla are fused with the vomer in the midline, forming a groove into which the inferior edge of the quadrangular cartilage intercalates in a "tongue-and-groove" manner.[4] Traumatic displacement of the quadrangular cartilage off of its midline perch on the maxillary crest can result in cartilaginous and bony septal spurs along the floor of the nose. At the articulation between quadrangular cartilage and maxillary crest, the mucoperichondrium of the septal cartilage is densely adherent to the periosteum of the maxillary crest, including decussating perichondrial fibers that cross the midline and interweave with the contralateral mucoperichondium[2,3] (Fig. 41.2). During septoplasty, the decussating fibers must be discretely divided to enable the elevation of a contiguous submucoperichondrial flap that extends from quadrangular cartilage to the nasal floor.[2]

Caudally, the superior aspect of the septum contributes to the internal nasal valve, which is a slit-like structure bounded by the upper lateral cartilage superiorly, the head of the inferior turbinate laterally, and the nasal floor inferiorly. The internal nasal valve is the narrowest segment in the human airway with an average cross-sectional area of only 0.73 cm^2.[3] Due to the narrow cross-sectional area of the internal nasal valve, this site contributes approximately 50% of the airflow resistance of the combined upper and lower airway.[4] Consequently, relatively subtle cartilaginous septal deviations that narrow the internal nasal valve have a seemingly disproportionate effect on airway obstruction.

The vascular supply of the septum originates from two primary sources: the internal and external carotid arteries (Fig. 41.3). The external carotid artery gives rise to the facial artery and internal maxillary artery. The former contributes the superior labial and angular arteries, while the latter gives rise to the sphenopalatine artery. The superior labial and angular vessels supply the anteroinferior nasal septum and columella. The posterior septal branch of the sphenopalatine artery supplies the posteroinferior septum. The ophthalmic branch of the internal carotid artery gives rise to the posterior and anterior ethmoid arteries, which supply the posterosuperior and anterosuperior septum, respectively. This rich blood supply maintains viability of the mucoperichondrium and mucoperiosteum flaps, and is critical for the survival of the underlying septal cartilage.[3] The incisive artery travels along the superior border of the vomer and passes into the incisive canal. Significant bleeding from the incisive artery can occur during resection of a deviated maxillary crest.

The external carotid branches contribute to a rich anastomotic plexus that also receives input from the internal carotid system. This area, Kiesselbach's plexus, is located in the anteroinferior septum where it is susceptible to the drying effects of nasal airflow and digital trauma. Consequently, the anteroinferior septum is the

most common site of epistaxis. The mechanosensory nerve supply of the nasal septum is provided entirely by the trigeminal nerve. The nasopalatine branch of the maxillary nerve (CN V2) supplies the posteroinferior septum. This nerve travels through the vomer and enters the incisive canal. Resection of the maxillary crest or vomer during septoplasty can result in a transient hypesthesia of the central incisors and premaxilla. The anterosuperior portion of the septum is supplied by the anterior ethmoidal branches of the nasociliary nerve that, in turn, arises from the ophthalmic nerve (CN V1). The olfactory nerve gives rise to multiple fila that perforate the cribriform plate and supply the superior septum.[3] Overly aggressive superior dissection can result in anosmia and cerebrospinal fluid leak through transected fila. A working knowledge of the discussed anatomic highlights is imperative for an understanding of the intricacies of surgical technique, as well as an appreciation of potential surgical complications.

SEPTOPLASTY

The most common indication for septoplasty is nasal obstruction, which is the most common presenting complaint in a rhinologic practice. As a result, septoplasty is among the three most commonly performed procedures in otolaryngology.[5] Septoplasty is performed for nasal obstruction in about 100,000 patients annually. However, up to 90% of people will have incidental septal deformity without any symptoms of nasal obstruction. In these individuals, obstructive symptoms only ensue with additional contributing factors such as mucosal edema.[6] These patients can often be managed using medications.

Septoplasty is commonly used as an adjunctive procedure to optimize surgical access for endoscopic sinus and skull base surgery, and to facilitate postoperative in-clinic evaluation. Significant septal deviation has been associated with chronic sinusitis and correction of septal deformity in this setting is indicated. Marked deviation of the septum may exacerbate obstructive sleep apnea; septoplasty may be indicated to improve nasal resistance and improve tolerance of continuous positive airway pressure devices. Less commonly, septoplasty is used for relief of contact point headaches and for the treatment of epistaxis related to mucosal drying from turbulent airflow generated by anteroinferior septal deviation. Lastly, septoplasty is indicated for cosmetic procedures in which concurrent changes to the nasal skeleton would otherwise produce nasal obstruction.[5,7]

History and Physical Examination

Diagnosis of clinically relevant septal deviation must begin with an adequate history. Specific points that should be elicited include the duration, frequency, and laterality of obstructive symptoms; the presence of perennial or seasonal obstruction; a detailed history of trauma and previous nasal surgery; the frequency and severity of epistaxis episodes; evidence of atopy; and the effectiveness of previously tried medical treatments. If obstructive symptoms are seasonal rather than perennial or occur only in certain environments, allergy must be considered as a significant contributor, which is better managed medically.[2] Medical comorbidities that may be contraindications to septoplasty should be identified, including Wegener's granulomatosis, intranasal cocaine use, bleeding diathesis, extensive prior nasal surgery, or large septal perforation.

The physical examination is performed to identify the sites of nasal obstruction and to discern fixed anatomic obstruction, such as that resulting from a deviated nasal septum or polyps, or from reversible or dynamic obstruction related to nasal mucosal inflammation or nasal valve collapse.[6,8]

The size, shape, and symmetry of the external nose are carefully evaluated. Significant deviation of the cartilaginous septum may be seen as an external deviation of the dorsum or twisting of the nasal tip.[7,9] In this situation, an open septorhinoplasty approach may be necessary in order to allow for correction of the nasal skeleton, as discussed elsewhere in this volume. The nares should be inspected for patency and symmetry; a deflected or widened columella may be seen with deviation of the caudal septum or malformed medial crural cartilages. The external nasal assessment ends with palpation of the nasal tip to evaluate for tip support and ptosis that may contribute to obstructive symptoms. The posterior and anterior septal angles are carefully palpated to assess for caudal septal deviation. Dislocation of the posterior septal angle off the anterior nasal spine will necessitate an open or endonasal approach.[8]

The patient should be evaluated for the laterality of any obstruction by occluding airflow through each nostril separately, and then asking the patient to breathe normally. The nasal sidewall should be inspected during nasal breathing and evaluated for collapse of the external nasal valve, the internal nasal valve, or both. The Cottle maneuver, which entails lateral distraction of the cheek skin to stent open the internal and external nasal valve, may reduce obstructive symptoms related to nasal valve

collapse or caudal septal deviation. False positive results are common.[9] A more accurate "modified" Cottle maneuver entails use of a cotton-tipped applicator placed in the nose to lateralize the upper lateral cartilage and, thus, assess the internal nasal valve in isolation. When mild-to-moderate inspiration collapses the nasal sidewall, correction of nasal valve stenosis will likely require not only septoplasty but also correction of the upper and/or lower lateral cartilages, as well as reduction in the inferior turbinate.[9]

Anterior rhinoscopy is performed after evaluation of the external nose, and should be conducted both before and after application of topical decongestants. Subjective and objective responses to topical decongestants allow the surgeon to discern the relative contributions of the nasal mucosa versus fixed anatomic lesions to the obstructive symptoms. Rigid nasal endoscopy is performed after decongestion (and topical anesthesia) to systematically evaluate for possible septal spurs and deflections, septal perforations, nasal valve compromise, polyps, purulent discharge, tumors, or hypertrophic adenoid tissue. In patients who report an improvement in obstructive symptoms despite an absence of objective correlates, the improvement is likely related to a very slight reduction in mucosal thickness. Optimal management for these patients is most likely to be medical therapy. Conversely, a minority of patients will deny any subjective improvement after topical decongestion despite overt objective evidence of airway enlargement. Such patients are likely to be poor surgical candidates.[2]

Overall, the initial clinical assessment has been shown to have a high predictive value in determining which patients are most likely to experience relief of nasal obstruction from septoplasty. In a retrospective analysis of 137 patients presenting with nasal obstruction and a deviated nasal septum, clinical assessment was highly accurate in predicting which patients would fail intranasal corticosteroid therapy and, ultimately, require a septoplasty.[6] Indeed, the positive predictive value of clinical assessment in determining the need for septoplasty was 93.6% with a negative predictive value of 96.4%.[6] This highlights the importance of a comprehensive history and physical examination.

SURGICAL TECHNIQUES FOR SEPTAL DEVIATION

Descriptions of treatment for septal deviation predate the modern era to the time of the ancient Egyptians. Killian and Freer were the first contemporary surgeons to describe the submucous resection (SMR). This involved elevation of mucoperichondrial flaps with resection of septal cartilage, thereby sparing the overlying mucosa. These two pioneers also recognized the importance of maintaining a generous L-shaped dorsal and caudal cartilaginous strut to maintain nasal support.[3] Septoplasty techniques have since evolved with the aim of preserving as much quadrangular cartilage as possible and avoiding trauma to the overlying mucosa.

ENDONASAL SEPTOPLASTY

Indications

Endonasal septoplasty can be used to treat osseous and cartilaginous septal deflections, including some caudal septal deviations, without an external incision. Relative contraindications include those septal deviations that are associated with marked external deformity or severe caudal deformity, in which an open approach is indicated. The endonasal septoplasty technique generally follows the seven steps proposed by Huizing and de Groot: patient analysis (discussed above), approach, mobilization, resection, reposition, reconstruction, and fixation.[10]

Surgical Technique

Approach

Endonasal techniques can be performed under general or local anesthesia. The surgical approach begins with application of topical decongestants such as oxymetazoline, 1:1000 epinephrine, or 4% cocaine. Bilateral submucoperichondrial injection of an anesthetic and vasoconstrictor – e.g. 1% lidocaine with 1:100,000 epinephrine – is performed.[6] Some authors advocate an additional injection into the greater palatine foramen bilaterally to provide posterior hemostasis. Radioanatomic studies have shown that the pterygopalatine fossa can be safely injected via the greater palatine foramen with minimal risk to intraorbital contents by bending a 27-gauge needle 45° and advancing the needle into the foramen to a distance of 2.5 cm in those greater than 12 years of age, 2.0 cm in those aged 6–12 years, and 1.2 cm in those under 6 years old.[24] Inclusion of sphenopalatine injection is especially indicated in patient undergoing concomitant endoscopic sinus surgery.

The initial incision is made with a #15 blade. Generally, the incision will be made on the side of the deflection as mucoperichondrial flap elevation can be easier over a convex surface. This is not a requirement, however, and

selection of the side of the incision can be modified by factors such as a septal spur, which complicates elevation of an intact mucoperichondrial flap.

The choice of incision—hemitransfixion versus Killian—is based on surgeon preference as well as the caudal extent of the deviation. The hemitransfixion incision is classically made at the leading edge of the caudal septum, at the transition between vestibular skin and septal mucosa (Fig. 41.4).[11] The primary advantage of this approach is that all parts of the cartilaginous and osseous septum can be accessed. One relative disadvantage of the hemitransfixion incision is that it can be more challenging to dissect the fibrous attachments near the caudal border of the septum in order to find the submucoperichondrial plane of dissection. In contrast to the hemitransfixion incision, the Killian incision is placed 1–2 cm posterior to the caudal edge of the septum, through the septal mucosa. A Killian incision is suitable for septal deflections involving the middle or posterior third of the septum (Fig. 41.4). Although identification of the submucoperichondrial plane is often easier through a Killian incision, relative disadvantages of the Killian incision include the inability to access caudal septal deviations, and the risk of tearing the delicate mucosal incision during flap elevation.[3]

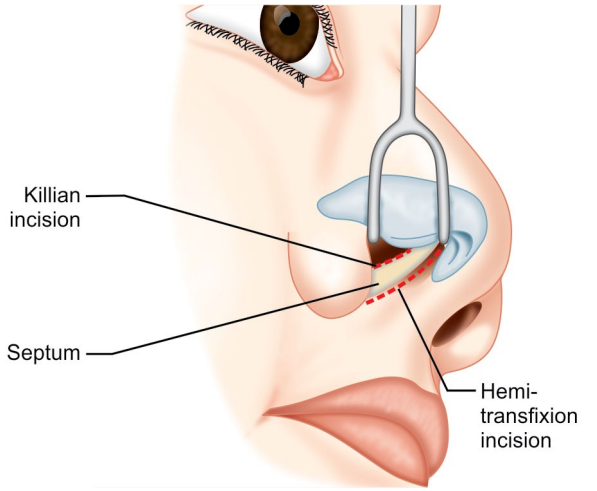
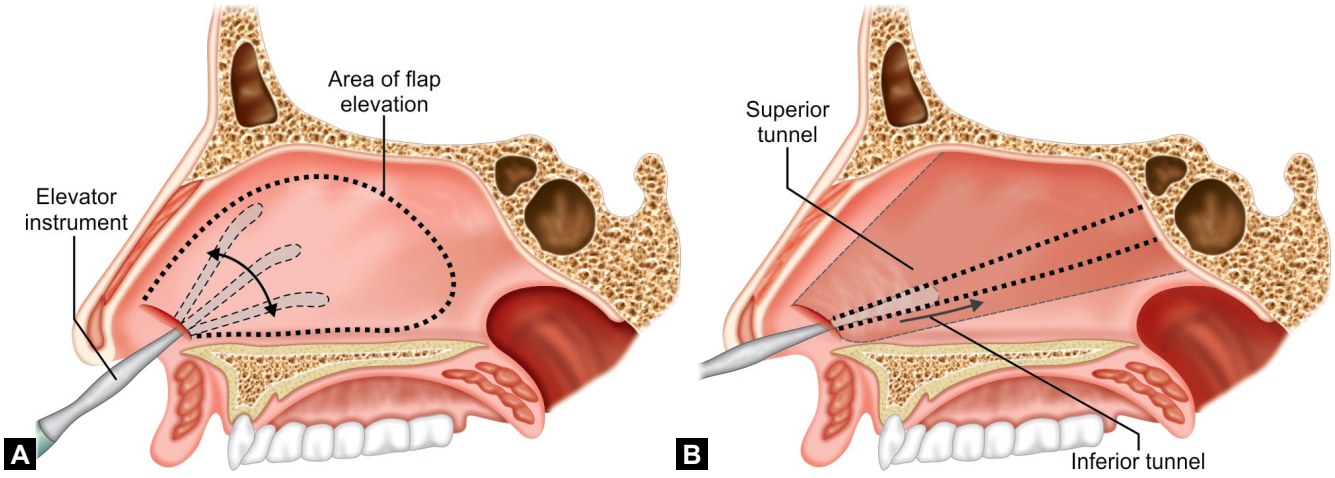


Fig. 41.4: Lateral view of the Killian incision and hemitransfixion incision. The Killian incision is placed 1–2 cm behind the edge of the caudal septum. The incision is designed such that it begins dorsally and curves downward toward the nasal floor, taking care to incise through the mucoperichondrium while leaving the underlying cartilage intact. The hemitransfixion incision is placed 2–3 mm behind the anterior columella, along the edge of the caudal septum.

Mobilization

All deformed parts of the septum must be exposed and mobilized.[11] Flap elevation proceeds in an anterior to posterior fashion. The classic approach to flap elevation, as initially described by Cottle, involves creation of a superior and inferior tunnel[12] (Figs. 41.5A and B). The superior tunnel, referring to the mucoperichondrial flap above the level of the maxillary crest, is routinely elevated in all septoplasty operations. The inferior tunnel, along the



Figs. 41.5A and B: Elevation of septal flaps. Flap elevation proceeds using a Cottle or Freer elevator. This can often be elevated as a single large flap. However, in cases with deviation of the caudal septum or maxillary crest, a "two tunnel" approach can be useful. The superior tunnel, above the maxillary crest, is first elevated. A second inferior tunnel is then created along the maxillary crest and nasal floor. Lastly, the decussating mucoperiosteal and mucoperichondrial fibers between the two tunnels are divided to create a single contiguous flap. A similar "two tunnel" technique can be used above and below a septal spur to preserve flap integrity.

nasal floor, is required in cases of quadrangular cartilage dislocation off the maxillary crest or deviation of the crest itself. By elevating the two tunnels separately, and then connecting them by sharply transecting the decussating fibers described in the "Surgical Anatomy" section above, the risk of tearing the flap is markedly reduced.[11]

The superior tunnel is elevated in a submucoperichondrial plane along the underlying septal cartilage, while using a nasal speculum to facilitate visualization. As the flap is elevated posteriorly, the use of a longer nasal speculum often becomes necessary to maintain adequate visualization. Avoidance of flap trauma can be facilitated by elevating along a broad front. The most likely sites of flap trauma overlie bony septal spurs. Here, flap elevation superior and inferior to the spur is performed initially, in order to provide some flap laxity while gently elevating the flap off the spur[3] (Figs. 41.5A and B). Once the flap has been elevated posteriorly beyond the bony cartilaginous junction, a contralateral flap dissection is performed in order to isolate the deviated portions of bone and cartilage from their contralateral mucoperichondrial and mucoperiosteal attachments. Contralateral access is typically achieved by sharply incising through the septal cartilage just anterior to the point of maximal deflection, in order to carefully enter the contralateral submucoperichondrial space. When both mucoperichondrial flaps have been raised, the intervening deviated septal cartilage and bone are fully exposed. When there is a deflection of the cartilaginous septum off the maxillary crest or deviation of the crest itself, an inferior tunnel is developed along the nasal floor using a sharp elevator to elevate a mucoperiosteal flap.[9] The inferior tunnels, after being elevated bilaterally, are then connected to the superior tunnels via sharp dissection.

Resection, Reposition, and Reconstruction

Submucous resection: The SMR is the most aggressive of modern resection techniques, and can be used to treat the range of septal deviations. It involves the removal of the majority of the quadrangular cartilage, with the preservation of 1 cm or greater width of caudal and dorsal cartilage, forming an inverted L-shaped strut (Fig. 41.6). Failure to preserve an adequate strut caudally can compromise tip support and lead to tip ptosis.[3] Compromising the dorsal strut can disrupt the integrity of the nasal dorsum leading to collapse. A scalpel, swivel knife, or scissors can be used to make the cartilage cuts and to disarticulate the quadrangular cartilage from the

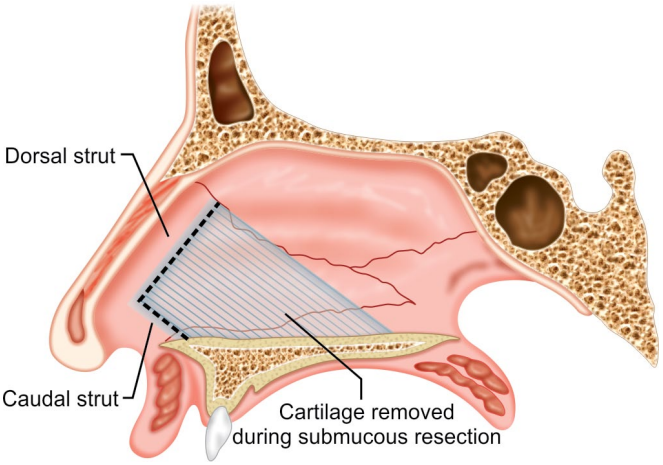
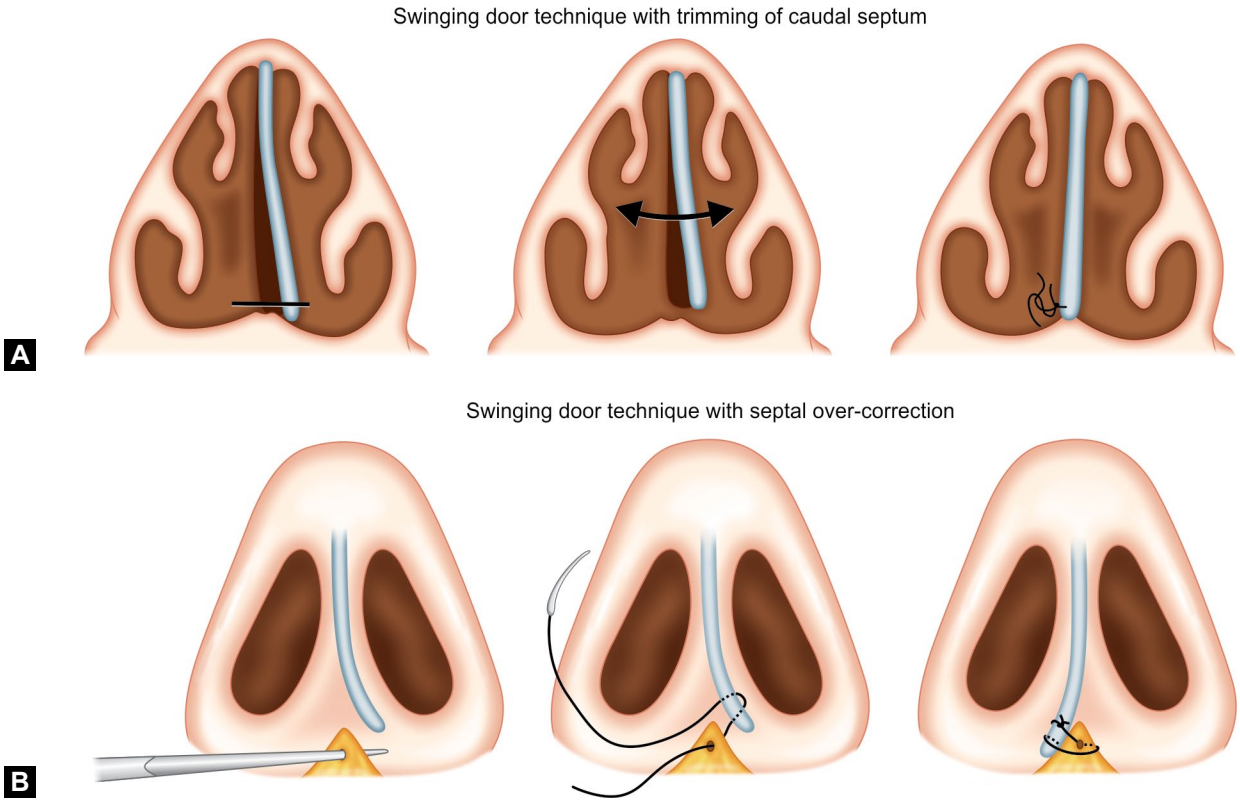


Fig. 41.6: Lateral view of the "L-strut." This is a 1.5 cm caudal and dorsal segment of the septal cartilage that must be preserved for structural integrity of the nasal septum. The shaded area represents the excised segment of septal cartilage.

osseous septum and maxillary crest. Deviations in the osseous septum can then be addressed using through-cut instruments or the Jansen-Middleton forceps.

Conservative septoplasty: The classic SMR has largely been replaced by conservative septoplasty where specific areas of septal deviation are resected, thereby preserving a maximal amount of cartilage.[3] Central septal deflections are identified and are selectively resected. It is often easiest to start with a posterior vertical cut that disarticulates the bony-cartilaginous junction, followed by horizontal cuts superiorly and inferiorly to the deflection. A vertical cartilaginous incision just anterior to the deflection frees the segment, which is then carefully removed with forceps.[3,9] There should be no pulling or twisting movements outside of the anteroposterior axis to minimize the risk of cribriform fracture due to torsion on the perpendicular plate of the ethmoid.

A similar method can be used to address cartilaginous or bony septal spurs. Septal spur removal can be facilitated by medial displacement of the spur using the nasal speculum, after making superior and inferior horizontal cuts above and below the spur. This reduces the risk of mucosal perforation.[3,11] Low spurs along the nasal floor are addressed using the two-tunnel approach with elevation of mucoperichondrium above and mucoperiosteum below the deviation, followed by elevation of the intervening mucosa (Figs. 41.5A and B). The deviated segment is freed by making a horizontal superior cut followed by fracture and removal with the Takahashi forceps.[9]



Figs. 41.7A and B: Septal correction using the swinging door technique. The top panel illustrates conservative resection of the caudal septum that is then brought to midline and reinserted along the groove of the maxillary crest where it is secured with monofilament suture. The bottom panel indicates overcorrection of the septum. The septum is not trimmed but is translocated to the opposite side of the maxillary crest and secured here with monofilament.

Septal reconstruction: Septal reconstruction techniques are used primarily for deviations in the quadrangular cartilage that involve critical portions of the dorsal and caudal "L"-strut. While cartilage can be scored with one-sided partial-thickness weakening incisions to allow for reshaping of the cartilage, the degree of change in curvature is challenging to predict and use of this method in isolation often results in relapse due to cartilage "memory."[13] Given this, we feel that scoring techniques are unreliable and should not be used in critical areas. Tangential shaving of thick cartilage can also be used to remove bowing.[9] High dorsal bowing can also be addressed by suturing a rectangular cartilage graft, harvested from excised septal cartilage, between the quadrangular cartilage and the upper lateral cartilage. This acts as a splinting spreader graft preventing dorsal septal bowing.[9]

A commonly encountered deformity involves displacement of the anteroinferior quadrangular cartilage off the maxillary crest or deviation of the maxillary crest itself. This is a major contributor to nasal obstruction. The Metzenbaum "swinging door" procedure can effectively address this caudal septal deviation (Figs. 41.7A and B). First, the two-tunnel method is used to effectively free the muco-periosteum and mucoperichondrium from the maxillary crest and nasal floor. A horizontal wedge of cartilage is then excised from the convex side of the septal deformity using a #15 blade.[14] Deviation of the maxillary crest is addressed by excision using an osteotome.[9] Thus, a superiorly based swinging septal flap is created and is repositioned to the midline maxillary crest. A modification of this technique encourages repositioning the septum to the other side of the anterior septal spine such that the spine acts as a buttress preventing the septum from returning to its native position[14] (Figs. 41.7A and B).

An excessively deviated caudal septum that cannot be straightened can be trimmed, although this must be done with care, as over-resection of the critical caudal strut cartilage can compromise tip support.[9] In these cases, a modified extracorporeal septoplasty, or anterior septal reconstruction, may be required.[15] Full discussion of this technique is beyond the scope of this text.

Once the cartilaginous septum has been addressed, resection of any posterior osseous deviation is performed using Jansen-Middleton and Takahashi forceps.[3] Care must be taken to avoid torque on the skull base during treatment of bony deviations. Furthermore, the dorsal strut at the bony cartilaginous junction must be preserved. This area is called the "keystone" as it is critical in maintaining dorsal support of the nose. Disarticulation of this area causes the dorsal L-strut of the septum to collapse, resulting in a saddle nose.

Fixation

Following SMR or conservative septoplasty, all cartilages that have been detached, mobilized, or repositioned must be fixed in position. Caudally deflected septal cartilage that has been corrected by the "swinging door" procedure described above is fixed by securing the repositioned cartilage to the maxillary crest and anterior nasal spine using absorbable monofilament suture (Figs. 41.7A and B). The caudal tip of the cartilage can be fixed in the midline by using the "tongue-in-groove" technique where retrograde dissection between the medial crura creates a pocket into which the caudal septum is interposed. Columellar-septal mattress sutures are then passed through both medial crura and the intervening caudal septum to provide stabilization.[16]

The mucoperichondrial flaps are laid back into position and the nasal cavity is carefully inspected bilaterally to ensure resolution of the deviated segment, and to detect unappreciated tears in the mucoperichondrial flaps. Some surgeons advocate morselization and reinsertion of unused, resected septal cartilage between the mucoperichondrial flaps. This potentially reduces the risk of postoperative septal perforation and flail septum (abnormal billowing of the septal mucosa with nasal breathing). Reimplantation of cartilage is particularly useful in situations where opposing, bilateral mucosal perforations have been created.[9]

A number of techniques can be used to reapproximate the mucoperichondrial flaps with goals of stabilizing the repositioned cartilage and bone, prevention of synechiae between the septum and lateral nasal wall, and avoidance of septal hematoma. Tacking sutures can be placed through-and-through the mucoperichondrial flaps at several points. Alternatively, a continuous quilting suture can be placed that begins anteriorly, runs posteriorly, and then returns anteriorly (Fig. 41.8). Large tears in the mucoperichondrial flaps should be considered for possible closure with absorbable suture, although most flap tears heal uneventfully without repair if the contralateral flap is intact in the area opposing the ipsilateral flap tear. Nonabsorbable packing can be used as an adjunct to or in place of suturing techniques, although the outcomes of septoplasty without postoperative packing are quite satisfactory. In a study of 697 patients who underwent septoplasty and were randomized to either trans-septal suturing or Merocel packing, there was no difference between groups in postoperative bleeding rates, synechiae formation, septal perforation, or hematoma formation. There was, however, significantly more postoperative pain in the patients who received nasal packing.[17] Coupled with the negative effects of nasal packing on sleep, increased risk of hypoxia in patients with obstructive sleep apnea, and reports of toxic shock syndrome, nasal packing in our experience is best avoided after septoplasty.[18,19] Silastic splints are a more recent alternative to nasal packing. One prospective, randomized trial demonstrated that, in comparison to nonsplinted controls, presence of a properly placed splint – such that it does not contact the nasal floor or roof – does not add to patient discomfort, and reduces mucosal erosions and synechiae.[20] After apposition of the mucosal flaps, the Killian or hemitransfixion incision is closed using absorbable suture.

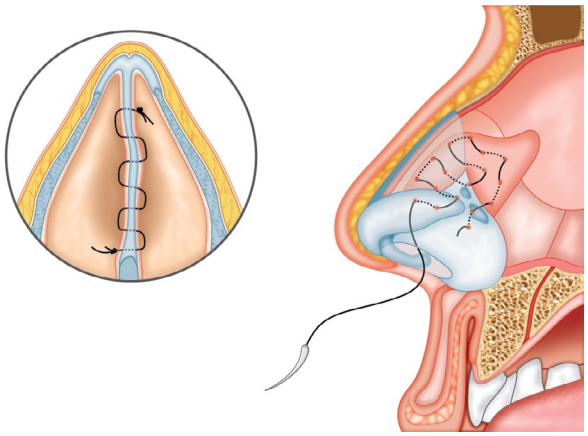


Fig. 41.8: Schematic representation of septal "quilting" suture technique. Absorbable suture is used to coapt the mucoperichondrial flaps starting anteriorly and working in a posterior direction before returning anteriorly.

ENDOSCOPIC SEPTOPLASTY

Indications

The development of functional endoscopic sinus surgery in the 1980s and its, subsequent, dissemination paved the way for novel endoscopic techniques. Lanza and Stammberger

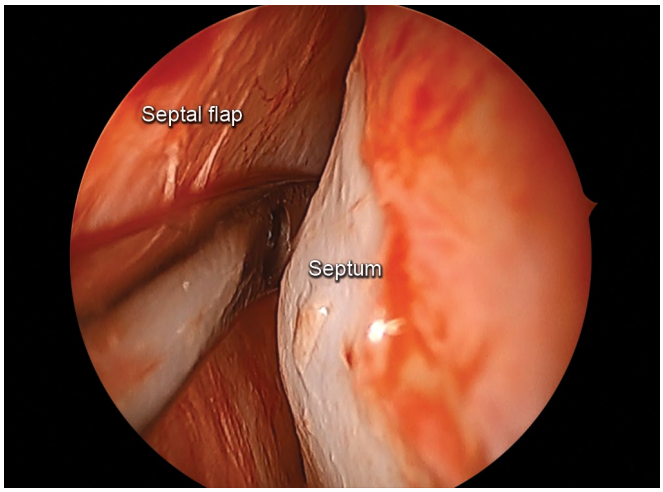


Fig. 41.9: Elevation of submucoperichondrial flap using endoscopic septoplasty technique. A submucoperichondrial flap is elevated with a suction Freer elevator through a Killian incision. The septal cartilage is brilliant white and avascular when elevation is performed in the correct plane as shown above.

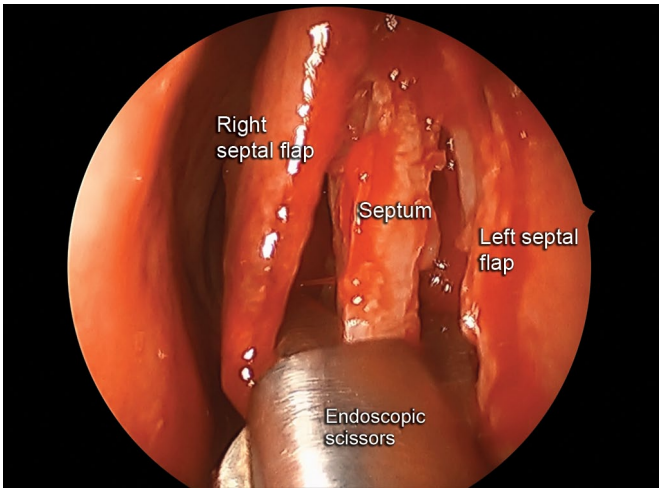


Fig. 41.10: Endoscopic resection of deviated septal cartilage. Bilateral submucoperichondrial flaps have been elevated and the intervening deviated septal cartilage isolated. This is incised superiorly and inferiorly with endoscopic scissors and then removed, taking care to preserve an adequate L-strut.

were the first to detail endoscopic septoplasty.[21,22] Use of an endoscope obviates the need for a nasal speculum and, thus, the nasal anatomy can be viewed without distortion.[23] Endoscopic septoplasty is suitable for the nearly all septal deflections that would otherwise be accessible via an endonasal approach. The endoscopic approach, owing to the combination of excellent illumination, magnification, and visualization, is particularly well suited to treating isolated posterior septal deflections, isolated septal spurs, and deviations in close proximity to septal perforations.[5,24] The high-definition view offered with modern endoscopic platforms has increased use of this approach for revision septoplasty due to enhanced visualization of tissue planes.[5] Relative contraindications for endoscopic septoplasty are significant caudal deflection and/or the presence of associated external deformity, for which an open septorhinoplasty approach would be indicated.[23]

Surgical Technique

Preparation of the nose for endoscopic septoplasty is the same as for traditional headlight septoplasty. The Killian or hemitransfixion incision is performed nonendoscopically under direct visualization and the subperichondrial plane of elevation is initiated for 1–2 cm.[23] The surgeon then transitions to an endoscopic view using a suction Freer instrument to continue flap elevation while concurrently aspirating blood so as to maintain an optimal view[5] (Fig. 41.9). The use of an irrigating endoscope sheath to prevent soiling of the scope tip by blood is helpful and improves operative efficiency. The magnified endoscopic view allows one to recognize areas of thinned, tenuous mucosa, and to evaluate the amount of tension being applied to the mucoperichondrium during elevation, potentially reducing the risk of septal perforation. Furthermore, flap lacerations can be recognized early before extension of the injury.[5,24]

Deviated portions of septal cartilage and bone are excised and/or mobilized in the same manner as in traditional septoplasty (Fig. 41.10). Removal of bone and cartilage using powered instrumentation has also been described with the endoscopic approach, offering the potential advantage of concurrent aspiration of debris and blood during tissue removal. Both microdebriders and drills can be used to safely resect cartilage and bone under endoscopic visualization. This technique is not indicated for caudal deflections but can, otherwise, be used without increasing the risk of perforation or postoperative hematoma.[25,26]

Following resection of the septal deviation, the mucoperichondrial flaps are laid back in position and the endoscope passed into the nasal cavities bilaterally to inspect and palpate any residual deviation that can then be corrected. Once all necessary deflections have been addressed, the mucoperichondrial flaps are reapproximated with a quilting stitch using 4-0 nonabsorbable suture on a small Keith

needle.[5,24] As discussed above, morselized cartilage can be placed between the mucoperichondrial flaps prior to closure.[23]

A major advantage of the endoscopic approach is the ability to perform a limited septoplasty. For example, a posterior deflection limited to the region of the bony-cartilaginous junction can be accessed by making a posterior mucosal incision just in front of the deflection, raising limited flaps and selectively resecting the deflected segment of cartilage.[5] Because of the limited dissection, no closure sutures or splinting is required. This is of particular benefit when treating a septal deviation in the setting of a pre-existing septal perforation. The mucosal incision and flap elevation can be limited to the area of the deflection, leaving the mucosa surrounding the perforation undisturbed, thereby reducing the risk of enlarging the perforation.

Septal spurs can be effectively addressed via a minimally invasive endoscopic approach by placing the septal incision horizontally along the apex of the spur. Mucoperichondrial flaps are elevated superiorly and inferiorly. The spur is then incised along its superior border and the contralateral mucoperichondrium is then gently elevated to isolate the spur. The spur can then be removed through the apical incision. The superior and inferior flaps are laid back into position; closure with absorbable suture is optional.[5,21]

EXTERNAL SEPTOPLASTY

Indications

External (or open) septoplasty is most commonly indicated when septal deviation is a component of a larger nasal deformity involving the nasal tip, dorsum and/or nasal bones, that cannot typically be addressed by more conservative approaches.[3] Severe deviation of the anterior septum within 2 cm of the caudal septal edge is another common indication for external septoplasty.[7] This is in contrast to less severe caudal septal deviation that can be addressed by the endonasal "swinging door" technique. Some authors advocate the external approach for all caudal septal deviations as it permits easy access and precise repositioning of the septum.[14] High deviations of the dorsal septum can also be addressed via this approach through the placement of spreader grafts.[7] Significant deviation of the septum, often with associated external deformity, may require near total excision of the septum and extracorporeal septoplasty via an external rhinoplasty approach. Lastly, disarticulation of the osseous and cartilaginous septum can also be addressed.

Surgical Technique

The surgical approach used for open septoplasty is, essentially, identical to that used for external (or open) septorhinoplasty. The surgery can be performed under intravenous sedation or general anesthesia, though the latter is recommended. In all cases, local anesthetic with a vasoconstrictor (1% lidocaine with 1:100,000 epinephrine) is infiltrated into the nasal dorsum, columella, and nasal base using a 30-gauge needle. A 27-gauge needle is then used to inject the septum in a submucoperichondrial plane to produce hydrodissection as discussed above. Decongestion is recommended in the preoperative area prior to induction, and can additionally be performed using oxymetazoline-soaked neurosurgical pledgets after injection.[7]

A standard columellar inverted "V" or "W" incision is made with a #15 blade with placement of the incision at the narrowest point of the columella. Marginal incisions are then made with the same blade just below the caudal edge of the lower lateral cartilage (Fig. 41.11). Converse or other fine scissors are used to begin elevation of the columellar skin anteriorly over the nasal tip. Nasal tip skin is retracted with skin hooks and dissection performed in

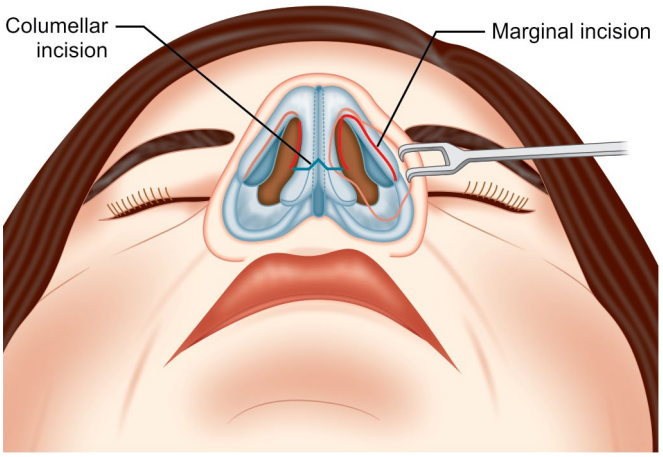


Fig. 41.11: Marginal and columellar incisions. Typically an "inverted V" configuration is used for the columellar incision that is performed with a #11 blade scalpel. The marginal incision can then be performed using a #15 blade and is connected to the previously made columellar incision. The marginal incision skirts the bottom edge of the lower lateral cartilage but care must be taken not to incise cartilage.

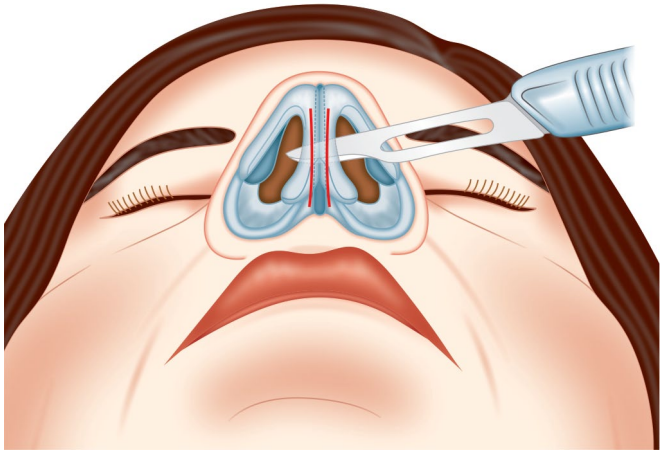


Fig. 41.12: Complete transfixion incision. The complete transfixion incision involves a through-and-through incision along the caudal edge of the septum and medial crura. This effectively separates the skin and soft tissue of the columella from the caudal septum.

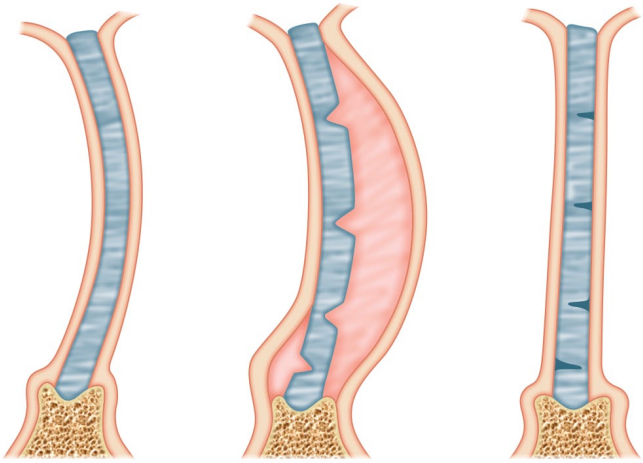


Fig. 41.13: Cartilage scoring techniques for septal correction. The convex side of the septal deviation is scored with a series of horizontal incision to weaken the integrity of the cartilage and permit reshaping. Alternatively, serial wedges can be excised from the convex side. The cartilage is then straightened and the mucoperichondrial flaps coapted.

the submusculoaponeurotic plane, beginning medially and then working laterally. The skin-soft tissue envelope is then retracted with an Aufricht or Gruber retractor. The skin-soft tissue envelope is thus elevated to the nasal bone junction (rhinion). At this point, a subperiosteal pocket is developed up to the nasofrontal suture.

In cases with central septal deflection or anterior septal deflection, the medial crura are separated via a complete transfixion incision to allow for direct access to the septum (Fig. 41.12). The anterior septal angle is identified and a Cottle elevator is used to sharply elevate the mucoperichondrium bilaterally. A Freer elevator is used to widely elevate the mucoperichondrial flaps. In order to facilitate access, the quadrangular cartilage is separated from the upper lateral cartilage up to the inferior edge of the nasal bones using a D-knife. This maneuver can be performed without the preceding transfixion incision in patients with isolated dorsal deviations.[7]

For the majority of central and posterior septal deviations, the bilateral mucoperichondrial flaps are elevated posteriorly beyond the bony-cartilaginous junction. A #15 blade or D-knife can be used to resect the deflected segment while preserving an adequate L-strut. It cannot be emphasized enough that preservation of the dorsalmost 1–1.5 cm of the bony-cartilaginous junction of the septum (the keystone) is critical to preventing complications of both airway compromise and saddle nose deformity. Dorsal septal deviation, accessed via the standard transfixion incision or through disarticulation of the upper lateral cartilage, can be addressed by placement of a unilateral spreader graft on the concave surface to correct the deformity. Symmetric and asymmetric bilateral spreader grafts can also be used to straighten and strengthen the dorsal septum. These can be harvested from the quadrangular cartilage.[7,9] Dramatic deviations in the dorsal septum may need to be excised and the dorsal septum reconstituted with a cartilage graft obtained from the septum or from rib. These rhinoplasty techniques are discussed elsewhere in this volume. Regardless of the technique used, the upper lateral cartilage must be reattached to the septum in order to avoid internal nasal valve collapse.

Caudal septal deflections are typically accessed via a transfixion incision. The most conservative methods of addressing caudal deviation involve wedging or scoring the caudal component of the L-strut. Generally we recommend against scoring methods, as these tend to unpredictably weaken this important strut. Incisions are made in the convex surface of the caudal strut, and can be partial-thickness scoring incisions or serial wedges (Fig. 41.13). This is effective for mild-to-moderate septal deviation, but cannot address severe deviations. Furthermore, there is concern that this technique compromises tip-support mechanisms and, in the long term, may result in tip ptosis.[14] Mild-to-moderate caudal deviation can also be managed through suture technique where the caudal strut

is scored, and then a series of two to four Mustarde-type sutures are placed to straighten the deflected segment.[14] Septal repositioning is an alternative technique where the deflected caudal septum is brought to the midline, and secured to the periosteum of the anterior nasal spine with mattress sutures (*see* Fig. 41.7). An overly long caudal septum may need to be trimmed, as discussed earlier, prior to repositioning in the midline. The tongue-and-groove technique can be readily used via the open approach as this allows for disarticulation of the medial crura, careful interposition of the caudal septum edge between the footplates, and precise placement of columellar-septal mattress sutures.[7,14] This technique also allows adjustment of tip projection and rotation if concomitant aesthetic changes are desired. A deviated caudal septum can also be stabilized through the use of rigid spreader grafts, harvested from the ethmoid perpendicular plate, and placed such that they extend beyond the caudal border of the upper lateral cartilages, and "sandwich" the caudal septum.[14] Care must be taken to avoid overly widening the columella.

Complete separation of the osseous and cartilaginous septum is a very difficult problem that must be avoided. If it occurs, it can be addressed by drilling holes in the perpendicular plate of the ethmoid, and then passing PDS suture through the holes and into the quadrangular cartilage to reapproximate the bony and cartilaginous components. This repair often needs to be combined with bilateral spreader grafts to stent the internal nasal valve, as well as a dorsal onlay graft to camouflage step off between the nasal bone and the nasal dorsum.[7] These techniques are discussed elsewhere in this volume.

Extracorporeal Septoplasty

Although first described by King and Ashley as an endonasal technique in 1952, most surgeons perform extracorporeal septoplasty via an external approach.[14] The most severe septal deformities resulting from trauma, previous surgery, or congenital malformations can be addressed by extracorporeal septoplasty where the entirety of the nasal septum is removed, straightened, and then reimplanted. This may serve to correct any resultant external nasal deformity as well.[3] The dorsal septum is separated from the upper lateral cartilages bilaterally after elevation of mucoperichondrial flaps. The premaxillary attachments are transected and inferior tunnels dissected along the nasal floor. Paramedian osteotomies are then performed to remove the bony septum from the nasal dorsum. The entire cartilaginous and osseous septum are then removed as a single unit.[27] A more recent modification to this technique is the anterior septal reconstruction, which involves leaving a portion of the native dorsal septum intact so as not to compromise dorsal support.[15]

Multiple strategies can then be applied to straighten the removed septum.[27] Redundant cartilage and fracture lines can be excised and sutured together into a stable, straightened construct. Partial-thickness incisions made on the concave side of a deflected segment of cartilage can reduce tension and facilitate reshaping of the cartilage. Bony irregularities can be smoothed with a drill. Overly pliable pieces of cartilage can be reinforced with spreader grafts sewn with PDS suture to the upper border of the septum. In post-traumatic cases with multiple fracture lines, the individual fracture segments are often straight and can be dissected apart and then reassembled into a neoseptum. This can be facilitated by using PDS foil as a stabilizing template to which the fragments can be sutured. The fractures must be overlapping, however, as end-to-end fusion of the cartilage in critical load-bearing areas is not reliable. In the postoperative scenario with minimal residual cartilaginous septum, the bony septal fragments can be used to construct an L-strut, thereby recreating the dorsal and caudal septum.

The reconstructed septum is then replanted between the mucoperichondrial flaps. Stable fixation is critical. This is achieved by aligning the upper border of the neoseptum with the upper lateral cartilage, temporarily fixing the construct with needles, and then passing PDS suture through both upper lateral cartilages and the interposed neoseptum. A hole is drilled through the anterior nasal spine and two sutures used to anchor the caudal cartilage to the spine.[27] Fascial onlay grafts can be used to prevent postoperative irregularities of the nasal dorsum. The skin-soft tissue envelope is returned to position and the columellar and marginal incisions closed with absorbable suture. A quilting suture and silastic splints are used to reapproximate the mucoperichondrial flaps.

Given the increase risk of notching and requirement for dorsal grafting in extracorporeal septoplasty patients, anterior septal reconstruction is a good alternative.[15] The approach is similar to the above, except a dorsal strut of 1.5–2 cm is left intact, extending from the bony-cartilaginous junction caudally (Fig. 41.14). The upper lateral cartilages are released, and a septal reconstruction graft, often taken from the native septum, can be used to reconstruct the caudal strut. Rather than suture to the maxillary

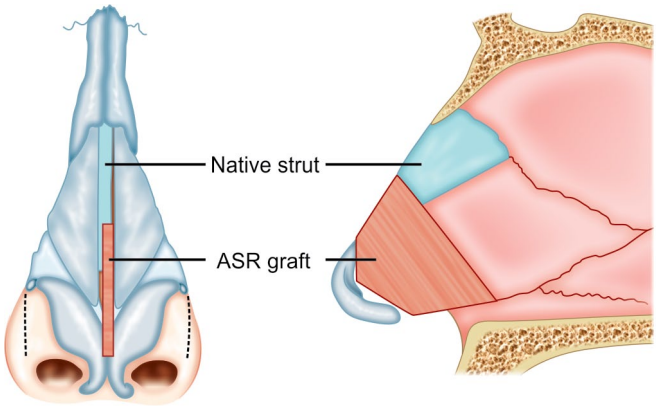


Fig. 41.14: Anterior septal reconstruction. This is a modified extracorporeal septoplasty technique allowing for the reconstitution of anterior septal deviations. The septal graft is taken from the native septum.

spine, the spine is gently split with a 4 mm straight osteotome, creating a 3 mm deep groove. The graft is notched at its inferior edge, and this notch is placed in the groove of the maxillary spine. This prevents lateral and anteroposterior movement of the graft. The graft is secured to the dorsal strut on its concave side, acting as a spreader graft. This can be augmented further with additional spreader grafts. This technique has been validated using the NOSE outcomes instrument—discussed below—and offers the advantage of reduced risk to the dorsal profile.

OUTCOMES

Multiple published studies have indicated that septoplasty produces improvements in nasal obstruction. Stewart et al. designed a multicenter, prospective observational study involving 59 patients with chronic nasal obstruction refractory to medical management who then underwent nonendoscopic septoplasty, with or without inferior turbinectomy. There was a significant improvement in scores on a validated instrument for assessing nasal obstruction (Nasal Obstruction Symptom Evaluation Scale) at 3 months postseptoplasty and this was sustained at 6 months after surgery.[28] The improvement in scores was at least two times the standard deviation of the baseline pretreatment scores indicating a large beneficial effect of surgery. Additionally, 94% of patients reported satisfaction postoperatively, and reported significant decreases in oral decongestant and nasal steroid use at 3 months after surgery.[28]

Clinical efficacy has been demonstrated for open, endonasal and endoscopic septoplasty approaches. Siegel et al., in a prospective study evaluating 93 patients undergoing nonendoscopic septoplasty, applied the general health survey (SF-12) and a nasal specific health measure (Nasal Health Survey) prior to surgery, and at 6 and 12 months postoperatively. At a mean of 9 months follow-up, both the symptom and medication usage scores on the Nasal Health Survey were significantly improved. These results held even when patients who underwent concurrent turbinate reduction or external nasal framework surgery were excluded from the analysis. Overall, 71% of patients demonstrated a clinically significant improvement as determined by at least a 50% decrease in duration of nasal symptoms.[29] Bothra and Mathur performed a prospective, randomized study to compare nonendoscopic versus endoscopic septoplasty techniques for limited septal deviations and spurs. They found no differences in outcomes or complications over a 2-year follow-up period.[30]

Recent studies using objective measures of nasal airway patency have indicated a measurable benefit from septoplasty. These objective measures include rhinomanometry, which measures nasal patency by quantifying nasal airflow and pressure gradients during normal breathing; acoustic rhinometry, which measures the minimum cross-sectional airway of the nasal airway; and nasal peak inspiratory flow, which provides a physiologic measure of nasal airflow with maximum effort.[31] In a systematic review of 14 studies—seven (460 patients) involving rhinomanometry, six (182 patients) using acoustic rhinometry, and one (22 patients) analyzing nasal peak inspiratory flow—septoplasty resulted in measurable objective improvements in nasal patency.[31] When comparing postoperative to preoperative readings, there were significant decreases in mean unilateral nasal resistance, increases in minimum cross-sectional area, and increases in peak nasal inspiratory flow.[31]

SEPTAL PERFORATION

Nasal septal perforations are common, occurring in up to 0.9% of the general population.[32] As detailed earlier in this chapter, a rich anastomotic network of blood vessels in the septal mucoperichondrium creates a redundant blood supply to nourish the underlying avascular cartilage. However, any disruption to this blood supply can lead to ischemia or necrosis of the underlying septal cartilage. When the vascular supply is disrupted bilaterally in the same region of septal cartilage, the patient is prone to full-thickness tissue loss and development of septal perforation.[33]

Pathophysiology

Septal perforations disrupt intranasal laminar airflow by causing turbulent eddy currents.[8] This turbulent airflow impairs mucosal function and induces ciliary loss, resulting in a dry, obstructed nasal cavity. Compensatory vasodilatation of the mucosal vasculature can induce rhinorrhea that can dry to propagate nasal crust formation.[33] A low-grade perichondritis can also contribute to significant crusting and bleeding.[34] Nose picking can worsen the perichondritis and lead to enlargement of the perforation.[33] Progressive enlargement of a septal perforation may compromise the integrity of the dorsal and caudal septal struts causing external nasal deformity.[32] Generally, the more anterior the perforation, the more likely a patient is to be symptomatic and to seek evaluation.[34]

Causes of Septal Perforation (Table 41.1)

Traumatic

Traumatic disruption of the mucosal vasculature is an extremely common cause of septal perforation. Trauma can be intentional, such as septal piercing to accommodate nose rings; habitual, as in the case of chronic nose picking; accidental, in the case of blows to the external nose that disrupt septal cartilage and overlying mucoperichondrium; or iatrogenic.[33] Septal trauma can induce a hematoma that, if untreated, can result in dissolution of the septal cartilage with eventual perforation.[34] Septoplasty is the surgical procedure most commonly associated with perforation, often as a result of opposing tears in bilateral mucoperichondrial flaps over an area where septal cartilage has been removed. Nasal cautery for epistaxis can also lead to perforation. The use of tight nasal packs – either for epistaxis control or post-septoplasty – can lead to ischemic mucosal damage and perforation. Nasogastric tubes and nasotracheal intubation can induce pressure necrosis and localized inflammation resulting in septal perforation.[34]

Systemic Disease

Chronic vasculitides such as Wegener's granulomatosis and sarcoidosis have been associated with septal perforation. Infectious diseases including tuberculosis, syphilis, diphtheria, fungal infections, and AIDS can also result in perforation, as can connective tissue diseases such as systemic lupus erythematosus, Crohn disease, dermatomyositis, and rheumatoid arthritis. Malignancies are a rare but well-established cause of septal perforation.[33]

Drugs

Illicit substances have long been associated with septal perforation. Cocaine is a potent vasoconstrictor, and with chronic use, the resultant necrosis of septal mucosa compromises the vascular supply to the underlying septal cartilage. However, the role of cocaine in inducing septal perforation is multifactorial. Cocaine is a potent local anesthetic and, consequently, trauma to the nasal mucosa—both digital and from drug paraphernalia—is not felt. Adulterants mixed into cocaine such as talcum

Table 41.1: Causes of septal perforation

Inflammatory	*Infectious*	*Traumatic/Iatrogenic*	*Neoplastic*	*Inhalants*
Sarcoidosis	Syphilis	Septoplasty	Lymphoma	Steroids
Granulomatosis with polyangiitis	Tuberculosis	Mucosal laceration	Squamous cell carcinoma	Decongestants
Systemic lupus erythematosus	Invasive fungal sinusitis	Cauterization for epistaxis	Melanoma	Cocaine
Churg–Strauss syndrome	Leishmaniasis	Nose picking	Cryoglobulinemia	Industrial exposure (chromic acid, potash fumes)
Rheumatoid arthritis	Leprosy	Nasogastric tube placement		
Crohn disease	Rhinoscleroma	Nasal piercing		
Dermatomyositis	Acquired immunodeficiency syndrome	Foreign body		

powder and borax directly contribute to mucosal necrosis.[33] Even a one-time use of intranasal cocaine can induce a perforation.[34] Chronic use of over-the-counter topical nasal decongestants can also induce perforation from a vasoconstrictive effect.

In rare cases, intranasal steroids have the potential to induce septal perforation. Inhaled corticosteroids, through their suppressive effect on proinflammatory cytokines, may produce a net reduction in angiogenesis, perfusion and permeability of the septal mucosa, potentially initiating an ischemic cascade that results in septal perforation.[33] Nasal spray preservatives such as benzalkonium chloride have been hypothesized to possibly contribute to the propensity for perforation by inducing local irritation and squamous metaplasia.

Chemical Irritants

Industrial irritants related to chrome plating cause severe inflammation of the nasal mucosa and perforation. Similarly, the inflammatory response induced by aerosolized dust—such as in grain silos, glass manufacturing, and cement factories—can also lead to perforation.[34]

History and Physical Examination

The initial workup for septal perforation must incorporate a detailed history. The presence of the aforementioned inflammatory, infectious, and malignant conditions should be determined as this may preclude surgical repair. Ongoing use of cocaine is an absolute contraindication to surgery as the repair will invariably fail.[32]

The most common symptom of perforation is bleeding (58%). Other symptoms include crusting (43%), obstruction (39%), pain (17%), whistling (10%), and foul nasal discharge. Approximately, 15% of patients are completely asymptomatic.[33] Smaller perforations are typically associated with worse whistling due to the increased velocity of airflow through the perforation. The time of onset of the perforation should be determined when possible. Contributing factors such as previous nasal cautery, septorhinoplasty, or occupational exposures to inhaled irritants should be queried. An understanding of the patient's nasal hygiene is also pertinent including the use of nasal saline irrigation, topical ointments, intranasal medications, and propensity for digital trauma.[32]

Examination of the external nose can reveal a saddle deformity or tip ptosis when the integrity of the cartilaginous L-strut is compromised by a large perforation. An abundance of nasal crusts may prevent examination, and these patients should receive a course of emollients and irrigation before evaluation.[34] Nasal endoscopy should be performed to characterize the anatomic location of the perforation and to measure the anteroposterior and superoinferior dimensions of the perforation.[32] The presence of generalized mucosal crusting, nodularity, or ulceration that is not limited to the perforation is suggestive of a granulomatous or vasculitic process. The septum should be palpated with a cotton-tip applicator to delineate the boundaries of the cartilage relative to the edge of the perforation. An absence of cartilage, as may occur in post-septoplasty perforations, can complicate the elevation of the mucoperichondrial flaps during repair. In contrast, perforations from cocaine abuse are often sharply demarcated with cartilage preservation up to its edges.[34]

The workup concludes with laboratory investigations, if warranted, to facilitate identification of the underlying etiology. For example, elevations in p-ANCA are associated with Churg–Strauss syndrome, increases in c-ANCA will occur with Wegener's granulomatosis, and ACE levels are increased in sarcoidosis. The posterior edge of the perforation can be biopsied and sent for culture and pathology in patients with an unclear cause for their perforation. Enlarging the vertical height of the perforation with biopsies should be avoided.[32]

NONOPERATIVE MANAGEMENT

The mainstay of nonoperative management of nasal septal perforation is the establishment and maintenance of adequate nasal hygiene. Digital trauma or instrumentation of the nose with, e.g. cotton swabs should be avoided. Nasal saline spray or irrigating solution can effectively debride the perforation and reduce the accumulation of crusts. Petroleum-based ointment, gently applied intranasally a few times daily, can also prove effective against crust accumulation. Visible mucosal inflammation or intranasal tenderness suggestive of an infective process should be treated with antibiotic-based ointments.[32]

In patients who elect to forego surgical closure of their perforation, who harbor comorbidities precluding safe surgery under general anesthesia, or in whom the configuration of the perforation prevents the use of the techniques described below to effect surgical closure, a septal button can be used as an alternative treatment. This prosthetic device is made of soft silicone (Silastic), and has been used since the 1970s to close septal perforations for months to years.[35] Septal buttons can be effective

in reducing the morbidity associated with nasal septal perforation. In one study, patients reported a 70% reduction in the severity of stenosis, crusting, and bleeding.[36]

The septal button device is available in a variety of sizes and placement can be performed under local or topical anesthesia. Insertion technique consists of folding the flanges on one side of the septal button and passing this through the perforation using an alligator or bayonets to pull the flanges through. Upon release, the septum should be sandwiched between the two round flanges of the septal button. The septal button should extend superiorly into the region of the internal nasal valve and inferiorly to the level of the nasal floor. Avoiding direct contact with the nasal floor permits for a more comfortable placement.[32]

Septal buttons have been associated with complications including increased frequency of epistaxis, intranasal pain, and enlargement of the perforation secondary to pressure necrosis around the edges.[32] Approximately, two-thirds of patients will require removal of the septal button within 4 years. Among this group, nearly two-thirds will have the septal button removed within 2 months. Removal rates are significantly higher in patients with nasal septal perforations resulting from septoplasty with cartilage resection.[36] In this group of patients, in those intolerant of the septal button, and in patients electing primary surgical repair, a variety of operative techniques can be used to affect closure of the septal perforation.

SURGICAL TECHNIQUES

The primary goal of surgical perforation repair is to restore the normal function of the nose. Consequently, recently described techniques entail the use of intranasal advancement flaps to maintain a functional intranasal lining. The use of skin or buccal mucosal grafts can effectively close the perforation, but may result in persistent nasal dryness due to replacement of the respiratory epithelium with nonphysiologic tissue.[32,34]

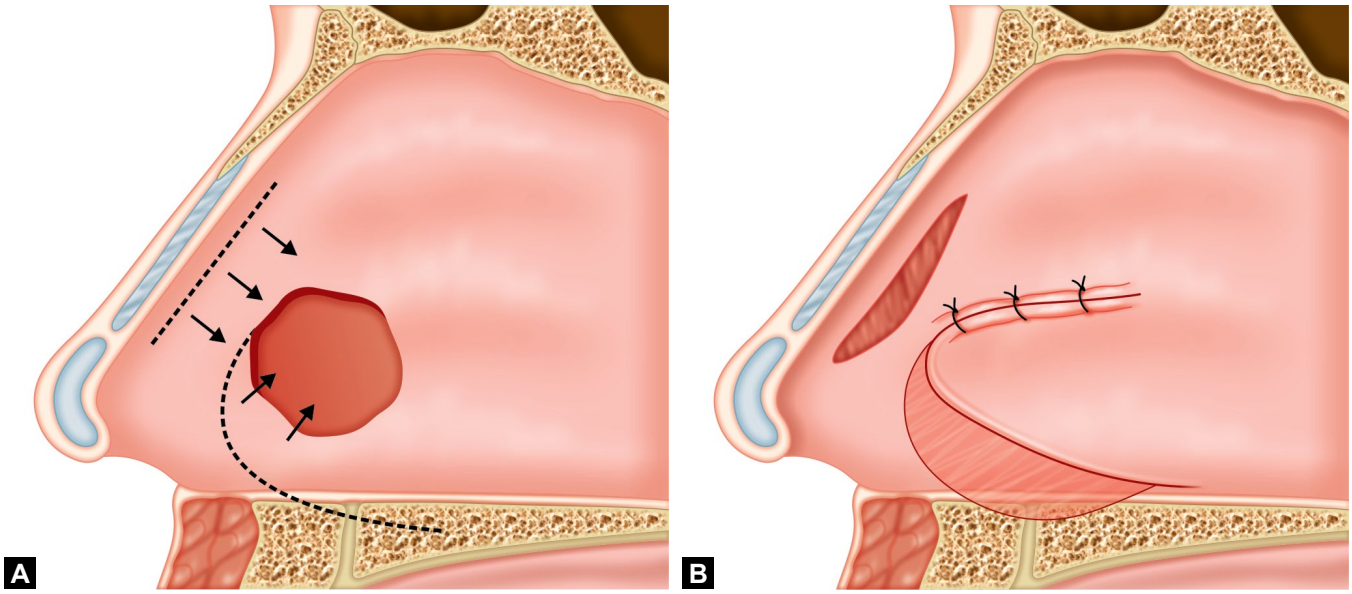
The second aim of surgery is to achieve a tension-free closure of the perforation as the septal mucosa, with its lack of elasticity, is particularly prone to dehiscence. Another significant determinant of success is the vertical height of the perforation and the size of the perforation relative to the available septal mucosa. A smaller perforation in the setting of plentiful mucosa is the most likely to be successfully repaired. Perforations that extend all the way to the nasal dorsum or down to the nasal floor are the most technically challenging to repair, as any advancement flaps cannot be reliably secured superiorly or inferiorly. The absence of septal cartilage is also problematic due to the difficulty in elevating the mucoperichondrial flaps.[34]

Endonasal Approach

The endonasal approach is indicated for the repair of small (0–10 mm) septal perforations. This approach can be facilitated through the use of an endoscope. A hemitransfixion incision is made and bilateral mucoperichondrial flaps are broadly elevated around the perforation and are extended posteriorly beyond the back edge of the perforation. Mucosal rotation/advancement flaps, typically based posteriorly, are configured from the septal mucosa superior and inferior to the perforation to provide the laxity necessary for mucosal closure (Figs. 41.15A and B). Optimal flap closure may require elevation of bilateral flaps to ensure satisfactory overlap of the advancement flaps. An interpositional graft can be placed between the mucoperichondrial flaps as a scaffold to reinforce the closure, but in general cannot serve as the sole layer for any part of the closure.[32,34] Septal or calvarial bone or cartilage, obtained from the nasal septum or auricular concha, is commonly used as an interpositional graft. Other options include pericranium, temporalis fascia, and acellular dermal allograft, the latter of which avoids donor site morbidity. The graft material is configured to be significantly larger than the perforation and is then sandwiched between the mucoperichondrial flaps. The mucoperichondrial flaps are then advanced to reapproximate the edges of the perforation and to conceal the interpositional graft.[32] Suture fixation of the flaps with monofilament absorbable suture helps to ensure satisfactory coverage of the perforation with viable tissue. Care is taken to stagger the closure lines on each side of the nose such that they are not directly apposed. Silastic splints are placed and left in position for 2–3 weeks.

External Approach

The external approach is advocated as the preferred approach for closure of most septal perforations up to 3 cm in diameter owing to excellent exposure around the perforation, and more complete mucoperichondrial flap elevation allowing for success rates exceeding 90%.[34] The surgical technique is essentially identical to that described earlier for external septoplasty. In brief, after application of a local anesthetic and vasoconstrictor, columellar and bilateral marginal incisions are made, the skin-soft tissue envelope is elevated, and the medial crura are separated to allow access to the septum.



Figs. 41.15A and B: Mucosal rotation-advancement flap for septal perforation closure. Use of a posteroinferior-based rotation-advancement flap, along with a superiorly based advancement flap, to affect closure of a large septal perforation.

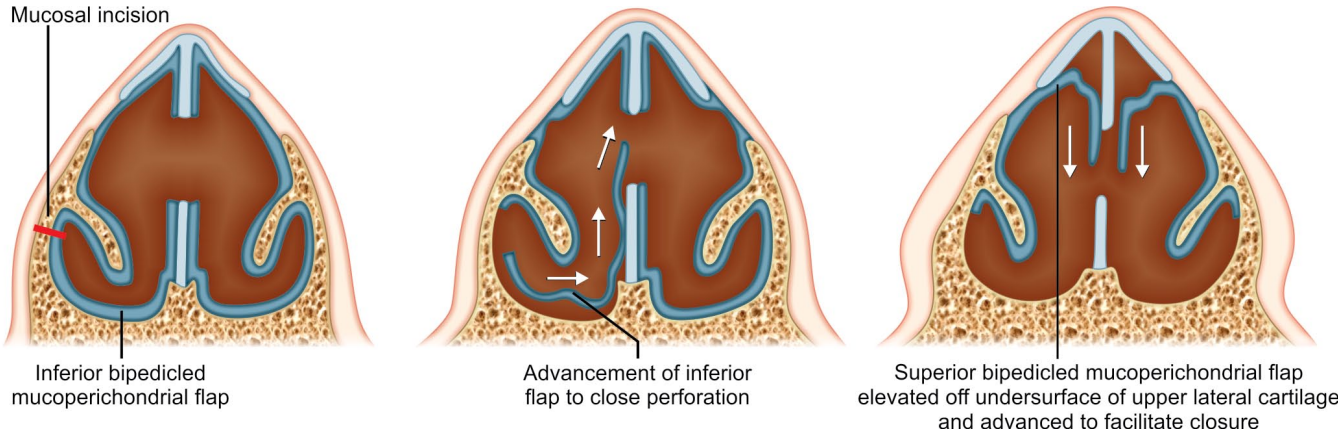


Fig. 41.16: Bipedicled mucoperichondrial flap for septal perforation closure. An inferior based bipedicled flap can be created through a lateral incision in the inferior meatus. The flap is then advanced toward the perforation. Closure can be facilitated by recruiting additional mucosa with a superior bipedicled mucoperichondrial flap that is mobilized downward to meet the inferior flap.

At this point, the mucoperichondrial flaps are elevated bilaterally as described earlier. The posterior extent of dissection must proceed, at a minimum, 1 cm beyond the edge of the perforation but, ideally, to just beyond the bony-cartilaginous junction. The flaps are elevated up to the upper lateral cartilages that are then separated sharply from the septum. The inferior portion of each mucoperichondrial flap is elevated off the nasal floor and this dissection continues laterally to the insertion of the inferior turbinate into the lateral nasal wall. If necessary, a septoplasty is performed to allow for greater laxity of the elevated mucoperichondrial flaps. At this point, the surgeon should have a clear view of the elevated mucoperichondrial flaps on each side and the intervening septal cartilage.[34]

A bipedicled mucoperichondrial flap is created by making a lateral releasing incision just inferior to the attachment of the inferior turbinate to the lateral nasal wall (Fig. 41.16). This can then be advanced medially to close the perforation. Further flap movement can be achieved by making a transverse incision that begins at the anterior nasal spine, travels just posterior to the

nasal sill, and then meets the lateral releasing incision. A similar transverse "back cut" incision can be performed from the posterior end of the lateral releasing incision. For larger perforations, a superiorly based flap that provides a few additional millimeters of movement may facilitate closure. The mucoperichondrium is elevated from the undersurface of the upper lateral cartilages and septum above the perforation.[32] Additional movement of the superior flap can be achieved by incising through the mucoperichondrium at the junction of the upper lateral cartilage and septum, effectively creating another bipedicled flap.[34]

The released mucoperichondrial flaps are then advanced to reapproximate the freshened mucosal edges of the perforation. Exposed bone along the nasal floor resulting from flap advancement will remucosalize. Foil from a suture pack is shaped to be slightly larger than the perforation and inserted between the mucoperichondrial flaps. This allows for closure of each mucosal defect with 5-0 chromic gut suture from posterior to anterior, without inadvertent catching of the contralateral mucoperichondrial flap. The foil barrier is then removed and an interpositional graft placed. The graft material must be advanced posteriorly to at least 1 cm beyond the edge of the perforation. Anteriorly, the graft may extend to within 1–2 mm of the caudal edge of the septum. The mucosal flaps and interpositional graft are then secured using 4-0 chromic gut suture on a straight needle.[32] A continuous quilting suture can then be placed.

The medial crural footplates are reapproximated as detailed above. Tension along the closure lines and significant flap elevation can cause unwanted tip rotation. Refinement of the nasal tip may be required, and is discussed elsewhere in this volume. The skin-soft tissue envelope is redraped and the columellar and marginal incisions closed. Bilateral Silastic intranasal splints are placed on either side of the septum, and are left in position for 2–3 weeks. The surgical site can be monitored through the clear Silastic sheeting and, if necessary, the splints can be left in place longer if there are nonhealing areas apparent on examination.

Alternative Techniques

Intranasal flaps may be inadequate for the closure of large perforations exceeding 2–3 cm in size, or those that are located in challenging anatomic areas. Alternative techniques have been developed to address these cases. The inferior turbinate pedicled flap can be used to repair perforations of the caudal septum up to 3 cm in diameter and those involving the columella (Fig. 41.17). The procedure can be performed through an endonasal approach.[37] Patients who have had previous turbinate surgery and those with atrophic rhinitis are not candidates for this technique. The flap is pedicled anteriorly and the inferior half of the turbinate is the donor tissue. Under endoscopic view, a knife incision is made vertically from the inferior edge of the medial, posterior turbinate in a superior direction. This transitions to a horizontal incision along the superior aspect of the turbinate toward the pedicle anteriorly. A through-and-through scissor cut is made along this incision line. The flap is rotated anteriorly to cover the perforation after opening the distal portion

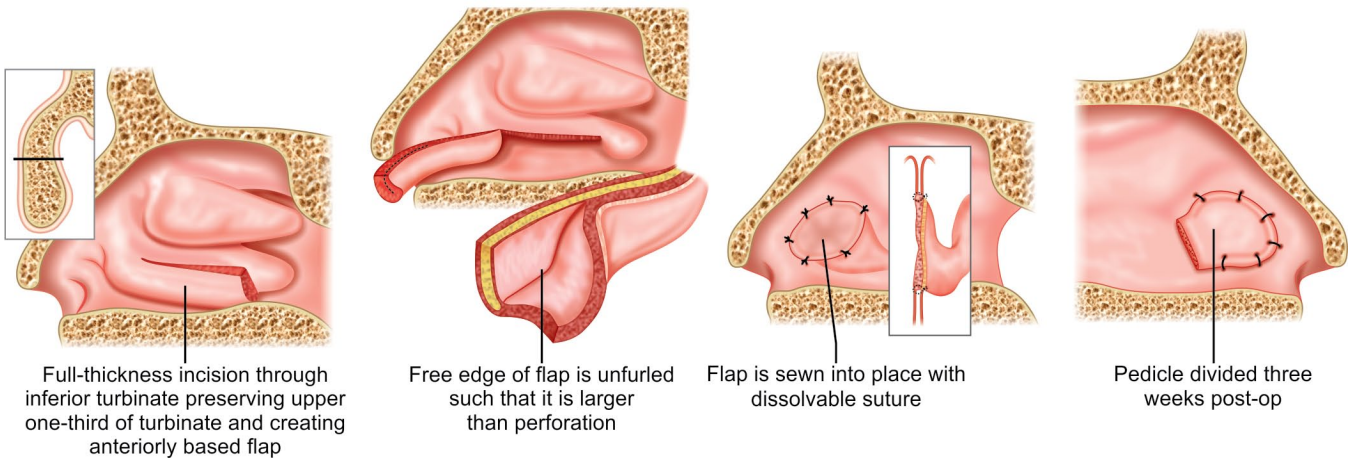


Fig. 41.17: Inferior turbinate flap for septal perforation closure. An anteriorly based inferior turbinate flap is created, and then swung forward toward the perforation. The free end is unfurled and stitched around the perforation with the mucosal surface facing outward. The pedicle is transected 3 weeks post-inset.

such that mucosa constitutes one surface and submucosa the opposite side. The flap is sutured in position using 4-0 plain gut. The submucosa is left exposed on one side to heal by secondary intention over approximately 3 weeks. Three weeks later, the pedicle is taken down under local anesthetic. Postoperative care includes intranasal saline spray and topical ointment to maintain humidification.[37] Reported complications include nasal obstruction from the bulkiness of the flap, synechiae between the septum and residual inferior turbinate, and a low risk of complete flap failure.

Tardy advocates the use of a tunneled sublabial mucosal flap for closure of large anterior perforations.[38] The ipsilateral buccal mucosa is incised and a medially based flap is raised and passed through a midline sublabial incision into the nose. This is then interposed between elevated septal mucoperichondrial flaps. Flap failure has been reported due to constriction of the oronasal tunnel. There is also a risk of a persistent oronasal fistula. This latter risk can be attenuated through use of the facial artery musculomucosal flap, which is based on the facial artery and can be used to close perforations 2–4 cm in size.[32] The buccal mucosa and mucosa of the inferior gingivobuccal sulcus is raised and tunneled into the piriform aperture using a subperiosteal dissection. The graft is then sewn into position. The largest perforations, such as those created through long-term cocaine abuse, can be closed using radial forearm free tissue transfer.[39] The flap, although initially quite bulky, thins with time, becoming less obstructive. However, this surgery is a last resort for perforation repair due to the technical challenges of microvascular anastomosis, the lengthiness of the procedure, and significant donor site morbidity.

OUTCOMES

The wide variety of septal perforation repair techniques in use and lack of standardization in reporting the size and configuration of a perforation have complicated outcome analysis. The absence of randomized prospective trials in the literature has prevented meta-analysis. However, systematic reviews evaluating outcomes have been conducted to identify factors that predict overall rates of successful repair.[40,41] Incorporating data from 59 studies, Kim and Rhee noted that large perforations, those greater than 2 cm in diameter, are successfully repaired in 78% of patients. Smaller and moderately sized perforations had a significantly higher closure rate of 93%.[40] Although not quantified in published studies, posterior perforations are anecdotally more difficult to repair. However, these posterior perforations are rarely symptomatic and often do not require repair.

Among pedicled mucosal flap techniques, lower closure rates of 30–70% have been associated with the inferior turbinate flap.[41] Consequently, it has been suggested that this flap be preferentially used in patients with scarred tissue precluding the use of a mucoperichondrial advancement flap. These mucoperichondrial flaps are associated with a significantly greater success rate. This is particularly true when bilateral mucoperichondrial flaps are used, as described above, rather than a single-layer unilateral flap (84.5% vs. 73.5%).[40] This success rate may be enhanced to greater than 90% through the use of an intervening interposition graft, such as septal cartilage, acellular human dermis, or temporalis fascia, to act as a scaffold for mucosal migration.[34,41]

Although the open rhinoplasty approach has been shown to have a higher surgical failure rate than the endonasal approach, this finding is confounded by the more frequent use of the open approach for the repair of larger, more technically challenging perforations.[40] There is no definitive evidence that surgical approach influences perforation closure rate.[41] There are, however, distinct advantages to each approach as described earlier.

In summary, the size of the septal perforation is the primary determinant in closure rate. The repair technique also influences success rates with higher closure rates achieved through the use of bilateral mucoperichondrial flaps. The use of an interpositional graft may further enhance the success rate. The surgical approach selected should be decided on the basis of surgeon experience and comfort as this is less likely to directly influence closure rates.

CONCLUSION

Successful surgery of the nasal septum is predicated on a detailed preoperative evaluation to identify appropriate operative candidates and, perhaps more importantly, to determine which patients will not benefit. The goal of the surgeon should be to maintain physiologic function of the nose whenever possible through conservative cartilage-sparing techniques. Maintenance of an adequate dorsal and caudal strut, as well as preservation of mucoperichondrium, forms the mainstay of good surgical technique. Adherence to these principles will often result in a satisfying outcome for both the patient and the surgeon.

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CHAPTER

42 Surgical Management of the Nasal Turbinates

Andrea S Wang, Nicole M Hsu, Michael G Stewart

INTRODUCTION

Inferior turbinate hypertrophy is a common cause of chronic nasal obstruction. While the normal inferior turbinates warm, filter, and humidify inhaled air, edema and engorgement of the inferior turbinates largely obstruct nasal airflow. Inferior turbinate hypertrophy may be bilateral or unilateral. Bilateral turbinate hypertrophy is associated with nasal inflammation from allergens, infections, other environmental factors such as tobacco smoke, or pregnancy.[1] Unilateral turbinate hypertrophy usually occurs in association with a deviated nasal septum toward the contralateral side. Turbinate hypertrophy may be primarily mucosal, osseous, or both.

Medical treatment consists of nasal steroids, decongestants, and antihistamines that address the mucosal turbinate hypertrophy. Surgery is reserved for cases that are refractory to medical treatment. Many surgical techniques and instruments have been described in the otolaryngology literature, with no consensus for a gold standard approach. Over the last three decades, there has been a gradual evolution away from total turbinate resection, toward more minimally invasive, submucosal reduction, or partial resection. In this chapter, we will review turbinate surgery by approach, beginning with turbinectomy (including total and partial turbinate resection), turbinoplasty (or submucous resection of turbinate bone), mucosal ablation, submucosal reduction, and turbinate lateralization (Table 42.1). For each approach, there are variations in technique and tools that may be used. In addition, some of the surgical tools may be used to accomplish multiple techniques. For example, microdebrider may be used in both partial resection and submucosal reduction in the turbinate. We will also review comparative outcomes of the various approaches (Table 42.2).

TURBINECTOMY

Turbinectomy, or turbinate resection, encompasses a variety of procedures, which can range from extensive resection of the entire inferior turbinate to limited resection of the anterior turbinate head.

Total Turbinate Resection

This technique, first reported around the turn of the twentieth century, typically requires an initial fracturing of the turbinate bone medially, toward the septum, with a Freer elevator. A clamp is applied to the portion of inferior turbinate to be resected in order to assist with hemostasis. Heavy scissors are then utilized to resect the turbinate. The cut is made along the lateral attachment of the inferior turbinate bone (Fig. 42.1). Additional hemostasis of the cut edge can be achieved with electrocautery.

Total or extensive subtotal resection is no longer commonly performed as it is believed to predispose patients to atrophic rhinitis or paradoxical nasal obstruction.[2] Moore et al.[3] performed a retrospective analysis of patients who had undergone total inferior turbinectomy and reported a significant morbidity associated with the procedure. Of the 18 patients who had undergone bilateral total turbinectomy and were followed for 3–5 years, 66% developed atrophic rhinitis (chronic nasal crusting

Table 42.1: Surgical techniques for inferior turbinate reduction

Technique	*Advantages*	*Disadvantages*
Total turbinectomy	Long-term relief of nasal obstruction	Increased risk of postoperative bleeding Risk of atrophic rhinitis Synechiae formation
Partial turbinectomy	Long-term relief of nasal obstruction	Bleeding
Turbinoplasty/submucous turbinate resection	Preserves mucosal function Reduces bony hypertrophy Excellent long-term nasal patency	Technically difficult to learn Bleeding
Mucosal electrocautery	Easy to learn May be performed in office under local anesthesia	Symptoms may return in months to years Postoperative crusting, pain, adhesions
Laser	May be performed in office under local anesthesia Minimal bleeding due to hemostasis	Cost of equipment Laser training required Postoperative eschar and crusting
Submucosal electrocautery	Easy to learn May be performed in office under local anesthesia	Symptoms may return in months to years Postoperative crusting, pain
Radiofrequency ablation (RFA)	Mucosal preservation Maintenance of ciliary function May be performed in office under local anesthesia Minimal bleeding, no need for postoperative packing Easy to learn	Symptoms may return after 1 year
Microdebrider-assisted turbinate reduction (MATR)	Submucosal resection with preservation of mucosa and ciliary function Excellent long-term results May reduce some bony hypertrophy	Possible bleeding and mucosal tears Equipment cost
Lateralization	Easy to learn Can be combined with other procedures	Does not address hypertrophied mucosa Minimal relief when performed alone

and foul odor), 22% experienced ozena (crusting, foul odor, and anosmia secondary to destruction of olfactory nerve endings), and only 11% were symptom free with an improved nasal airway.

Chhabra and Houser[4] described paradoxic nasal obstruction, otherwise known as "empty nose syndrome," which is another potential complication of turbinate resection. They estimated that approximately 20% of patients who have undergone total inferior turbinectomy develop this iatrogenic disorder. It is thought to result from paucity of mucosal surface area within the nasal cavity, leading to a paradoxical sensation of nasal obstruction due to lack of sensation of airflow despite a widely patent nasal passage.

However, there have been various studies that have reported good long-term effectiveness after total turbinectomy with minimal complications.[5-8] Ophir et al.[7] performed a long-term follow-up of 186 patients over 10–15 year period after total turbinectomy. They demonstrated 82% of patients had subjective relief of obstruction and widely patent airway on rhinoscopy. And, despite living in a dry, dusty climate, none of the patients in their study suffered excessive crusting or dryness, suggesting the function of the remaining mucosa within the nasal cavity was not impaired.

Although the long-term outcomes of inferior turbinectomy and the risk of potential complications remain controversial, total turbinectomy has largely fallen out of favor. This is largely secondary to the availability of more physiologic treatments and the desire to avoid the potentially permanent morbidity associated with empty nose syndrome in a patient with a quality of life symptom.

Partial Turbinate Resection

Partial resections are believed to have lower risk of potential complications because there is greater preservation of the

Table 42.2: Surgical management of inferior turbinate literature

Author (year of publication)	*Type of study*	*Patient selection*	*Surgical techniques*	*Number of patients*	*Outcome measures*	*Follow-up period*	*Key findings*
Aksoy[29] (2010)	Case series	Turbinate hypertrophy	Lateralization	40	CT	6 months	Inferior turbinates remained in lateralized position at 6 months
Cingi[38] (2010)	Prospective	Nasal obstruction	MATR, RFA	268	Rhinomanometry, subjective symptoms, patient satisfaction	3 months	Nasal obstruction improved in microdebrider and RFA at 3 months, but greater in microdebrider
Lin[26] (2010)	Retrospective	Allergic rhinitis	RFA	146	VAS, patient satisfaction questionnaires	5 years	15% received other nasal surgery for RFA failure. VAS scores while improved at 6 months, trended back to baseline at 5 years
Porter[39] (2009)	Prospective, randomized, single blinded, placebo controlled	Nasal obstruction	RFA	32	VAS	2 years	Sustained symptom improvement at 2 years compared with baseline.
Liu[35] (2009)	Prospective, randomized	Allergic rhinitis	MATR, RFA	120	VAS, anterior rhinomanometry, saccharin test	3 years	All outcomes improved in microdebrider group at 3 years. RFA group improved up to 1 year, but declined at 3 years
Kizilkaya[34] (2008)	Prospective, randomized, single blinded	Turbinate hypertrophy	MATR, RFA	30	VAS, saccharine transit time, ciliary beat frequency, anterior rhinomanometry	6 months	Significant and equal improvement in VAS and rhinometry at 6 months STT and CBF unchanged
Yanez[28] (2008)	Prospective cohort	Turbinate hypertrophy	MATR	350	VAS, nasal endoscopy, acoustic rhinometry, mucociliary saccharin transit time	10 years	Significant and equal improvement in VAS and rhinometry at 6 months; STT and CBF unchanged.
Harrill[37] (2007)	Prospective, nonrandomized	Nasal obstruction	In office RFA, in OR RFA and septoplasty	77	NOSE validated on form questionnaire	6 months	Improvement in both groups; consider in-office cost savings.

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Author (year of publication)	*Type of study*	*Patient selection*	*Surgical techniques*	*Number of patients*	*Outcome measures*	*Follow-up period*	*Key findings*
Sroka[16] (2007)	Retrospective	Turbinate hypertrophy secondary to allergic or vasomotor rhinitis	Ho:YAG, diode laser	113	Symptom questionnaire, rhinomanometry	3–5 years	Subjective improvement in 67.5% after Ho:YAG and in 74.4% after diode laser treatment. Both groups had improved airflow on rhinomanometry at 6 months and 3 years after treatment. Ho:YAG laser had shorter period of postoperative edema and crusting than diode laser
Testa[40] (2006)	Retrospective	Nasal obstruction	CO_2 laser	308	Symptom questionnaire, rhinomanometry	7.8 years	Significant long-term improvement in nasal obstruction and blockage in both hypertrophy rhinitis and allergic rhinitis. Allergic rhinitis patients had reduced rhinorrhea and sneezing. However, severe chronic allergic rhinitis patients continued to require H2 antagonists or steroids during allergy season.
Cavaliere[25] (2005)	Prospective	Turbinate hypertrophy	Turbinoplasty, RFA	75	VAS, nasal endoscopy, anterior active positional rhinomanometry, saccharin tests	3 months	Both monopolar and bipolar RFA resulted in similar reduction in nasal symptoms, nasal resistance, and maintenance of nasal function at 20 months
Nease[23] (2004)	Prospective, randomized, single blinded, placebo controlled	Turbinate hypertrophy	RFA	32	VAS	6 months	Significant improvement in treatment group at 6 months
Passali[30] (2003)	Prospective, randomized	Chronic allergic or vasomotor rhinitis	Turbinectomy, laser, electrocautery, cryotherapy, submucosal resection, submucosal resection with lateralization	382	Anterior rhinomanometry, acoustic rhinometry, nasal mucociliary transport time, measurement of secretory immunoglobulins	6 years	Only SMR resulted in long-term nasal patency and restoration of mucociliary clearance and local secretory IgA production. Lateral displacement of the inferior turbinate improved the long-term results.

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Author (year of publication)	*Type of study*	*Patient selection*	*Surgical techniques*	*Number of patients*	*Outcome measures*	*Follow-up period*	*Key findings*
Sapci[32] (2003)	Prospective, randomized	Turbinate hypertrophy	RFA, CO_2 laser, partial turbinectomy	45	VAS, rhinomanometry, nasal mucociliary transport time	3 months	Nasal mucociliary transport time in RFA and partial turbinectomy were near normal at 3 months. Nasal mucociliary transport time in CO_2 laser was twice that of normal
Talmon[8] (2000)	Retrospective	Nasal obstruction	Total turbinectomy	357	Symptom questionnaire	6 years	No atrophic rhinitis. 1.7% with postoperative bleeding
Friedman[41] (1999)	Prospective	Nasal obstruction, turbinate hypertrophy	MATR	120	Symptom questionnaire, objective grading of inferior turbinates	6 weeks	75% had no post-op nasal obstruction
Lippert[42] (1998)	Retrospective	Turbinate hypertrophy secondary to allergic or vasomotor rhinitis	CO_2 and Nd:YAG laser	118	Symptom questionnaire, rhinomanometry	5 years	At 5 years after treatment, 77.1% of CO_2 laser patients and 64.5% in Nd:YAG laser patients reported improved nasal airway
Lippert[43] (1997)	Retrospective	Turbinate hypertrophy secondary to allergic or vasomotor rhinitis	CO_2 laser	112	Symptom questionnaire, rhinomanometry	2 years	80.4% patients with improvement after 2 years with no significant difference in outcomes between allergic and nonallergic rhinitis patients
Lippert[44] (1997)	Retrospective	Turbinate hypertrophy secondary to allergic or vasomotor rhinitis	CO_2, Nd:YAG laser, submucosal diathermy	227	Symptom questionnaire, rhinomanometry	2 years	Both laser groups had better long-term satisfaction (79.6% CO_2 laser and 68.3% Nd:YAG) compared with submucosal diathermy (36%) at 2 years. Nd:YAG caused prolonged postoperative edema and crusting compared with CO_2. However, the entire turbinate is ultimately reduced with Nd:YAG, while CO_2 laser affects only the anterior head.

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Author (year of publication)	*Type of study*	*Patient selection*	*Surgical techniques*	*Number of patients*	*Outcome measures*	*Follow-up period*	*Key findings*
Mucci[12] (1994)	Retrospective	Chronic rhinitis	Partial turbinectomy, septoplasty	55	Symptom questionnaire	12–39 months	13 patients underwent inferior partial turbinectomy alone; 92.3% reported improved nasal obstruction
Cook[45] (1993)	Prospective, randomized, double-blind	Nasal obstruction due to perennial allergic or non-allergic rhinitis	CO_2 laser, submucosal diathermy	29	Symptom questionnaire and peak nasal flow meter	1 year	Laser therapy patients maintained improved nasal flow 1 year after surgery, while submucosal diathermy patients did not
Kawamura[46] (1993)	Retrospective	Perennial allergic rhinitis	CO_2 laser	72	Subjective symptoms	24 months	84.7% had improvement in symptoms at 2 years. However, 37.5% of patients required a second treatment due to recurrence of symptoms within 24 months.
Ophir[7] (1991)	Retrospective	Turbinate hypertrophy	Total turbinectomy	186	Symptoms questionnaire, anterior rhinoscopy	10–15 years (mean 12.3 years)	82% with sustained improvement in nasal obstruction. No patients with atrophic rhinitis.
Wight[47] (1990)	Retrospective	Turbinate hypertrophy secondary to allergic or vasomotor rhinitis	Total turbinectomy, partial turbinectomy (anterior trimming)	27	Rhinomanometry, subjective symptoms, questionnaire	Mean 20.5 months for total turbinectomy, mean 22.8 months for partial turbinectomy	Decrease in nasal resistance in 83% of total turbinectomy patients. However, 37.5% had worsening nasal obstruction between 2 and 20 months, and 18.8% felt that postoperative nasal obstruction was the same as preoperative obstruction. Partial turbinectomy patients had decreased resistance, but no improvement in sensation of nasal obstruction; 67% of these patients converted to total turbinectomy

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Author (year of publication)	*Type of study*	*Patient selection*	*Surgical techniques*	*Number of patients*	*Outcome measures*	*Follow-up period*	*Key findings*
Mabry[14] (1988)	Case series	Turbinate hypertrophy	Turbinoplasty	40	Subjective symptoms	3–5 years	Improved nasal airway with no complications of bleeding, persistent crusting or dryness, or foul nasal discharge
Wight[48] (1988)	Prospective, randomized	Turbinate hypertrophy secondary to allergic or vasomotor rhinitis	Total turbinectomy, partial turbinectomy (anterior trimming)	18	Rhinomanometry, subjective symptoms	2 months	Total turbinectomy resulted in decreased subjective and objective nasal obstruction. Partial turbinectomy had decreased objective nasal resistance, but did not decrease subjective nasal obstruction
Meredith[31] (1987)	Retrospective	Nasal obstruction	Mucosal electrocautery with lateralization, partial turbinectomy	162	Symptom questionnaire	33 months	69% who underwent mucosal electrocautery with lateralization reported improvement in nasal obstruction, compared with 86% who underwent partial turbinectomy and reported improvement in nasal obstruction.
Fanous[12] (1986)	Retrospective	Turbinate hypertrophy	Partial turbinectomy (anterior turbinectomy)	220	Subjective symptoms	6 months to 4 years	94% with good to excellent improvement. No patients with atrophic rhinitis. 2.7% with postoperative bleeding

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Author (year of publication)	*Type of study*	*Patient selection*	*Surgical techniques*	*Number of patients*	*Outcome measures*	*Follow-up period*	*Key findings*
Fukutake[49] (1986)	Retrospective	Perennial allergic rhinitis refractory to conservative treatment	CO_2 laser	140	Subjective symptoms	1–12 months	At 1 month, 36% with excellent reduction in nasal obstruction, rhinorrhea, and sneezing. At 1 year, 77% with excellent or good results. 17% had recurrence of symptoms requiring revaporization within 9–12 months
Moore[3] (1985)	Retrospective	Turbinate hypertrophy	Total turbinectomy	18	Symptom questionnaire	3–5 years	66% with atrophic rhinitis and 22% with ozena. Only 11% symptom-free with improved airway
Martinez[5] (1983)	Retrospective	Turbinate hypertrophy	Total turbinectomy	29	Symptom questionnaire	2–60 months	25 patients with marked improvement in airway.

(RFA: Radiofrequency ablation; MATR: Microdebrider assisted turbinate reduction; VAS: Visual analog scale; NOSE: Nasal Obstruction Symptom Evaluation scale).

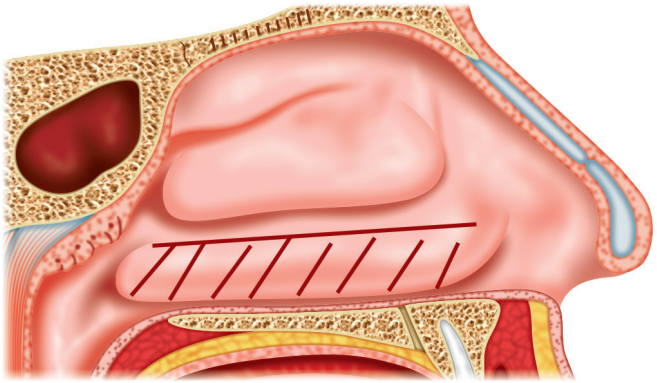

Fig. 42.1: Total turbinectomy.
(Figure created by David Hsu.)

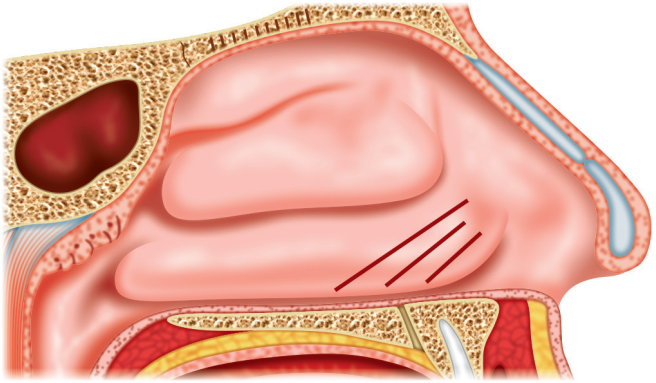

Fig. 42.2: Partial anterior turbinectomy.
(Figure created by David Hsu.)

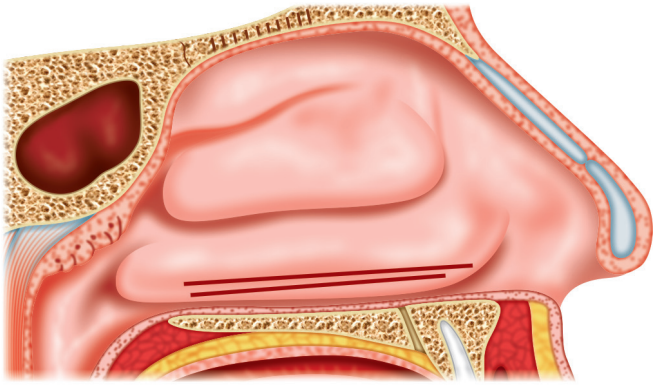

Fig. 42.3: Microdebrider partial turbinectomy.
(Figure created by David Hsu.)

normal mucosa. By limiting resection to specific areas of the inferior turbinate known to restrict airflow, nasal aerodynamics can be improved while being mindful of soft tissue conservation. The resection is usually limited to the anterior turbinate head (Fig. 42.2), relieving obstruction at the internal nasal valve, or along the anteroposterior length of the caudal aspect of the turbinate, which can improve airflow along the nasal floor.[9,10]

Partial resections may be performed with endoscopic turbinectomy scissors or a microdebrider. The scissors may be implemented in a similar fashion to total turbinectomy, where the resection is limited to the anterior head of the inferior turbinate. When using the microdebrider, the blade is placed along the inferior aspect of the turbinate and used to remove some of the mucosa and bone. Depending on the area of obstruction, the microdebrider can be used to selectively debulk the head of the turbinate, the posterior aspect, or the entire length of the turbinate (Fig. 42.3). Hemostasis is achieved with coagulation and/or nasal packing.

Fanous[11] performed a review of 220 patients who had undergone anterior turbinectomy and were followed for 6 months to 4 years. In 61 patients, anterior turbinectomy was performed alone; of these patients, 35 had previously undergone septoplasty with no significant improvement in breathing. The remaining 159 patients underwent concurrent septoplasty with anterior turbinectomy. He found 94% of patients reported good to excellent improvement in their nasal obstruction after anterior turbinectomy, while none developed atrophic rhinitis. Of the 35 patients who had undergone previous septoplasty, all reported a satisfactory improvement in their breathing.

Mucci and Sismanis[12] reported a case series of 54 patients with chronic rhinitis who underwent inferior partial turbinectomy and were followed for 12–39 months (mean follow-up 18 months). Of these patients, 39 had concurrent septoplasty and 2 had functional endoscopic sinus surgery, while 13 patients underwent inferior partial turbinectomy alone. They found that 92.3% of all patients reported an improvement in their nasal obstruction with no cases of atrophic rhinitis reported. Of the 13 patients who underwent inferior partial turbinectomy alone, 92.3% reported improved nasal obstruction.

Based on these and other results, partial turbinectomy has been favored over total turbinectomy. Decreased nasal obstruction can be achieved with lower rates of atrophic rhinitis and no significant change in other complications, such as bleeding, crusting, or synechiae.[13]

TURBINOPLASTY

Submucosal turbinate bone resection, also commonly referred to as inferior turbinoplasty, can be implemented when there is a significant bony component of the turbinate

contributing to nasal obstruction. To determine if bony resection is necessary, careful preoperative evaluation of the inferior turbinate is imperative. If the turbinate mucosa responds well to decongestion with a significant improvement in the nasal obstruction, it suggests that submucosal/mucosal hypertrophy is the major cause of obstruction. However, if the inferior turbinate appears bulky and there is persistent obstruction despite adequate decongestion, the inferior turbinate bone itself could be the obstructive source.

An L-shaped incision is made from the anterior turbinate head extending along the caudal margin of the inferior turbinate. The mucoperiosteum is elevated off both the medial and lateral surfaces of the turbinate bone with a Freer elevator. The bone is resected using biting forceps (such as a Jansen-Middleton rongeur) or turbinate scissors. The redundant mucosa is trimmed and the lateral mucoperiosteal flap is then redraped over the reduced inferior turbinate bone. The medial and lateral mucoperiosteal flaps can be reapproximated using absorbable sutures or by applying gentle packing along the inferolateral aspect to allow for adhesion and healing of the mucoperiosteum to the residual turbinate bone. While this procedure facilitates functional mucosal preservation, it is technically more challenging than most other procedures discussed (Fig. 42.4).

Mabry[14] described his long-term outcomes with inferior turbinoplasty in 40 patients. Patients had decreased nasal obstruction with no bleeding, crusting, foul nasal discharge, or atrophic rhinitis after 3–5 year follow-up, which he attributed to the remaining flap of soft tissue and mucosa. Mabry emphasized that the etiology of nasal obstruction from inferior turbinate hypertrophy (bony versus mucosal hypertrophy) needs to be identified in each patient to determine the appropriate surgical technique. If the underlying cause of the turbinate hypertrophy is not aptly addressed, recurrent obstruction can and probably will occur.

MUCOSAL ABLATION

For patients with significant nasal obstruction secondary to mucosal hypertrophy of the inferior turbinates, procedures focused primarily on mucosal ablation are effective surgical options. Unfortunately, mucosal ablation can lead to loss of mucosal ciliary and secretory function, as well as significant postoperative pain, crusting, and scarring, when compared to other methods.

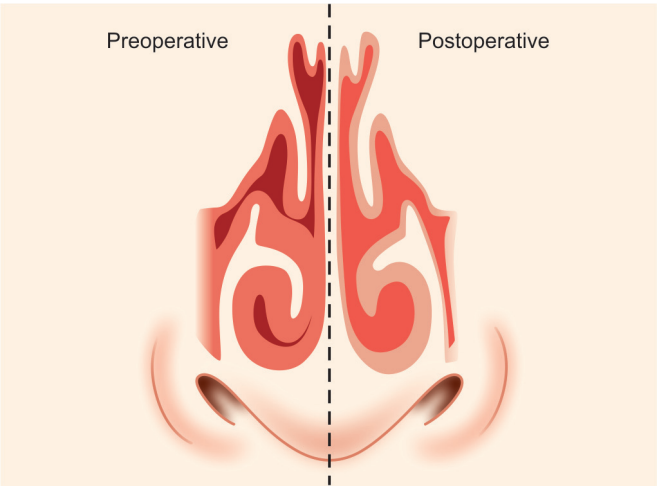

Fig. 42.4: Preoperative and postoperative views of turbinoplasty. The postoperative view shows the resection of bone. (Figure created by David Hsu.)

Electrocauterization

Mucosal electrocautery with a monopolar or bipolar device has been used to cauterize the inferomedial surface of the turbinate linearly in a posterior to anterior manner. The coagulated tissue shrinks in size, and the scarring that occurs during the healing process leads to additional tissue reduction. Electrocautery results in impaired mucosal function, as well as increased irritation, crusting, and scarring compared to submucosal techniques. Effects are commonly short lived and repeat cauterization is often required. While otolaryngologists frequently utilize this simple technique, there are very little data on the long-term outcomes of mucosal electrocautery.

Lasers

Various lasers have been used for mucosal ablation, including carbon dioxide (CO_2), diode, neodymium-yttrium aluminum garnet (Nd:YAG), potassium-titanyl-phosphate (KTP), argon-ion, and holmium-yttrium aluminum garnet (Ho:YAG) lasers.[15] Lasers generate a beam of coherent light absorbed by the tissue, and the extent of absorption and the depth of effect depend on the wavelength of the laser. CO_2 laser light (λ = 10,600 nm) is strongly absorbed by water, which makes CO2 laser ideal for cutting and superficial vaporization of tissue. Nd:YAG laser light (λ = 1,064 nm) is able to penetrate deeply into the tissue, thereby inducing large coagulation areas in noncontact mode. Additionally, Nd:YAG laser can be utilized with contact application that generates effective

cutting and vaporizing qualities. Diode laser light (λ = 940 nm) is predominately absorbed by water and blood, and also provides excellent coagulation capabilities in noncontact mode.[15-17]

KTP (λ = 532 nm) and argon-ion laser (λ = 488/514 nm) emit light that are absorbed by endogenous chromophores, such as hemoglobin, and hence are often used for the management of vascular malformations. Ho:YAG laser (λ = 2,100 nm) provides good cutting capabilities for both bone and soft tissue and achieve good hemostasis. All these lasers, except the CO_2 laser, are applied with the use of a flexible quartz fiber in a contact or noncontact mode.[16]

When utilizing these lasers, the light is applied to the mucosa but the energy is transmitted to the deeper layer, producing less mucosal injury and allowing for submucosal soft tissue destruction and scarring. Typically, the laser fiber is used to make linear stripes along the inferior surface or a crosshatch pattern on the medial surface of the turbinate. Alternatively, lasers can be utilized in a single- or multiple-spot technique on the anterior head of the turbinate to induce shrinkage and scarring of the soft tissue. Lasers allow for precise ablation of the hypertrophic region with limited damage to the surrounding tissue, and minimal bleeding and discomfort. Many have favored this technique as it can be performed in an outpatient or office setting under local anesthesia. An eschar forms at the site of treatment and patients can experience crusting for several weeks after the procedure. There is concern for potential stray laser injury, and the cost of equipment and laser safety training must be incorporated when determining the cost-effectiveness of this technique. Additionally, similar to the electrocautery technique, the mucosa often regenerates and repeated laser treatments may be needed.

As there are numerous types of lasers available, the outcomes of laser reduction in the inferior turbinate are difficult to summarize from the literature. Janda et al.[15] performed a comparative review on the various types of lasers that have been used for turbinate reduction. They reported that after 1 year of follow-up, studies showed laser treatment had comparable results to most of the conventional surgical techniques, including electrocautery, cryotherapy, chemical cauterization with fewer complications of bleeding, nasal dryness, synechia, and pain. The variations in laser type, laser parameters, and treatment areas on the turbinates within the referenced studies did not allow for a meaningful comparison of the different lasers. The effectiveness of laser reduction in the turbinate hypertrophy is contingent on the surgeon's knowledge and experiences with the chosen laser, along with parameters used, and technique.

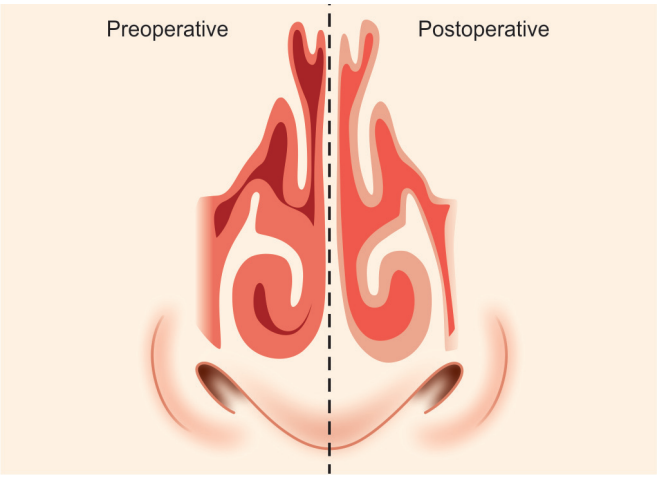

Fig. 42.5: Preoperative and postoperative view of submucosal reduction. The reduction can be accomplished via electrocautery, radiofrequency ablation, or microdebrider.
(Figure created by David Hsu.)

SUBMUCOSAL REDUCTION

Several studies have shown that submucosal resection results in restoration of mucociliary clearance and long-term nasal patency. However, submucosal resection or turbinoplasty can be technically difficult to perform without injuring the overlying mucosa, resulting in mucosal tears, bleeding, and crusting. In recent years, surgical techniques that reduce the volume of the inferior turbinates and preserve mucosa with few incisions have become increasingly preferred (Fig. 42.5). These techniques include submucosal electrocautery, radiofrequency ablation (RFA), and microdebrider-assisted turbinate reduction (MATR).

Submucosal Electrocautery

The oldest of these techniques, submucosal electrocautery or diathermy, was first reported in 1907 by Neres,[18-19] who directed a current to a gold needle buried in the turbinate. Further popularized by Simpson and Groves in 1958,[19] submucosal electrocautery involves the longitudinal insertion of monopolar or bipolar needles into the inferior turbinate with the application of electrocautery as the needles are withdrawn. This produces thermal injury and necrosis of the tissue. Postoperative inflammation, fibrosis, and scar

contracture result in reduction in tissue. While several devices are available, submucosal electrocautery may also be performed with a spinal needle inserted along the length of the inferior or medial aspect of the turbinate. Electrocautery is then applied to the needle as it is slowly removed. This technique may be performed as an office procedure.

The main disadvantage of this technique is regrowth of the inferior turbinate tissue with return of symptoms, which has been reported after months or years.[20-21] Complications include crusting and nasal dryness. There have also been reports of bone necrosis requiring local debridement.

Radiofrequency Ablation

RFA or radiofrequency volumetric turbinate reduction similarly utilizes a probe that delivers a low-power radiofrequency current to the turbinate, causing ionic agitation and a thermal lesion of the tissue. The main difference between RFA and submucosal electrocautery is the temperature and degree of surrounding thermal injury. With RFA, the temperature ranges from 60°C to 90°C, whereas with submucosal electrocautery, the temperature ranges from 750°C to 900°C.[22] As cell death occurs when temperatures reach 49.5°C, submucosal electrocautery results in excessive heat and far more adjacent tissue damage. There are several systems available, which vary in probe design (monopolar or bipolar), temperature control, and use of conductive gels, which theoretically cause tissue ablation with less heat.

To perform the technique, the probe is inserted into the head of the inferior turbinate and passed through its length, being careful to keep the probe in a submucous plane. Similar to electrocautery, the ablation occurs as the probe is slowly withdrawn. Several passes may be performed to produce multiple tunnels of thermal injury and to achieve greater tissue volume reduction. Initially, there may be turbinate edema that resolves within 1 week. Other complications include crusting and nasal dryness; postoperative packing is generally not needed. Like submucosal electrocautery, this procedure can be performed in the office with local anesthesia.

Clinical studies have shown excellent short-term results. Nease and Krempl[23] conducted a prospective, randomized, single-blinded, placebo-controlled study of 32 patients to evaluate the short-term efficacy of RFA with the use of visual analog scales (VAS). The placebo group underwent a sham procedure, in which a radiofrequency probe was inserted into the turbinate, but no current was delivered. They found a significant improvement in frequency of nasal obstruction, severity of obstruction, and ability to breathe at 2 months and 6 months after RFA treatment compared with placebo.

Garzaro et al.[24] reported on 40 consecutive patients who received RFA and were followed at 2 months and 2 years with nasal endoscopy, anterior rhinomanometry, Nasal Obstruction Symptom Evaluation (NOSE) scale, and olfactory testing. Thirty-five patients completed follow-up, and improvements in total basal nasal resistance, olfactory function, and NOSE score were noted, and were sustained 2 years after treatment. Cavaliere et al.[25] compared monopolar and bipolar RFA in a randomized, prospective study in 150 patients. They reported that both instruments provided similar reduction in nasal symptoms, decreased nasal resistance, and maintenance of nasal function at 20 months.

Long-term outcomes with RFA have been more variable, with several studies reporting a return of nasal obstruction symptoms. Lin et al.[26] reported on long-term outcome and efficacy of RFA in patients with allergic rhinitis in a retrospective review of 146 consecutive patients. One-hundred nineteen of these patients were followed for 5 years postoperatively. Almost 15% of patients were unresponsive to RFA and went on to have other inferior turbinate surgery. The remaining 101 patients were evaluated with a VAS and a patient satisfaction questionnaire. The patient satisfaction questionnaire included an item on whether the patient would undergo the same procedure again. The mean VAS for nasal obstruction improved greatly from baseline (6.65) to 6 months (2.74). However, at 5 years, the mean VAS for nasal obstruction had increased to 4.45, trending toward the preoperative value. In terms of patient satisfaction, 37.6% of patients would not undergo the same procedure again.

Some variables that may improve long-term results include multiple treatment sessions, multiple passes in the turbinate, and the power of the radiofrequency energy. Atef et al.[27] conducted a prospective nonrandomized study of 102 patients who received up to five treatments of RFA with 1-year follow-up. Outcome measures included symptom evaluation with VAS and acoustic rhinometry. They found that 88% of the study population achieved relief of nasal obstruction, and that at least three sessions were required to maintain results at 1-year follow-up.

Microdebrider-Assisted Submucosal Turbinate Reduction

Microdebrider-assisted endoscopic sinus surgery has naturally led to MATR, with the development of specialized microdebrider turbinate blades that allow for submucosal resection of tissue. In contrast to tissue reduction through thermal injury, MATR mechanically removes the tissue.

The head of the turbinate is injected with local anesthetic with epinephrine for hydrodissection and vasoconstriction of the tissues. A stab incision is made in the head of the turbinate with a scalpel or the leading edge of the turbinate blade. The turbinate blade is then inserted into the head of the inferior turbinate just medial to the bone and a submucosal tunnel is created. The blade is then passed repeatedly from anterior to posterior and is rotated 360° for debridement and suction of soft tissue, being careful to stay within the submucosal plane. The anterior portion of the turbinate is especially important to address, because this is the most significant area of nasal airflow obstruction. The posterior portion of the turbinate can also be addressed with extension of the submucosal tunnel; however, care must be taken to avoid injury to branches of the sphenopalatine artery. The microdebrider can sometimes provide a limited resection of the bone as well as soft tissue. The original stab incision may be cauterized, and nasal packing may or may not be used. Complications include bleeding and mucosal injury.

Yanez and Mora[28] performed a prospective cohort study to evaluate the long-term efficacy of MATR. Three-hundred fifty nonallergic patients with chronic hypertrophy of the inferior turbinates who underwent MATR and 323 normal patients with no nasal obstruction symptoms were followed for 10 years, with periodic assessments including VAS, endoscopy, mucociliary clearance, and acoustic rhinometry. About 91.3% of the surgical patients reported no nasal obstruction at the 10-year follow-up. The surgical group also had improved nasal resistance, normal mucociliary clearance, and improved nasal endoscopy at 10-year follow-up.

LATERALIZATION

Lateralization or "outfracturing" of the inferior turbinate alters the turbinate's angle of attachment to the maxillary and palatine bones. This lateral displacement of the turbinate allows for better airflow through the nasal cavity. While this procedure is rarely sufficient as a stand-alone procedure, it is often combined with other turbinate reduction procedures to enhance the nasal airway.

In order to laterally displace the turbinate, a flat, blunt instrument, such as a Boies/Goldman elevator, is used to apply force in an inferolateral vector along the bony attachment to the lateral nasal wall. This technique typically results in adequate lateralization; however, the turbinate bone will occasionally only "greenstick" fracture, and will not stay lateralized. Initial fracturing of the turbinate medially (often referred to as "infracturing") followed by a lateral fracture ("outfracturing") can be helpful in obtaining a complete fracture and sustained lateralization. A Freer elevator is placed lateral to the inferior turbinate in the inferior meatus and force is applied in a superomedial vector until a "crack" is heard or felt. Then the turbinate can easily be displaced laterally as described above. Fracturing the turbinate in multiple locations additionally helps promote a lateralized position. Packing the nasal cavity is not necessary; however, it does promote maintenance of this lateral position during the healing process. There are few studies examining the benefits of isolated lateralization, although Aksoy et al.[29] showed that patients who underwent the turbinate lateralization maintained the lateralized position for at least in the first 6 months postoperatively.

COMPARATIVE OUTCOMES

Passali et al.[30] conducted a prospective randomized trial of 382 patients comparing six surgical techniques (total turbinectomy, laser cautery, electrocautery, cryotherapy, submucosal resection, and submucosal resection with lateralization) with a 6-year follow-up period and multiple outcome measures. Of the six techniques, only submucosal resection resulted in long-term nasal patency, mucociliary clearance, and IgA production after 6 years, with the addition of lateralization of the turbinates improving the results. Patients who underwent total turbinectomy also experienced an improvement in long-term nasal patency; however, mucociliary transport time and secretory IgA concentration remained below normal. Laser cautery, electrocautery, and cryotherapy provided only short-term improvements in nasal resistance and volume. In terms of complications, patients receiving total turbinectomy, laser cautery, electrocautery, and cryotherapy had more chronic crusting. Synechiae was most common in the electrocautery group, while bleeding was more common in the submucosal resection and total turbinectomy groups.

Meredith[31] reported a case series of 162 patients comparing outcomes of mucosal electrocautery with lateralization, versus partial turbinectomy. From July 1979 to August 1981, there were 81 patients with nasal obstruction

due to inferior turbinate hypertrophy who underwent electrocautery and lateralization. Of these patients, 69% had improvement in their nasal obstruction at 33 months after surgery. However, 31% of patients complained of recurrent obstruction due to a return of their inferior turbinate hypertrophy. Therefore, the author elected to change his surgical technique. From August 1981 to December 1982, there were 81 patients who underwent resection of the inferior aspect of the turbinate. Of these patients, 86% showed improvement in nasal obstruction at 33 months after surgery. Meredith concluded that patients who underwent partial turbinectomy had significantly better long-term improvement in nasal obstruction when compared to mucosal electrocautery and lateralization.

There have been prospective studies that have shown comparable results between RFA and other methods, with short-term follow-up. Sapci et al.[32] compared RFA, CO_2 laser ablation, and partial turbinectomy in a prospective randomized clinical trial. Forty-five patients were randomized into one of three groups: group A received laser ablation on one side and partial turbinectomy on the other side, group B underwent RFA on one side and partial turbinectomy on the other side, and group C were the control subjects and did not receive surgery. Outcome measures included subjective change in symptoms measured with VAS, nasal resistance measured by rhinomanometry, and mucociliary clearance measured by nasal mucociliary transport time. At 12 weeks, all patients in groups A and B experienced significant symptom improvement and decrease in nasal resistance. RFA and partial turbinectomy resulted in preservation of mucociliary function with near normal mucociliary transport times, while laser ablation disrupted mucociliary function with mean mucociliary transport time more than double the control. There was no difference in subjective (symptoms) or objective nasal obstruction (as measured by rhinomanometry) between sides.

Cavaliere et al.[33] conducted a prospective trial of 75 patients randomized into three groups—group A turbinoplasty, group B RFA, and group C control. Nasal endoscopy, VAS, rhinometry and saccharin tests were used to assess outcomes with a follow-up of 3 months. Significant symptom improvement was seen in both treatment groups, compared to control at 3 months. Both Sapci and Cavaliere studies were limited by very short follow-up periods.

Several prospective randomized trials have compared MATR with RFA turbinate reduction. Kizilkaya et al.[34] compared RFA and MATR in 30 symptomatic patients with inferior turbinate hypertrophy. VAS, saccharin test, ciliary beat frequency, and acoustic rhinometry were done preoperatively and postoperatively at 3 months and 6 months. Significant and equivalent improvements in VAS and acoustic rhinometry were found in both groups, whereas saccharin test and ciliary beat frequency were essentially unchanged in both groups at 6 months.

While this follow-up period was just 6 months, Liu et al.[35] conducted a prospective, randomized trial of 120 patients, comparing the long-term results of MATR and RFA. Outcome measures included VAS, anterior rhinomanometry, and mucociliary clearance with saccharin transit time, with follow-up at 6 months, 1, 2, and 3 years after surgery. They found an improvement in all three outcome measures at all time periods for the MATR group. The RFA group, however, had improvement from 6 months to 1 year, but no further improvement and a gradual return to preoperative baseline values at 2–3 years postoperatively.

CONCLUSION

Many surgical treatment options exist for the management of inferior turbinate hypertrophy. In general, surgeon experience and preference dictate the choice of one over another. Some authors have advocated for a treatment algorithm that initially favors office based minimally invasive techniques. If this fails, partial turbinectomy or submucosal resection would be performed next, followed by more extensive turbinectomy if all other treatments are ineffective.[36] Another consideration is that laser, electrocautery, and RFA may be performed in an office setting, with significant cost reduction. Harrill et al.[37] compared office-based radiofrequency inferior turbinate reduction and hospital-based radiofrequency reduction with septoplasty in patients with both septal deviation and turbinate hypertrophy using the NOSE patient-based outcome scale. Results demonstrated significant and equivalent improvement in NOSE scores in both groups at 6-month follow-up. The author estimated that hospital-based septoplasty and radiofrequency turbinate ablation cost over 25 times that of office-based radiofrequency turbinate ablation. Even with several studies showing that these office-based procedures may have only short-term efficacy and potential necessity of retreatment, the cost-effectiveness of these procedures may still support them as first-line treatment. There is an additional level of consideration – beyond this chapter – on the

cost-effectiveness of office-based versus operating room-based procedures. Obviously, much depends on the need for additional procedures, such as septoplasty or sinus surgery, but these factors should be considered as surgeons decide on the best treatments for their patients.

While there are limited direct comparisons, it does appear that partial resection is effective and well tolerated in many patients, but might have a higher complication rate. Among reduction procedures, the microdebrider-assisted submucosal reduction technique is quite effective, with some evidence of improved long-term outcomes when compared to cautery and radiofrequency reduction.

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CHAPTER

43

Functional Rhinoplasty

Rebecca E Fraioli, Satyen Undavia

INTRODUCTION

Nasal airway obstruction is a common symptom prompting otolaryngologic evaluation. There are a myriad potential sources of nasal obstruction, and it is important to rule out neoplastic, allergic, or medical causes before considering surgical intervention. Anatomic causes of nasal airway obstruction that may be improved with surgery include nasal septal deviation, inferior turbinate hypertrophy, and nasal valve compromise.

In cases where nasal septal deviation is found to be the cause of airway obstruction, nasal septoplasty has been shown to improve nasal airway patency and quality of life.[1,2] However, there remains a subset of patients whose airway obstruction is more complex and cannot be effectively treated by traditional septoplasty and inferior turbinate reduction alone. Functional rhinoplasty may be necessary to address the nasal obstruction in these patients.

ANATOMY

The upper one third of the nose is bony, whereas the lower two thirds are cartilaginous. The upper lateral cartilages (ULCs) sit just caudal to the nasal bones, and help maintain the patency of the nasal airway through their tight attachments cephalically to the nasal bones, medially to the nasal septum, and laterally to the maxillary bone. However, the caudal margin of the ULCs is not attached to any rigid support, and may move somewhat with inspiration.[3,4]

Caudal to the ULCs sit the paired lower lateral cartilages (LLCs). The LLCs are not tightly attached to the ULCs the way the ULCs are tightly attached to the nasal bones, and they do not reach laterally to the piriform aperture. Instead, a variable number of small sesamoid cartilages are embedded in thick connective tissue extending laterally toward the piriform aperture.

First described by Mink in 1903, the term "nasal valve" refers to the narrowest portion of the nasal airway.[5] Currently, the nasal valve is understood to have two distinct portions: the internal nasal valve (INV), which in most people is the site of highest airway resistance, and the external nasal valve (ENV), which can contribute to increased airway resistance in certain pathologic situations.

The INV is located at the junction of the caudal edge of the ULC with the dorsal septum (Fig. 43.1). The normal angle of the INV is 10°–15°. Figure 43.2 shows a normal INV on nasal endoscopy. The inferior turbinate sits just inferior to the INV, and the area between the INV and the inferior turbinate is referred to as the INV area. Pathology in this area will narrow the space available for airflow and thereby increase the nasal airway resistance. Pathology may be mucosal (e.g. edema, polyps, or synechiae), or it may be structural (weakness and inward collapse of the ULC narrowing the INV angle).

The ENV begins at the alar rim, and it extends up the nasal sidewall to the level of the INV (Fig. 43.1). Certain pathologic situations may cause static or dynamic narrowing of the ENV that may make this the site of maximal resistance to nasal airflow.

As discussed above, the ULCs have strong attachments both to the nasal bones cephalically and to the maxillary bone laterally. Because of these strong attachments, in the nonpathologic nose, the ULCs are able to resist moderate deforming forces such as the negative pressure of inspiration. By contrast, the lack of similar bony attachments

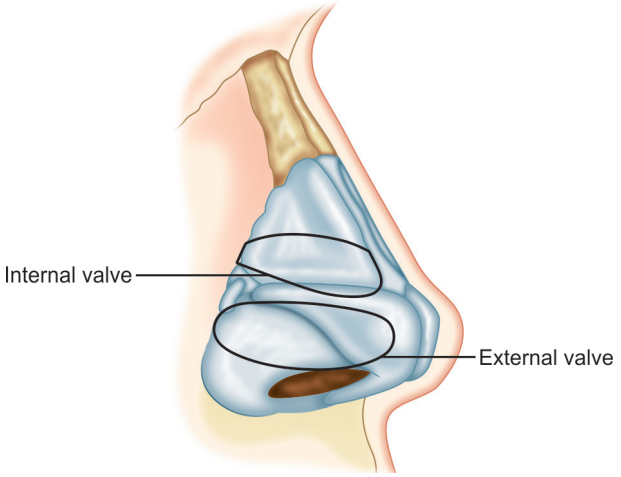


Fig. 43.1: Boundaries of the internal nasal valve and external nasal valve.

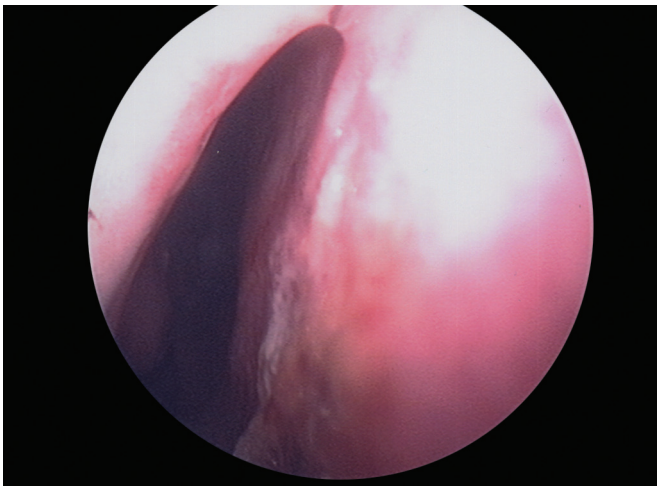


Fig. 43.2: Normal internal nasal valve (INV) as viewed on nasal endoscopy. The normal INV angle is 10–15°.

for the LLCs means that the LLCs are much more susceptible to such deforming forces.[4] A strong, rapid inspiration, even in a normal individual, can cause collapse of the ENV. In patients with weakened skeletal support of the nasal sidewall in the ENV area, this collapse occurs at a lower pressure threshold, and may occur even with normal inspiration. An analogous collapse may also occur in the area of the INV when there is weakness of the ULCs, however, usually to a lesser degree.

PHYSIOLOGY

The external nose plays a key role in the regulation of airflow into the respiratory tract. The nasal valve acts as a resistor to airflow through the nose, essentially channeling air from a large diameter tube to a narrow tube. This decrease in cross-sectional airway at the nasal valve has several effects on the velocity and pattern of flow through the nose. The laws of fluid dynamics govern these changes.

Resistance in the nasal airway is frequently described using Poiseuille's law, which states that in an idealized tube with laminar airflow and a constant circular cross-sectional diameter, the resistance (R) of the airway is inversely proportional to the radius (r) to the fourth power: $R = 8l\eta/\pi r^4$. Although the nose is not an idealized tube, the relationship holds that even a very small decrease in cross-sectional radius of the nasal cavity will significantly increase nasal airway resistance.

Bernoulli's principle can also be used to understand the dynamics of airflow through the nasal cavities. Bernoulli's continuity equation states that the rate of mass flow stays constant as it flows through a tube of varying diameter. Therefore, as the cross-sectional area of the nasal passageway decreases, the velocity of airflow increases. This increased airflow velocity (increased kinetic energy) in turn causes the pressure of the air inside the nose to decrease, as total energy in the system must be constant. Therefore, the more narrow the airway, the faster the velocity of the inspired air, and the more negative the pressure inside the airway compared to the atmospheric pressure outside of the nose. This negative pressure inside the nose then places significant stress on the nasal sidewall. At some point, the deforming force of the negative pressure will be sufficient to overcome the strength of the nasal sidewall support, resulting in collapse of the lateral nasal wall and nasal airway obstruction. This effect, based on Bernoulli's principle and the continuity principle, is called the Venturi effect.

PATHOLOGY

There are many different causes of nasal valve obstruction. It is important to properly diagnose both the site and the cause of the obstruction, because the treatment options vary depending on the etiology. Terminology is also important. Nasal valve compromise and nasal valve collapse are not synonymous. Nasal valve compromise may refer to any cause of narrowing of the nasal valve, including a high septal deviation narrowing the valve, circumferential scarring with stenosis, and inward collapse of the ULC due to weakness of the nasal sidewall. Nasal valve collapse refers only to the last of these. A brief discussion of the common causes of nasal valve compromise follows.

Causes of INV Compromise

INV compromise results from any process that narrows the angle between the dorsal septum and the ULC. Both medialization (inward collapse) of the ULC toward the septum and lateralization (deviation) of the dorsal portion of the septum toward the ULC will narrow this angle and result in INV compromise.

Nasal Sidewall Collapse

Inward collapse of the ULCs is often a result of weakness caused by prior surgery or trauma. Trauma may weaken the attachments of the ULCs to the nasal bones or maxilla. Rhinoplasty with dorsal hump reduction may likewise weaken or sever these attachments and cause nasal valve collapse. In fact, it was the long-term follow-up of rhinoplasty patients who developed INV collapse that prompted Sheen to describe the spreader graft, the initial technique developed for treating INV collapse.[3] Sheen described three patient characteristics that predispose to INV collapse following aesthetic rhinoplasty. These are short nasal bones, thin skin, and weak cartilages. Sheen recommended that spreader grafts be placed in all primary rhinoplasties where resection of the cartilaginous roof was necessary. It is particularly important to place primary spreader grafts in the patients that Sheen identified as high risk for developing postoperative nasal valve collapse. Figure 43.3A demonstrates INV compromise due to inward collapse of the ULC.

High Septal Deviation

Dorsal nasal septal deviation may also narrow the INV angle and cause a fixed INV compromise. Because the dorsal septum comprises part of the supportive "L-strut" of the nose, deviations in this area cannot be addressed via a traditional septoplasty approach. Functional rhinoplasty is often necessary in these cases in order to straighten the dorsal septum and open the INV angle. Moreover, in cases of post-traumatic deviated noses, the deviated dorsal septum is often held in place by its attachment to the deviated nasal bones and perpendicular plate of the ethmoid bone; in these cases the nasal bones must be straightened in order to maintain the dorsal septum in the midline. Figure 43.3B shows a dorsal septal deviation narrowing the right INV. Figure 43.3C shows compromise of the left INV in a different patient due to a combination of a high septal deviation and inward collapse of the ULCs.

Saddle Nose Deformity

Collapse of the cartilaginous nasal dorsum, as is seen in patients with a saddle nose deformity, causes loss of support for the nasal sidewall and results in INV compromise. Intranasal findings in cases of traumatic saddle nose deformity may show inward collapse of both the ULCs and the dorsal septum. A nasal endoscopy image of a patient with a fixed nasal airway obstruction due to post-traumatic collapse of the dorsal septum and ULCs is shown in Figure 43.3D.

Inferior Turbinate Hypertrophy

The inferior turbinate forms the inferior border of the INV area. As a result, turbinate hypertrophy can reduce the space for airflow and cause INV compromise. Figure 43.3E demonstrates obstruction of the right INV by a combination of a dorsal septal deviation and right inferior turbinate hypertrophy.

Synechiae

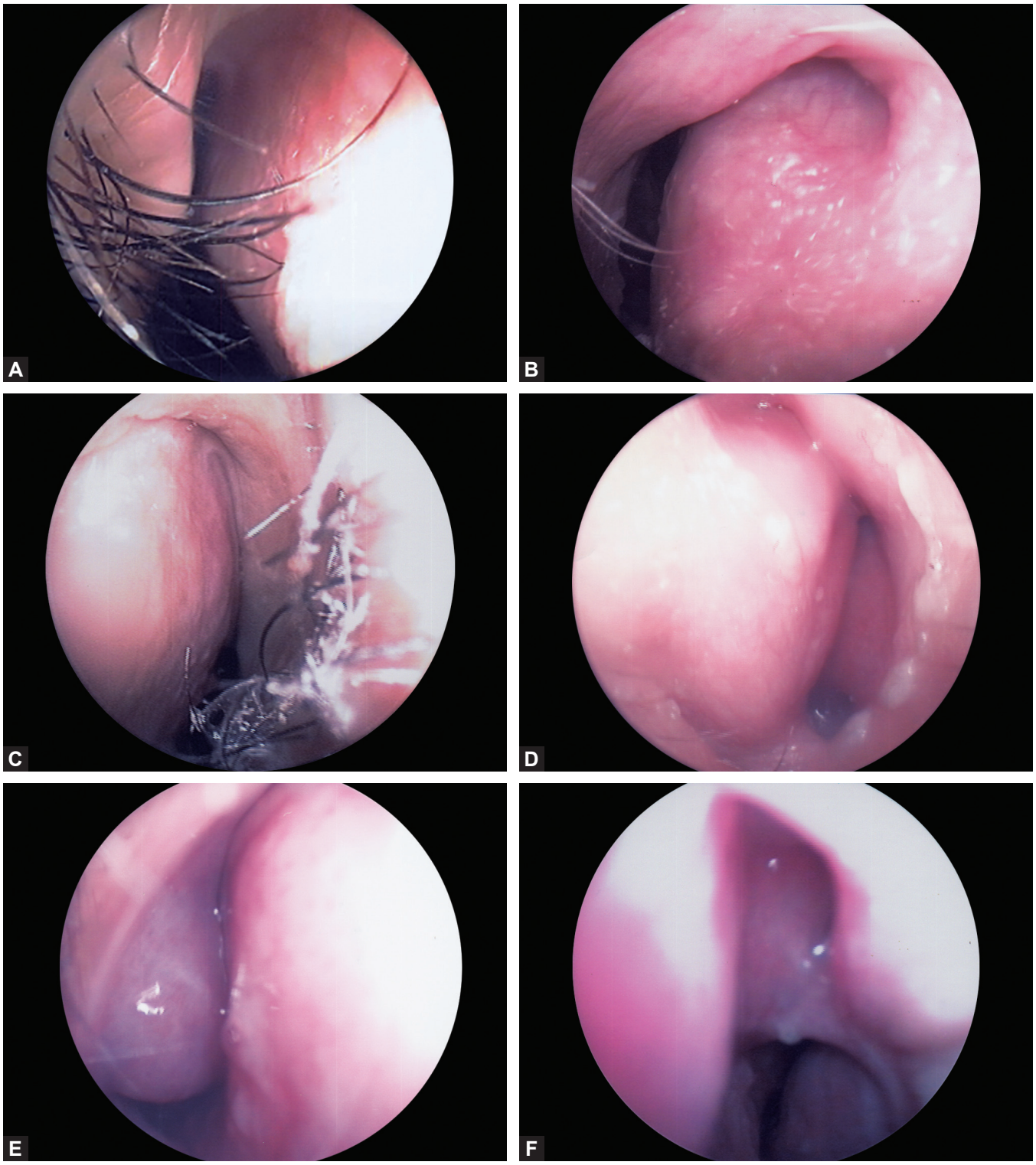
Synechiae or cicatricial narrowing may occur in the nasal valve area and cause nasal valve compromise. An example of synechiae narrowing the INV is shown in Figure 43.3F.

Causes of ENV Compromise

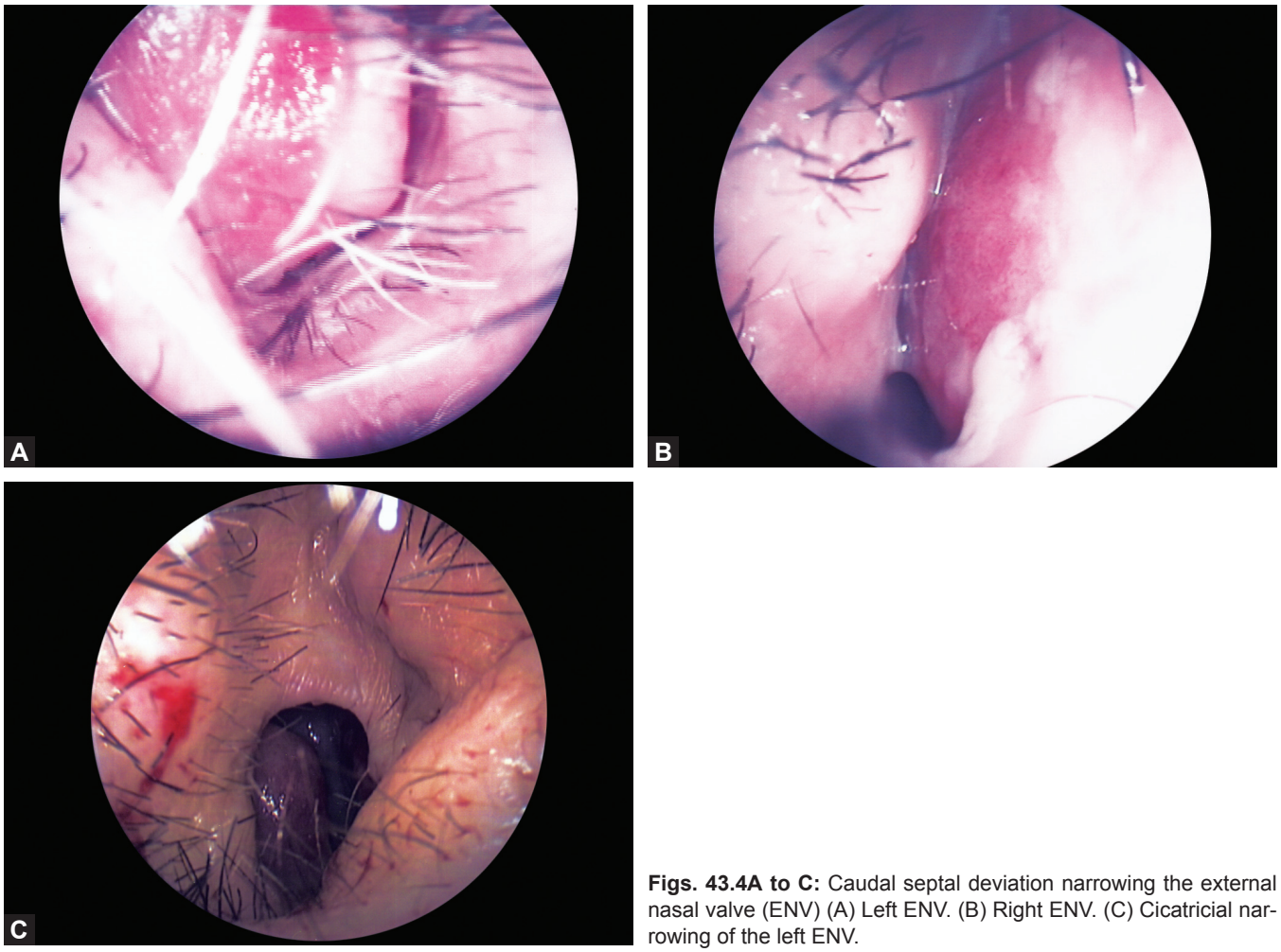
As with the INV, ENV compromise may be caused by inward collapse of the lateral nasal wall, septal deviation, or scarring. Weakness of the lateral nasal wall usually results in a dynamic collapse that occurs with inspiration due to the Venturi effect. Caudal septal deviation and scarring, by contrast, tend to cause a fixed, static obstruction.

Collapse of the Alar Rim

Inward collapse of the lateral nasal wall in the area of the ENV is frequently caused by overzealous cephalic trim of the LLCs during aesthetic rhinoplasty. A minimum lateral crural width of 6 mm should be maintained during cephalic trim; 8–10 mm is preferable to prevent postoperative weakness and buckling. Weakness of the lateral crura causing dynamic inward collapse of the ENV with inspiration may also be seen following trauma, or can be idiopathic. Trauma may also cause fracture, buckling, weakness, or scarring of the LLCs, which can all lead to inward collapse of the lower nasal sidewall and alar rim.



Figs. 43.3A to F: Causes of internal nasal valve pathology. (A) Right upper lateral cartilage (ULC) collapse causing internal nasal valve (INV) narrowing. (B) Dorsal septal deviation narrowing the right INV. (C) Left INV narrowing caused by a combination of a dorsal septal deviation and inward collapse of the left ULC. (D) Obstruction of the left INV due to inward collapse of the dorsal septum and ULC in a patient with a post-traumatic saddle nose deformity. (E) Obstruction of the right INV caused by a combination of dorsal septal deviation and right inferior turbinate hypertrophy. (F) Synechiae narrowing left INV.



Figs. 43.4A to C: Caudal septal deviation narrowing the external nasal valve (ENV) (A) Left ENV. (B) Right ENV. (C) Cicatricial narrowing of the left ENV.

Cephalically Oriented LLCs

In some patients, the lateral crura are oriented in a cephalic direction rather than extending laterally toward the piriform aperture. Cephalically oriented lateral crura can be suspected based on physical examination findings, including a "parenthesis deformity" of the nasal tip. In such cases, the nasal sidewall in the area of the ENV is weak due to the absence of the supportive lateral crura in this area. Surgical reorientation of these cartilages more caudally into their native position will increase the support of the sidewall and improve both the nasal airway and the appearance of the nasal tip.[6]

Over Projected Nose with Narrow, Slit-like Nostrils

An over projected nose often results in long, slit-like nostrils with easily collapsible sidewalls, likely due to the fact that the nasal sidewall is longer than the lateral crus. This results in an unsupported nasal sidewall, similar to the situation in cases of cephalically oriented lateral crura.

Caudal Septal Deviation

Deviations of the caudal septum are analogous to those of the dorsal septum in that they similarly affect the septal L-strut and also often require a rhinoplasty approach. However, caudal septal deviations often narrow the external, rather than the INVs. Figures 43.4A and B show nasal endoscopy views of caudal septal deviation narrowing the ENV.

Circumferential Scar

Trauma or prior surgery may result in cicatricial narrowing of the ENV, causing a static ENV obstruction. A patient

with a history of a nasal injury in infancy followed by a failed prior functional rhinoplasty with subsequent cicatricial narrowing of the right ENV is shown in Figure 43.4C.

PATIENT EVALUATION

Medical History

The evaluation of a patient with nasal obstruction begins with a thorough medical history. It is important to fully explore the patient's symptoms including the onset and duration of symptoms, the severity of the obstruction, and any aggravating or alleviating factors. Airway obstruction that is seasonal or that is associated with sneezing, itching, or watery eyes may be caused by allergic rhinitis. However, edematous mucosa and turbinate hypertrophy may coexist with a structural deformity of the nose, and both problems must be identified and treated for maximum improvement in the nasal airway.

Patients should be questioned regarding the adequacy of their olfaction. Decreased olfaction is a common symptom in patients presenting with nasal obstruction. Complete loss of olfaction is often a sign of an inflammatory condition such as chronic rhinosinusitis or nasal polyposis, but these problems may also coexist with structural problems of the nose. Likewise, facial pain or pressure and chronic rhinorrhea, especially if the nasal discharge is thick or discolored, may indicate chronic rhinosinusitis. Such patients should be treated with culture-based antibiotics and undergo workup including CT scan prior to making a final determination as to the surgical plan.

It is also important to ask the patient to describe his or her subjective sensation of nasal obstruction. Specifically, the examiner should inquire as to whether one side of the nose is more obstructed than the other, and whether any activities aggravate or alleviate the obstruction. Patients with dynamic nasal valve collapse often report worsening of their obstruction with exercise. Other patients may have discovered that they can breathe better when they digitally manipulate their cheeks (Cottle maneuver) or nasal tip. Still others will have tried Breathe Right strips, or silicon nasal stents and report that these help ease their obstruction.

It is also important to ask the patient what treatments they have tried, including allergy medications and over-the-counter nasal sprays. Prior use of antihistamine or nasal steroid sprays without improvement makes the diagnosis of allergy less likely as the cause of nasal obstruction. Chronic use of over-the-counter nasal decongestant sprays (oxymetazoline, phenylephrine) is responsible for the rebound nasal congestion known as "rhinitis medicamentosa." This condition may be contributing to the patient's nasal obstruction; however, it is the authors' experience that patients who become chronic nasal decongestant users often do so in response to a structural nasal deformity underlying their chronic nasal obstruction and predating their decongestant use.

In addition, inquiry must be made as to any history of prior nasal trauma or nasal surgery. A history of prior functional nasal surgery should prompt the examiner to look for scarring, truncated turbinates and nasal septal perforation, which may contribute to nasal dryness and a sensation of decreased nasal airflow.

If a patient presents with a history of prior aesthetic rhinoplasty, it is important to determine whether the airway obstruction preceded the cosmetic surgery or developed postoperatively. Jessen and colleagues demonstrated an increase in postoperative nasal airway resistance in patients undergoing rhinoplasty without functional septoplasty.[7] Dorsal reduction in cosmetic rhinoplasty may weaken the ULCs that support the middle third of the nose, and if this is not recognized and the ULCs resupported at the time of the initial surgery, airway compromise in the area of the INV may result.[3] Finally, overzealous cephalic trim or dome division of the LLCs may cause ENV collapse.

It is also important to ask patients whether one side of their nose is more obstructed than the other. Patients frequently note obstruction on the side contralateral to the visualized septal deviation.[8] Although the reasons for this may be complex, this may be an indication that nasal valve compromise rather than septal deviation is the source of the airway obstruction.

Physical Examination

The physical examination should begin with an evaluation of the patient at rest. This initial observation may be done best while taking the history from the patient, before the patient knows that he is being observed. Note should be made of mouth breathing or of collapse of the nasal alae on routine inspiration. Nasal deviation and asymmetries of the nasal bones or cartilaginous dorsum may often be visible from across the room, before approaching the patient for the formal examination.

A crooked nasal dorsum may indicate the presence of a deviated dorsal septum. A narrow middle third of the nose

suggests that there may be a narrow INV. An "inverted V" deformity, where the demarcation between the nasal bones and the ULCs is visible as an inverted, V-shaped depression, is a sign of ULC collapse and INV compromise. Similarly, deep alar grooves or a pinched nasal tip may indicate weakness of the LLCs and should prompt the examiner to look for evidence of ENV compromise. A ptotic nasal tip may indicate weakness of the nasal cartilages with poor tip support, or conversely may be a result of an overly long caudal septum.

The nose should then be formally inspected and palpated for any less obvious deviations, saddle deformities, scars, and asymmetries. The nasal base should be inspected for alar collapse or asymmetry. Caudal deflections of the septum may also be appreciated on the basal view. Palpation should be performed to assess the structural rigidity of the cartilages of the nose. Gentle downward pressure on the nasal tip toward the upper lip allows assessment of the degree of cartilaginous support for the tip. Release of the downward pressure allows assessment of the tip recoil, which helps determine how much inherent strength lies within the cartilages. The alar cartilages should be inspected with bimanual palpation to assess for thickness and resilience. Palpation of the caudal septum is also critically important, as very anterior deviations of the septum are easy to underappreciate with both anterior rhinoscopy and nasal endoscopy.

The nasal cavities should be carefully examined with anterior rhinoscopy using a nasal speculum and a light source. The INVs should be visualized to assess their shape and approximate angle. Care should be taken not to iatrogenically open the valve with the speculum. A zero degree telescope can be helpful in assessing the INV and the posterior septum. The posterior septum should be inspected for any bony spurs and high deviations. The nasopharynx should also be visualized to rule out adenoid hypertrophy or a mass obstructing the posterior nasal airway. Visualization of the nasal cavities should be performed both before and after topical decongestion of the nose so as to assess the relative contribution of mucosal edema versus fixed obstruction to the patient's sensation of nasal obstruction.

The entire septum should be evaluated for the presence of a septal perforation. A septal perforation may be contributing to the patient's feeling of nasal obstruction. It is also an indicator that septal cartilage may not be available for use as graft material. Preoperative identification of the septal perforation also allows a preoperative discussion with the patient regarding their increased risk for a symptomatic septal perforation, and allows a plan to be made for intraoperative closure of the existing septal perforation. Additionally, in a patient without a prior history of septoplasty or nasal trauma, identification of a septal perforation should prompt an evaluation for the cause of the perforation.

In addition to the static nasal examination, it is also important to functionally assess the nose. The Cottle maneuver is a method by which the nasal valve angle is manually opened in order to assess whether this improves nasal airflow. The Cottle maneuver is positive when it improves the subjective sense of nasal airflow on the side being examined. In the traditional Cottle maneuver, the skin over the maxilla is pulled superiorly and laterally to open the nasal valve. In practice, the modified Cottle maneuver is more useful for identifying the site of the valve compromise. In this technique, a cerumen curette is placed in the area of suspected cartilage weakness or valve narrowing and is lifted superiorly and laterally. The modified Cottle maneuver mimics the expected result from the placement of surgical support grafts, and can direct the surgical plan. However, it is important not to overcorrect when performing the modified Cottle maneuver, and not to overpromise: patients should be counseled that their postsurgical result may not be as open as when the curette manually opens the nasal valve.

Another technique that can help identify nasal valve pathology is the use of Breathe Right strips. Although these may be used in the office to help identify the site of obstruction, it is generally more useful to ask patients to use them at home during their normal activities and during sleep. If a patient reports improvement in their nasal breathing when using the Breathe Right strips, it is another indicator that the patient's pathology may lie in the area of the nasal valve.

Patients with tip ptosis causing ENV narrowing may demonstrate, via digital manipulation of their nose, that their breathing is improved when they push upward on their nasal tip. In patients with a ptotic nasal tip who do not volunteer this information, the examiner may manually support the tip upwards and ask the patient if this subjectively improves the breathing.

Standardized color photography is essential in the preoperative planning for functional rhinoplasty. Although done for functional and not aesthetic purposes, rhinoplasty may still change the shape of the nose from its preoperative appearance. Standard views for rhinoplasty photography

include a minimum of six views: frontal, basal, right and left lateral, and right and left oblique. A solid background of a single color is necessary. A blue background is ideal for the photographs because it complements rather than detracts from skin tone and allows for a greater depth of field than a dark background.

Patient Counseling

Patients should be counseled, as with aesthetic rhinoplasty, regarding preoperative nasal and facial deviations and asymmetries, as well as to what they can realistically expect their nose to look like after surgery. Patients with a severely deviated nose from trauma should be counseled that their nose should be straighter, but will not be identical to the nose that they had pretrauma. Patients requiring spreader grafts should be counseled that these might cause slight widening of the middle one third of the nose.

Preoperative counseling for patients requiring functional rhinoplasty is as important as for patients undergoing aesthetic rhinoplasty, and in some cases may be more difficult. A patient with a narrow middle third of the nose and INV collapse may nonetheless be happy with the appearance of the nose and may not like the idea that surgery may make the nose wider. A patient with an overly long caudal septum and a resultant ptotic nasal tip may feel that "all the members of my family have this nose" and may respond to the surgeon's suggestion to trim the caudal septum and resupport the nasal tip by replying "I don't want to have an upturned nose." Conversely, other patients may require only limited functional rhinoplasty, such as spreader grafts or alar batten grafts, but may expect a complete aesthetic rhinoplasty to be performed "because you're going to be there anyway." It is important to communicate clearly and effectively with the patient preoperatively to ensure that the surgeon and patient have the same expectations regarding the outcome of surgery.

Objective Measurements

Several attempts have been made to objectively measure nasal function. Traditionally, the two main techniques for objective assessment of nasal patency have been rhinomanometry and acoustic rhinometry. However, both techniques have significant limitations for clinical practice. Most importantly, measured nasal airway resistance does not always correlate with the patient's subjective nasal obstruction. Furthermore, objective nasal airway examinations require specialized equipment and may be cost and time prohibitive. As a result, these techniques are mostly relegated to research studies and are rarely used in clinical practice. Nevertheless, a brief discussion of these techniques is presented below.

Rhinomanometry is a dynamic test that can simultaneously measure nasal airflow and transnasal pressure (the pressure difference between the nostril and the nasopharynx). In active rhinomanometry, which is most commonly used, the patient actively breathes through one nostril while an intranasal probe and an external, tightly fitting facemask measure pressure differences. Nasal resistance at a given transnasal pressure can then be calculated from these two measurements. The results are graphed on a pressure curve that can be interpreted to provide the objective pressure needed to inhale and exhale through the nose.

Acoustic rhinometry, by contrast, is a static test that is done while the patient is not breathing. To perform the test, a probe is fed into the nasal vestibule with an emitter and a microphone. The acoustic impedance changes as a function of the cross sectional area; therefore, this technique can be used to measure the cross-sectional area of the airway at a varying distance from the nostrils. These measurements can then be used to calculate the volume of the airway between two points.

Each study has advantages and disadvantages. Rhinomanometry studies flow, whereas acoustic rhinometry measures topography. Acoustic rhinometry is faster and less invasive to perform, and has the additional advantage that it can identify the site of obstruction within the nasal cavity. However, because it is a static study, it may not accurately reflect the state of the airway during physiologic breathing. Rhinomanometry studies active breathing, but with a nasal sensor and facemask in place, which may alter pressure and flow data as compared to normal respiration. Moreover, both tests require specialized equipment and an experienced test operator.

The nascent field of computational fluid dynamics (CFD) shows promise as an objective method by which to study nasal airflow. CFD uses CT images to reconstruct a three-dimensional model of a specific patient's nasal airway. Complex mathematical models and advanced computer technology then allow simulation of nasal airflow and nasal resistance in this virtual nasal cavity. However, many limitations must still be overcome before the utility of CFD for clinical practice can be evaluated. At this point, even the generation of the computer model of

the nasal airway from the CT scan images requires the input of the surgeon and can be time-consuming. Moreover, CFD technology requires a decision as to whether to use a laminar or turbulent flow model. Because we do not fully understand which factors cause turbulent flow, it is hard to accurately make this decision. CFD may turn out to be very useful in helping us to understand which local factors correlate with the patient's sensation of nasal obstruction. However, as with the other objective studies, at this time CFD is not useful for clinical practice.[9]

Imaging studies may have a role in the workup of a patient with nasal obstruction if findings from the history and physical exam suggest that there may be an infectious, inflammatory, or neoplastic cause of the obstruction. A suspicion of chronic sinusitis or a large concha bullosa may be verified with a CT scan following appropriate medical therapy. However, CT or MRI imaging is not routinely indicated for the evaluation of septal deviation or nasal valve compromise.

Subjective Measurements

The goal when evaluating the objective measures of nasal airway obstruction is to find a measure that will accurately predict which abnormalities will cause nasal obstruction, and which surgical modifications will best relieve this obstruction. However, because of the complexities of dynamic versus fixed obstruction, humidification versus dryness of the nasal mucosa, and laminar versus turbulent airflow, no objective test has so far been able to reliably predict the patient's subjective feeling of obstruction. As a result, subjective measurements of nasal airway obstruction are generally felt at this point to be as useful or more useful than objective studies in determining a patient's response to therapy[10] In particular, validated quality of life surveys such as the Nasal Obstruction Symptom Evaluation (NOSE) Scale[11] have been useful in demonstrating the utility of surgery in improving patient quality of life.[1 12,13]

In summary, nasal valve compromise, including both weakness of the lateral nasal cartilages and dorsal or caudal septal deviations, is best diagnosed based on the history and physical examination. Rigid zero-degree nasal endoscopy may aid in diagnosis and in ruling out other intranasal pathology. Conventional imaging studies are generally not felt to be beneficial in the diagnosis of nasal valve compromise. Objective tests of nasal patency including rhinomanometry and acoustic rhinometry are more commonly used for research purposes than for clinical diagnosis. As agreed upon in the clinical consensus statement by Rhee et al., there is no current gold standard for the diagnosis of nasal valve compromise.[10]

TREATMENT OPTIONS

Nonsurgical Options

In patients with symptoms of nasal allergy or chronic rhinitis, or with signs of mucosal edema on physical examination, a trial of allergy medication including nasal steroid spray should be given prior to considering surgical options. Some of these patients may benefit from evaluation with allergy testing and even immunotherapy. However, a trial of nasal steroids is not indicated for patients whose history and physical examination do not have findings consistent with allergic rhinitis.[10]

Breathe Right strips (GlaxoSmithKline), discussed above for their utility as a diagnostic tool, were designed as a therapeutic device. Likewise, soft silicon intranasal stents that physically hold open the nasal valve are available in a variety of sizes for both daytime and nighttime use. For patients with medical contraindications or who wish to avoid surgery, these options may provide temporary relief of nasal obstruction. However, neither option is well tolerated long term, and given the option, most patients opt for surgery over permanent dependence on these devices.

Surgical Options

Several studies have demonstrated postoperative improvement in both nasal airflow as measured by rhinomanometry and in validated quality of life measures following rhinoplasty with treatment of the external and/or INVs.[8,12,13]

The first step in the surgical management of nasal valve obstruction is to identify the site and cause of the obstruction. Different techniques are indicated based on the identified pathology. In some cases, there are several techniques that may have benefit. Techniques will be discussed below based on their indication.

INV Collapse

The classic treatment for INV collapse, described by Sheen in 1984,[3] is placement of spreader grafts. Spreader grafts are thin, rectangular pieces of cartilage that are placed between the septum and ULC, thereby pushing the ULC out laterally and increasing the INV angle. Figure 43.5 demonstrates the ideal placement of spreader grafts. Dimensions of the spreader graft are generally 2–3 mm

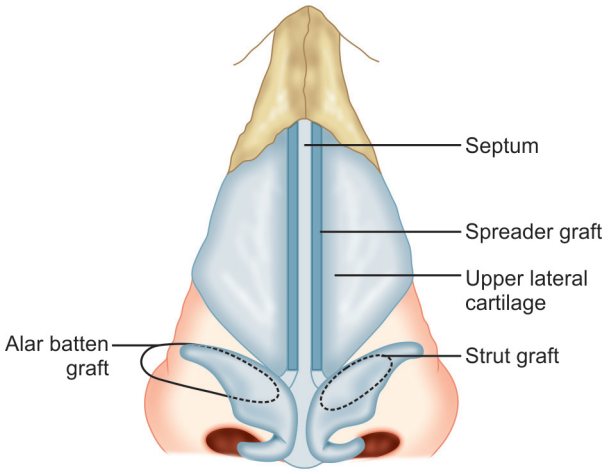


Fig. 43.5: Illustration of the proper placement of spreader grafts, alar batten grafts, and alar strut grafts.

high by 15–25 mm in length; the graft should be long enough to span the length of the ULC. Spreader grafts are ideally carved from septal cartilage, as septal cartilage most often provides a straight and resilient graft. If septum is not available, conchal cartilage grafts can be used for the purpose of opening the valve angle. However, when it is also necessary for the spreader grafts to splint a deviated dorsal septum into place, conchal cartilage may not have the necessary rigidity. In such cases, an autogenous or allogenic costal cartilage graft may be necessary.

Sheen originally described placement of spreader grafts via an endonasal rhinoplasty approach into a tight submucoperichondrial pocket between the septum and ULC. When placed in this manner, spreader grafts generally do not need to be sutured in place. This is still a useful technique for patients who have pathology limited to weakness and inward collapse of the ULCs, as seen as a late complication of aesthetic rhinoplasty.

When performing functional rhinoplasty on a patient without a history of prior rhinoplasty, isolated ULC weakness and collapse is less common, and in many patients, surgical correction of a dorsal septal deviation may also be necessary. In such patients, the submucosal dissection necessary to address the septal deflection often precludes the creation of a tight pocket for the endonasal placement of the spreader graft. In these cases, the ULCs may be sharply divided from the dorsal septum, and the spreader grafts placed in between the dorsal septum and the ULCs. The grafts are then fixated in place and the ULCs reattached to the septum and spreader grafts using horizontal mattress sutures. Care should be taken not to enter the mucosa of the nasal cavity while placing these sutures.

Since the original description of spreader grafts by Sheen, several other options for the surgical management of INV collapse have been described. The choice of which technique to use should be based on the other problems that need to be addressed in the nose, the choice of cartilage graft material available, and the surgeon's comfort with the technique. A brief description of these techniques follows.

The "autospreader" flap[14] is similar to a spreader graft, but uses excess width of the ULC following dorsal hump removal rather than a septal cartilage graft to act as a spacer between the ULCs and the dorsal septum. The medial aspect of the ULC is detached from the septum and turned inward; the free edge is then advanced to approximately the same location that a spreader graft would have, and is then sutured in place in a fashion similar to that used to place spreader grafts via the open approach. This technique has two main advantages: it does not require septal cartilage, and because it is an attached flap rather than a graft, it retains some spring and may help further lateralize the INV.

Clark and Cook have described the use of a conchal cartilage "butterfly graft," carved into an elliptical shape and placed over the cartilaginous dorsum at the caudal border of the ULCs (supratip region). The graft is held in place using suture fixation to the ULC. The graft can be placed via an endonasal or external rhinoplasty approach. Resection of the dorsum in the area of the graft may be required to prevent contour irregularities. Clark and Cook found that 97% of patients undergoing secondary rhinoplasty reported complete resolution of breathing problems after functional rhinoplasty using this technique.[15] A subsequent study by Friedman and Cook reported that 90% of patients undergoing primary rhinoplasty using the butterfly graft reported improved breathing postoperatively.[16] Because this technique relies on conchal rather than septal cartilage, it may be a good choice when no septal cartilage is available for spreader grafts.

Guyuron and colleagues describe a conchal cartilage "splay graft" that is placed in a pocket between the caudal ULCs and the mucosa.[17] Islam and colleagues described a modification of this technique that allows the use of an endonasal approach for graft placement.[18]

Alar batten grafts, traditionally used to strengthen the lateral nasal wall in the area of the ENV, may also help

correct INV collapse if placed in a slightly more cephalic position.[19] Alar batten grafts are discussed in more detail in the discussion of treatment options for ENV collapse.

The use of sutures has also been described to open the nasal valve. Park described the use of a 4-0 nylon flaring suture placed vertically through the caudal aspect of each ULC and tied over the dorsum.[20] The suture is designed to pull the ULCs up and out in order to increase the angle of the nasal valve. A follow-up study evaluating this technique in cadavers using acoustic rhinometry revealed this technique to be most helpful as an adjuvant to the placement of spreader grafts.[21]

Several authors have described variations of suspension sutures that attach to the nasal cartilages at the point of maximal dynamic collapse, and extend out superiorly and laterally to be anchored through a bony opening or bone-anchored screw to the bony facial skeleton.[22] Advantages of this technique are that it does not require a rhinoplasty approach and is relatively quick to perform. In this technique, a suture anchored to the bone at the infraorbital rim is passed subcutaneously to the ULC at the region of maximal collapse. A long curved needle is used to aid in proper placement of the suture. The suture is then threaded back to the anchor and tied down until the collapse is properly corrected. To expose the infraorbital rim, a small cutaneous incision can be made just below the lid, or a transconjunctival approach can be used to avoid external scars. Permanent sutures are used, but loss of suspension has been reported in up to 35% of patients. High infection rates (up to 24%) have also been reported.[23] Nevertheless, in the properly selected patient this can be a very useful procedure. This technique is particularly useful in the rehabilitation of patients with INV compromise due to facial paralysis. It may be performed early on without waiting to fully assess for recovery, and it does not preclude structural rhinoplasty in the future.[22]

External Nasal Valve Collapse

In some patients with anatomical variations of the LLCs, repositioning or other modification of the patient's native cartilage may improve nasal sidewall support and decrease ENV collapse. In patients with an over projected nose and long, slit-like nostrils, deprojection of the nose allows the length of the nasal sidewall to better correspond with the length of the lateral crura of the LCs. This allows better for support of the lateral nasal wall and the ENV. In patients with cephalically oriented lateral crura, repositioning of the lateral crura to a more caudal position will increase the support for the nasal sidewall in the ENV and will often prevent ENV collapse.

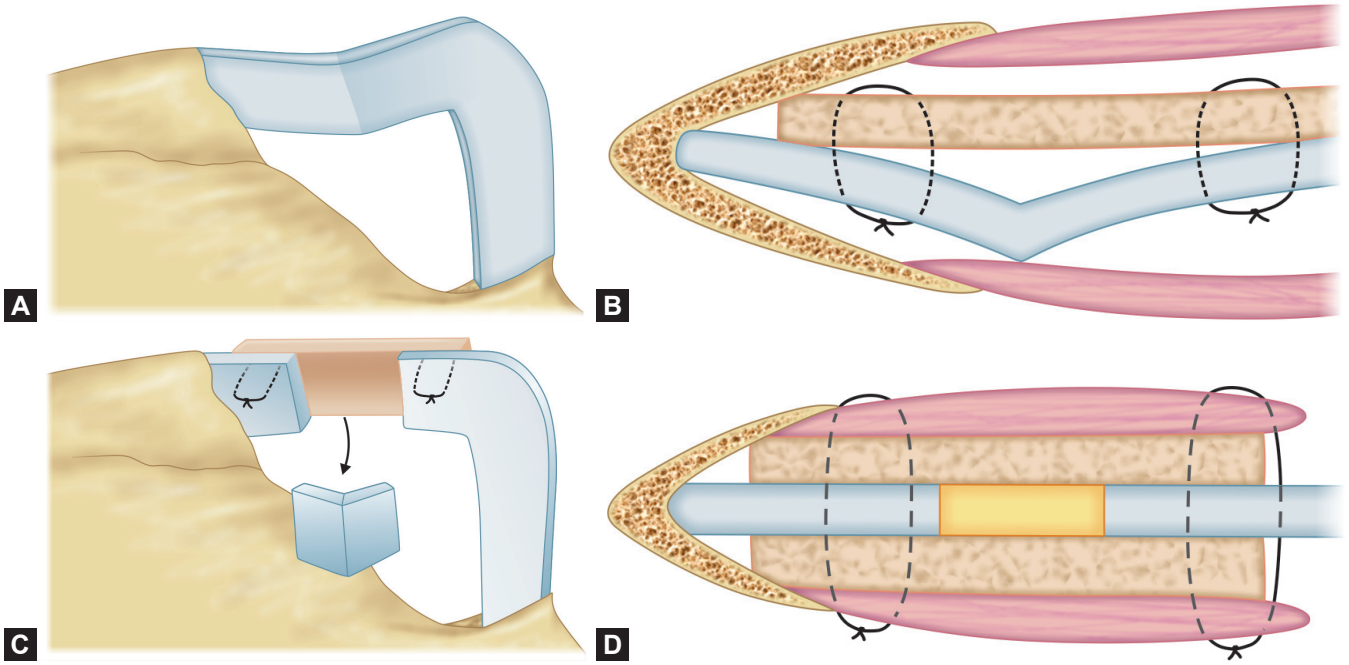
If ENV collapse is not fully improved with the procedures described above, further cartilage grafting to strengthen the nasal sidewall may be necessary. Such grafts are also used in cases of secondary rhinoplasty, when the nasal sidewall is weak due to over-aggressive cephalic trim of the lateral crura. Patients with a history of nasal trauma may have severely scarred, twisted, and weak, LLCs, and cartilage grafting techniques may be necessary in these patients as well. The two main structural grafts to strengthen the LLCs and prevent ENV collapse are alar batten grafts and alar strut grafts.

Alar batten or alar strut grafts are used to strengthen the lateral crura of the LLCs and provide support to the ENV area. Alar batten grafts are rectangular grafts measuring 10–15 mm long and 5–8 mm wide. Septal or conchal cartilage may be used. Batten grafts overlap the lateral surface of the lateral crus and are placed into a precise pocket overlying the piriform aperture. In this way, the cartilaginous support for the nasal sidewall in the area of the ENV is established all the way to the maxillary bone at the area of the vestibular aperture. To aid in proper positioning, it is often helpful to mark the skin externally at the desired location of graft placement. The pocket can be created via either open or closed approaches. It is important not to place the pocket too superficially, as that can lead to contour irregularities or undesirable fullness.[19] The proper placement for these grafts is illustrated in Figure 43.5.

First described by Gunter, the lateral crural strut graft is a thin rectangular cartilage graft measuring 3–4 mm by 15–25 mm.[24] The strut is ideally made of septal cartilage, but conchal or costal cartilage may also be used. The strut graft is then placed in a pocket deep to the lateral crura and sutured to the undersurface of the lateral crura. A subcutaneous pocket is created laterally in a location that will best relieve the obstruction. This can be either at the piriform aperture or the alar base. It is often helpful to taper the medial aspect to create a natural contour of the graft. The lateral end of the graft should be placed caudal to the alar groove to minimize visibility.

Dorsal or Caudal Septal Deviation Narrowing the Internal Nasal Valve

In cases where the dorsal or caudal septum is severely deviated and narrowing the INV or ENV, a rhinoplasty approach is often necessary in order to straighten the septum



Figs. 43.6A to D: Excision and resupport of a severely deviated L-strut.

and open the valve angle. It is critical to recognize these patients on preoperative examination, as traditional septoplasty will often fail in these patients. Although some caudal deflections may be managed through an endonasal approach, the only options for managing dorsal septal deviations endonasally are to resect the deviation or to leave it untouched. Leaving the deviation untouched will often cause the surgery to be unsuccessful, but resecting these areas without reconstructing the L-strut can result in a saddle nose deformity or loss of tip support. Eventually, worsening nasal airway obstruction will result.

Via a rhinoplasty approach, the dorsal septum may be separated from the ULCs to allow better access and evaluation. The cartilages should be freed from scar tissue, as the scar tissue may be tethering the septum and contributing to the deviation. The concave side of the deviation may be gently scored, releasing some of the tension and helping to straighten the septum. Spreader grafts may be placed on either side of the dorsal septum to splint the straightened septum in place. For a deviated caudal septum, the spreader grafts may be left long as extended spreader grafts, which can extend caudally to the anterior septal angle and can help stent the caudal septum in the midline.

A severely deviated segment of the L-strut that cannot be straightened with the techniques described above must be excised and reconstructed. Spreader grafts or a similar cartilaginous strut graft may be sutured to the cartilage on either end of the gap, thereby bypassing the gap and providing support to the septum. This technique is illustrated in Figures 43.6A to D.

Another option for the severely deviated L-strut is extracorporeal septoplasty.[25] In this technique, the entire quadrangular cartilage with the adjacent portions of the perpendicular plate is separated from its attachments and taken to the back table. Once removed, the surgeon may thin, modify, and reconstruct the septum as needed. PDS plate may be helpful in reinforcing the reconstructed septum. The new septal construct is then replanted between the septal leaflets and closed as described for the placement of spreader grafts. Spreader grafts are also helpful in this situation.

Caudal septal deviations may also be addressed by the above techniques. Several other techniques are also available to help straighten a deviated caudal septum. A suture may be placed from the caudal septum into the fascia overlying the nasal spine. If the fascia is absent, an 18-gauge needle may be used to bore a hole through the nasal spine itself; a suture can then be passed through this hole and through the caudal septum to anchor it in the midline.

Another option, known as the swinging door technique, involves flipping the septum from where it sits on one side of the nose over the nasal spine, and suturing it

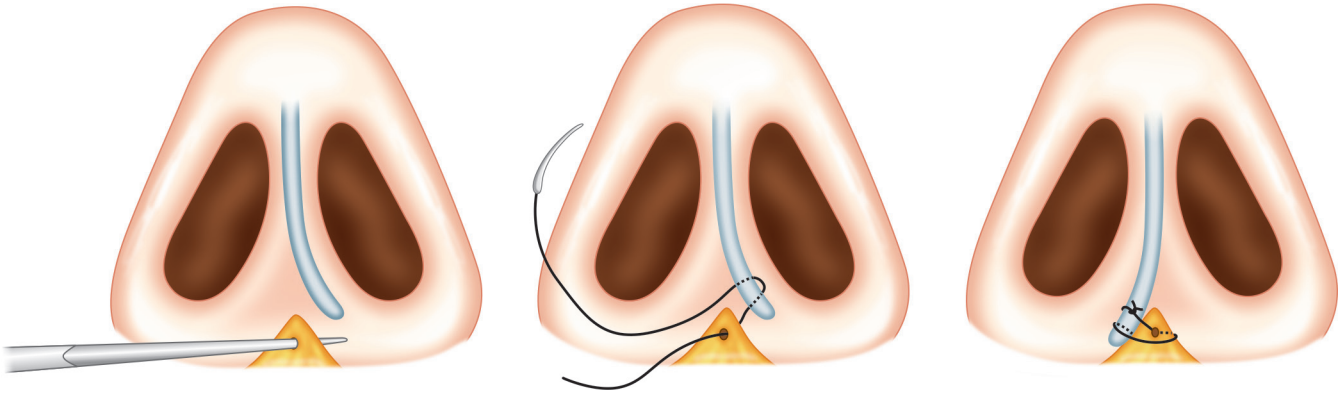


Fig. 43.7: The swinging door technique for straightening a deviated caudal septum.

in place so that it sits on the contralateral side to the initial deviation. This technique is illustrated in Figure 43.7. Another maneuver to straighten the caudal septum is to advance it between the medial crura in a tongue-in-groove fashion, where it serves in place of a columellar strut graft to support the nasal tip. In order for this to be an option, the cartilage must have excess length. If it does not, a caudal septal extension graft may be sutured to the native caudal septum and will serve to extend the length of the septum. The extension graft may then be placed between the medial crura with the same effect as described above. Finally, a thin rectangular or square graft of cartilage or perpendicular plate may be carved from donor cartilage and placed on the convex side of the caudal septum in order to help stabilize the deviated cartilage in the midline. This graft is called a caudal septal strut graft, and it will help straighten a caudal septal deviation with weak or scored cartilage. However, for a strong and severely deviated caudal septal deviation, excision of the deviated segment may still be necessary.

Other Causes of ENV Compromise

For nasal valve compromise caused by scarring and circumferential narrowing of the ENV, Z-plasty may be beneficial in opening the airway in cases of small defects. More severe defects may require release of the scar and placement of a composite graft of skin and cartilage from the ear.

CONCLUSION

Functional rhinoplasty is a general term for a collection of techniques that can be performed via rhinoplasty approaches in order to improve the nasal airway. Nasal valve compromise is the indication for functional rhinoplasty, and there are many causes of nasal valve compromise. The specific techniques used in a particular patient will vary based on the patient's specific pathology. A patient's subjective evaluation of improvement in nasal airway is as good or better an outcome measure than currently existing objective measures.

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SECTION 9

Surgery for Inflammatory Sinusitis

CHAPTER

44

Office-Based Rhinologic Procedures

Oscar Trujillo, Ashutosh Kacker

INTRODUCTION

As a result of several trends in medical practice in the United States, there has been a shift of operative procedures from the operating room (OR) to the physician's office. Contributing to the shift are factors such as improved technology, the advent of minimally invasive procedures, improved cost structure, and increased efficiency in the healthcare industry. These factors will become increasingly important as the healthcare reform initiatives take effect in the near future.

A retrospective study conducted from 2006 to 2011 compared current procedure terminology codes to perform a cost analysis of office-based versus OR procedures in rhinology. The study demonstrated that mean total charges in office-based procedures were significantly lower than OR procedures, and that office-based procedures were reimbursed at similar or higher rates than OR procedures.[1] Accordingly, in appropriate patient populations, performing simple rhinologic procedures in the office, instead of in the OR, has the potential to lower costs without affecting reimbursement rates. This is not to imply that the physician's office can completely supplant the OR given the equipment, anesthesia, and level of invasiveness required by most procedures. Based on these and other factors, successful patient and procedure selection are paramount to a physician's ability to establish a successful office-based surgical practice. Notwithstanding the potential benefits discussed herein, it is important to recognize at the outset that transition to office-based surgery does not alter the appropriate, medically accepted course of action required for proper diagnosis and management of disease.

CLASSIFICATION OF OFFICE PROCEDURES

Facilities in which office-based procedures are performed are classified as Level I, II, or III based on the type of anesthesia used and the complexity of the procedures performed. A Level I facility performs minor procedures under topical, local (including digital block), or no anesthesia. Such categories of anesthesia do not involve drug-induced alteration of consciousness. Preoperative medications are not required or used in such procedures, other than minimal preoperative and perioperative oral or intramuscular antianxiety drugs. In a Level I office setting, the likelihood that complications will arise that are severe enough to require hospitalization is remote.

A Level II facility performs procedures that require administration of minimal or moderate intravenous, intramuscular, or rectal sedation and analgesia. In this setting, anesthesia includes local or peripheral nerve block, minor conduction blockage, and Bier block. This level of sedation or analgesia therefore requires postoperative monitoring. Level II facilities are limited to procedures associated with only a moderate risk of surgical and anesthetic complications. The likelihood of hospitalization as a result of such complications remains relatively remote. A Level III facility performs any procedure that may require the use of deep sedation and analgesia, general anesthesia, or major conduction blockade. The known complications of the proposed surgical procedure may be serious or life threatening.

In order to perform surgical procedures in an office setting, a practitioner is subject to certain requirements.

It is the acceptable and prevailing medical practice that a practitioner only performs those surgical procedures and anesthesia services that are commensurate with the practitioner's level of training and experience. In order to demonstrate competence to perform such procedures, a physician must possess state licensure, procedure-specific education, training, experience, and must have completed a successful evaluation appropriate for the patient population being treated (e.g. pediatrics and geriatrics). For the physician practitioner, certification or eligibility by the American Board of Medical Specialists (ABMS) or an equivalent certification as determined by the board or other entity governing the regulation of nonphysician practitioners is required. Alternatively, a training program in a field of specialization recognized by the Accreditation Council for Graduate Medical Education (ACGME) for expertise and proficiency in the field is completed. The practitioner should also participate in peer and quality review, possess documentation related to any professional misconduct or malpractice, have adequate professional malpractice insurance coverage with regard to the specialty, and participate in continuing education consistent with the requirements of statute and of the practitioner's professional organization.

In addition to these general requirements, the practitioner must be competent with regard to the specific procedure including indications, technique, equipment, and complication management. The scope of competence encompasses education, training, experience and evaluation, including, but not limited to, the following: (i) adherence to the standards of the relevant professional society, (ii) hospital and ambulatory surgical privileges for the scope of services performed in the office-based setting, (iii) credentials approved by a nationally recognized accreditation and credentialing organization, and (iv) a didactic course complimented by hands-on experience subject to professional observation and review. Training should also be complemented by the performance of a specific number of cases supervised by a practitioner already competent in the respective procedure, in accordance with the standards and guidelines of the relevant professional society.

RHINOLOGIC OFFICE-BASED PROCEDURES

Most of the office-based procedures in rhinology are classified as Level I. Level I procedures require proper selection of patient and anesthesia. The practitioner must also select the appropriate procedure under the specific clinical circumstances. It is the acceptable and prevailing medical practice for the practitioner to pursue continuing medical education in such subject areas as proper drug dosage, management of toxicity, and hypersensitivity to local anesthesia and other drugs administered in this setting. The practitioner should obtain Advanced Cardiac Life Support certification, and if performing procedures on neonates, infants, or children, Pediatric Advanced Life Support.

Some mildly sedating drugs are used in Level I procedures. The use of any sedatives or analgesic drugs that may cause cardiorespiratory depression mandates the presence of certain emergency equipment during the procedure, including basic intravenous supplies, basic airway management equipment, advanced airway management equipment, pharmacologic antagonists, and emergency medications. With regard to basic airway management equipment, the facility should have available a source of compressed oxygen, a source of suction (including Yankauer-type suction as well as suction for oral and nasal airway), lubricant, and a positive pressure ventilation device.[2] For practitioners with intubation skills, laryngoscope handles, endotracheal tubes, and a stylet are recommended in the event of an emergency.[2] Medications that should be available in case of emergencies include epinephrine, atropine, antihistamine, corticosteroids, naloxone, flumazenil, amiodarone, nitroglycerin, ephedrine, vasopressin, diazepam, or midazolam.[2] According to prevailing medical practice for Level I office-based procedures, assistance is not required unless it is dictated by the surgical procedure, and accreditation is not necessary.

Patient Selection

Patient selection is the cornerstone of a successful office-based practice. A detailed history and physical examination will aid in the identification of patients who will tolerate well and be suitable candidates for office-based procedures. As only mild sedation is administered, in the form of oral benzodiazepine or mild narcotic, patients with a lowthreshold for pain or very anxious patients are not good candidates. An anxious patient may be extremely ingratiating, have rapid speech, or otherwise demonstrate agitation. Patients with a history of significant cardiovascular disease, bleeding disorders, or difficulty tolerating a nasal endoscopy examination are not ideal candidates. Additionally, directing a patient to suspend the course of medications that may prolong bleeding will help to keep blood loss at a minimum.

Anesthesia Selection

With regard to anesthesia, the preference for rhinologic office-based surgery is a combination of topical and injectable local anesthesia with mild sedation. Options for topical anesthesia include lidocaine, pontocaine, and cetacaine, each in liquid, viscous, and gel form. Topical cocaine is also an alternative, but the cost and misuse potential associated with this anesthetic are considerations that likely discourage its utilization in the office. Use of aerosolized 4% lidocaine with oxymetazoline or phenylephrine is highly effective for topical anesthesia, both clinically and with regard to cost. Regarding injectable local anesthesia, lidocaine with epinephrine in various strengths and bupivacaine are excellent options.

Another important consideration is the interaction of various drugs, such as commonly prescribed antibiotics and depressants, which can inhibit the metabolism of lidocaine, as lidocaine is processed through the cytochrome P450 oxidase system. Patients consuming such medications may be more susceptible to lidocaine toxicity. The practitioner should screen for medications including but not limited to macrolides, antidepressants, antihistamines, benzodiazepines, antiulcer medications, anticonvulsants, cholesterol lowering agents, and antifungal agents.[3] Regardless of the type selected by a practitioner, it is crucial to allow for sufficient time for the topical anesthesia and decongestant to become effective prior to injecting local anesthesia. Commonly used anxiolytics or sedatives include short-acting benzodiazepines, such as midazolam, which are particularly useful for outpatient procedures because it has a short recovery period.

In 2001, a placebo-controlled double-blinded study was performed to investigate the use of oral premedication with local anesthesia while performing procedures on the face and hair-bearing areas of the skull in an office-based setting. The study compared procedures in which midazolam, morphine, and clonidine were used as anxiolytics and sedatives, with local anesthesia provided by 1% lidocaine with epinephrine. The study's conclusions suggested that patients undergoing procedures on the head and neck would benefit from the use of clonidine, as patients to whom this medication was administered had stable or low blood pressure both intraoperatively and postoperatively.[4] Such conditions aid in the maintenance of a blood-free surgical field, as well as in the prevention of postoperative hematomas. While it is arguable that the study of 150 patients may have been too small to yield statistically significant comparisons among groups, the conclusions nonetheless suggest that clonidine was superior to morphine and midazolam in decreasing anxiety, relieving pain, and stabilizing cardiovascular hemodynamics. Accordingly, clonidine in combination with local anesthesia may be preferable to alternative forms of anesthesia when performing procedures on the face in the office. It should be noted that clonidine must be administered to the patient 60–90 minutes prior to the procedure in order to fully realize the benefit suggested by this study.[4]

Procedure Selection

Equally as important as patient population selection and anesthesia selection, the practitioner must select the appropriate procedure in light of the circumstances. The most common office-based rhinologic procedures are integral to the care of the postoperative sinus surgery patient, including removal of packing material, debridement, and resection of synechia. Additional procedures that may be performed in an office-based setting include (i) minor septal surgery; (ii) inferior turbinate procedures including reduction by any modality; (iii) sinonasal and nasopharyngeal biopsies; (iv) primary and revision sinus surgery including clearance of obstructive synechia, stenosis, bony partitions, and limited polypoid tissue; (v) limited revision ethmoid and maxillary sinus surgery using conventional ESS techniques and instrumentation; (vi) maxillary, frontal, and sphenoid sinus balloon procedures; (vii) resection of limited sinonasal lesions; and (viii) control of epistaxis. It is important to note that the only procedures that should be performed in the physician's office are those whose complications can be managed in the physician's office.

The practitioner should create an appropriate setting for performing the procedure, taking into consideration privacy, ease of movement, and the availability of proper assistance, if required. With regard to performance of the aforementioned procedures in an office-based setting, equipment should include the following: a comfortable procedure chair, video endoscopy arranged with a light source, a basic sinus tray, a microdebrider, and options for hemostasis, including chemical, electrocautery, and packing options. The following commonly used instruments in office-based rhinology procedures should be available: (i) frontal and maxillary sinus seekers, (ii) Freer elevators, (iii) both curved and straight suction tips in varying sizes connected to an adequate suction

apparatus, (iv) backbiters, (v) angled and straight-through cutting forceps, (vi) giraffe forceps, (vii) Kerrison rongeurs, and (viii) both straight and angled mushroom punches.[5] It is essential for the practitioner to train office medical assistants, physician assistants, and nurses so that members of the office staff are familiar with the procedures and able to assist in the event of an emergency. There should be a well-coordinated effort between the physician and assisting staff in order to instill confidence in the patient.

KEY POINTS

A practitioner performing office-based surgery must select a patient who is likely to tolerate an office-based procedure well, both medically and mentally. A complete and appropriate assessment includes the performance of all indicated workup, as well as a thorough history, physical examination, and review of all medications. To ensure prompt and proper reimbursement, the practitioner should establish administrative protocols for the purpose of obtaining preapproval from insurance companies prior to performing the procedure.

To improve both skill and confidence in the performance of the particular procedure, the practitioner should perform the procedure in the OR prior to any attempt in an office-based setting. In the office, the practitioner must allow for adequate time in administering topical and local anesthesia, both for the comfort and safety of the patient, and to ensure for the practitioner a calm atmosphere in which to perform the procedure. In certain cases, a mild anxiolytic administered prior to the operation may be required. Once anesthesia has been administered and is effective, the practitioner should perform a nasal endoscopy and palpate the necessary structures prior to opening any disposable products. As a final note, the use of any anesthesia or anxiolytic mandates the availability of proper resuscitation equipment in the event of an emergency.

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CHAPTER

Endoscopic Sinus Surgery for Chronic Rhinosinusitis: Historical Evolution, Indications, and Outcomes

45

Robert T Adelson, David W Kennedy

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and paranasal sinuses of multifactorial, incompletely elucidated etiology and great individual and societal impact. CRS is presently defined by the presence of at least two of the following symptoms for > 12 weeks (hyposmia, nasal obstruction, facial pain/pressure, and anterior/posterior nasal drainage) in addition to endoscopic and/or radiographic evidence of sinonasal inflammation.[1] Symptoms of CRS can be debilitating, with patients reporting quality of life (QOL) scores in some domains akin to those for patients with chronic obstructive pulmonary disease and congestive heart failure.[2] With an incidence of approximately one in seven adults in the United States,[3] CRS has a prevalence three to four times greater than asthma, peptic ulcer disease, and chronic bronchitis.[4] An estimated 4.7 million emergency room visits and 61.2 million lost workdays are estimated to be attributed to CRS.[4] As a result, CRS is responsible for billions of dollars in healthcare-related costs, with parallel loses resulting from decreased productivity and absenteeism from work.[5] The personal and public ramifications of CRS are significant, especially as the incidence of this chronic condition appears to be increasing.[1,6] Despite this, our understanding of the pathogenesis of CRS remains incomplete and therefore our treatment options remain similarly compromised.

While initially considered to be either an infectious process driven by pathogenic bacteria or the result of obstructive anatomic abnormalities of the nose and sinuses, CRS is now widely accepted as a complex interplay of multiple host, environmental and disease related factors with a phenotypic endpoint of persistent sinonasal mucosal inflammation[1] (Table 45.1). As in other multifactorial disease states with incompletely understood etiologies, a variety of treatment strategies are available. The mutually aligned goals of decreasing mucosal inflammation, improving mucociliary clearance, controlling infection, removing inflamed bone, and improving the delivery of medication to the target organ are approached through a variety of medical and surgical interventions. While the management of CRS remains medical, functional endoscopic sinus surgery (FESS) plays a powerful role as an adjunctive procedure when medical therapy has failed to provide the desired control of sinonasal inflammation. In these cases, FESS provides a method for the removal of inflamed tissue and bone, widening the natural outflow tracts of the paranasal sinuses, and facilitating the penetration of topical medical therapy into the sites of disease. Furthermore, the techniques of FESS established the foundation for extended techniques in surgery of the nose, paranasal sinuses and skull base, allowing the endoscopic technique to become the preferred method for addressing epistaxis, CSF (cerebrospinal fluid) leaks, and a wide range of benign and malignant tumors. An understanding of the historical evolution of FESS, its general principles, surgical indications, and treatment outcomes better illuminates the role of FESS in the treatment paradigm of CRS.

HISTORICAL EVOLUTION OF ENDOSCOPIC SINUS SURGERY

Evolution is certainly an appropriate term when applied to the story of surgery of the nose and paranasal sinuses.

Table 45.1: Multifactorial etiology of chronic rhinosinusitis

Host, environmental, and pathogen features contribute in variable degrees to the development and persistence of sinonasal inflammation
Infection
Bacterial
Viral
Fungal
Biofilms
Local abnormalities
Ciliary dyskinesia
Scarring from previous surgery
Odontogenic infection
Foreign bodies
Anatomic abnormalities
Septal deviation
Haller cell
Concha bullosa
Local inflammation
Gastroesophageal reflux disease
Allergic rhinitis
Osteitis
Bacterial superantigens
Biofilms (bacterial/fungal)
Systemic conditions
Asthma
Cystic fibrosis
Systemic lupus erythematosus
Churg–Strauss syndrome
Diabetes
Allergy
Allergic fungal rhinosinusitis
Aspirin sensitive asthma
Food allergy
Atopy
Immune disorders
HIV/AIDS
Selective immunoglobulin deficiency
IgA deficiency
IgG deficiency
Common variable immune deficiency
Immunosuppression
Organ transplantation
Bone marrow transplantation
Chemotherapy
Autoimmune disorders
Wegener's granulomatosis
Sarcoidosis
Deficiencies of innate immunity
Environmental
Cigarette smoke
Pollutants

It has not been a straight-line march of progress to the present moment as its teleological end, but rather multiple lines of progress and departure, fits and starts, and improvements in our knowledge and instrumentation over the past 150 years. With this, we recognize that the present state of the art is far from the final or perfect formulation for rhinologic operations, but rather somewhere along a continuum, with further innovations certain to humble us in the future.

The earliest endeavors of rhinologists were directed toward infectious conditions of the nose and sinuses. During the era prior to the introduction of penicillin, intracranial infections from sinus and otologic disease were responsible for 1 in every 40 mortalities.[7] As such, the earliest rhinologic operations were undertaken to address complicated sinusitis and tended to be more destructive in nature. Heightened attention was paid to conditions of the frontal sinus as complications from these infections posed the greatest risk of mortality to the patient. Simple incision and drainage of purulent conditions of the frontal sinus were reported as early as 1870.[8] More extensive operations to obliterate the frontal sinus by removing the anterior wall were described by Kuhnt in 1895.[9] Further efforts to exenterate the frontal sinus culminated in Reidel's 1898 description of removal of both the anterior wall and floor, though the disfiguring nature of the procedure remained a major barrier to acceptance.[9]

External procedures remained common, yet advancements in surgical technique recognized the importance of procedures that would provide for normal drainage of the frontal sinus through its outflow tract. Caldwell's landmark description of the canine fossa approach to the maxillary sinus codified an open approach to this location that would be familiar to the modern rhinologist.[10] Knapp published his method of addressing this goal through an external ethmoidectomy and surgery of the frontal recess in 1908.[11] Lynch had developed an external approach for frontoethmoidectomy by 1921, which was later modified by subsequent surgeons who employed mucosal flaps to reduce the rate of stenosis of the frontal sinus drainage pathway.[12,13] Lothrop developed the concept of creating a median frontal sinus drainage pathway in 1917, which foreshadowed some of the advances that are commonplace in the modern practice of rhinology. Lothrop's cadaver studies of the frontal sinus drainage pathway allowed this deft surgeon to remove the frontal sinus floor through both a transnasal approach and a small supraorbital trephination, though the technical difficulty placed this operation

beyond the scope of his contemporary surgeons until modern instrumentation and improved methods of visualization revived the concept in the 1990s.[14–16]

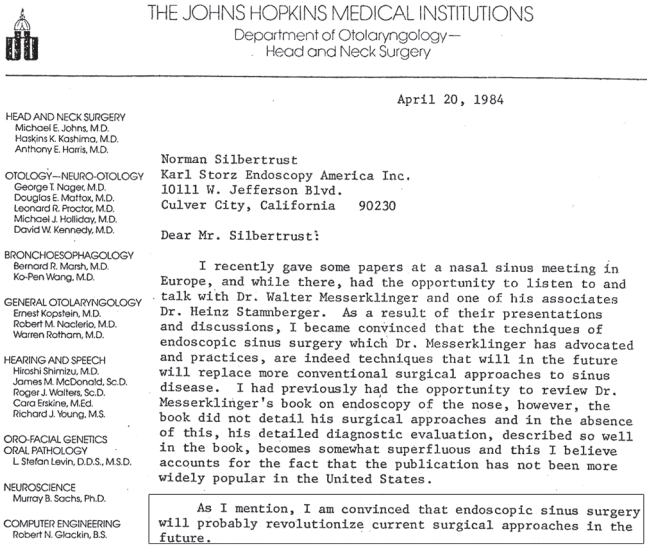
For a period of time between the development of modern endoscopic sinus surgery and the aforementioned destructive operations of the frontal sinus, osteoplastic flap procedures represented the pinnacle of surgical intervention for disease in this location. Obliteration of the frontal sinus through an osteoplastic flap was initially described by Hoffman in 1904, preserving a normal contour of the frontal bone while removing the offending sinus mucosa.[17] By 1956, Goodale and Montgomery published the classical description of frontal sinus osteoplasty, including obliteration with abdominal fat.[18] Despite excellent surgical exposure and meticulous technique by experienced surgeons, this operation was associated with complication rates above 50% and early failure in 10–15% of cases.[19,20] Advances in understanding and instrumentation, as well as issues with postoperative imaging, would soon encourage surgeons to migrate from frontal sinus osteoplasty and obliteration to the novel surgical techniques that enhance normal drainage pathways rather than obliterative procedures that attempt to remove the frontal sinus. While obliteration is distinctly rare in the modern era, the frontal osteoplastic flap retains a role for the management of frontal sinus pathology that remains inaccessible to completely endoscopic approaches.[21]

Endoscopes, or their early analogs, have been introduced into nearly every anatomical space over the past 100 years. Hirschmann likely became the first nasal endoscopist in 1901, when he introduced a modified cystoscope into the nose.[22] Reichert similarly could lay claim to the first endoscopic sinus surgery when he utilized a 7-mm endoscope through an oral-antral fistula to operate on a diseased maxillary sinus.[23] Although Maltz had, by 1925, recognized the diagnostic value of endoscopy in evaluating the nose and sinuses, a process he referred to as "sinuscopy" was limited by the technology of his era.[22]

While endoscopes are the basic working tools of modern rhinology and one of the great sparks for innovation in the field, these instruments were not the first attempt by surgeons to improve the magnification and illumination of the nasal cavity. The operating microscope that revolutionized otology in the 1960s and 1970s had been applied to the ethmoid labyrinth by the 1970s, yet technical difficulties precluded both a consistent binocular view and widespread acceptance. The magnification afforded by an operating microscope was translated in a monocular fashion with the rod optic endoscope system patented by the British Professor Harold Hopkins in 1959 and first put into production by Karl Storz in 1967, providing the keystone instrument that would facilitate a great leap forward in surgery of the nose and paranasal sinuses.[24] Draf is credited with the first published report of endoscopic examination of the nose in 1973.[25] It now became possible to perform detailed examination and surgery of the lateral nasal wall and paranasal sinuses with a portable system that, while lacking the depth perception of a binocular view, did provide important advantages over the operating microscope. The introduction of endoscopes with deflected viewing angles allowed the application of high illumination, and crisp image resolution to overcome line of sight issues and view regions of the nose that had not been previously accessible.

Within the paranasal sinuses, modern endoscopes ushered in a renaissance in the basic science and clinical practice of rhinology. European surgeons were the first to incorporate this novel technology into their nasal operations, and the senior author traveled to spend time with Wigand, Draf, Baum, and Messerklinger at their home institutions, observing the methods by which these pioneers were advancing the diagnosis and performing early surgical management of sinonasal disease. In 1978, Messerklinger published his classic work illustrating mucociliary clearance patterns of the paranasal sinuses in human cadavers and the intricate diagnostic and anatomic details that could be delineated by technical advances in nasal endoscopy. However, the concept of endoscopic surgical intervention was not mentioned.[26] Endoscopic demonstration of the consistency of mucociliary transport patterns in humans, initially documented in rabbits by Hilding in the 1930s, would prove to be an important foundational concept in constructing the modern surgical approach to CRS.[27]

The senior author's background in neuro-otology, prior surgical experience with microscopic endonasal ethmoidectomy and skull base surgery, and his earlier research in sinus mucociliary transport enabled him to begin the process of incorporating, refining, and transmigrating the early European experience to the American medical community.[28] By 1985, sufficient experience with endoscopic surgery and a recognition of the potential impact of these techniques on CRS allowed the senior author to publish two landmark papers that detailed the theoretical and diagnostic principles, as well as the surgical techniques of what he modified to become functional endoscopic sinus surgery. The early success of this procedure, designed to



THE JOHNS HOPKINS MEDICAL INSTITUTIONS
Department of Otolaryngology—
Head and Neck Surgery

April 20, 1984

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Robert N. Glackin, B.S.

Norman Silbertrust
Karl Storz Endoscopy America Inc.
10111 W. Jefferson Blvd.
Culver City, California 90230

Dear Mr. Silbertrust:

I recently gave some papers at a nasal sinus meeting in Europe, and while there, had the opportunity to listen to and talk with Dr. Walter Messerklinger and one of his associates Dr. Heinz Stammberger. As a result of their presentations and discussions, I became convinced that the techniques of endoscopic sinus surgery which Dr. Messerklinger has advocated and practices, are indeed techniques that will in the future will replace more conventional surgical approaches to sinus disease. I had previously had the opportunity to review Dr. Messerklinger's book on endoscopy of the nose, however, the book did not detail his surgical approaches and in the absence of this, his detailed diagnostic evaluation, described so well in the book, becomes somewhat superfluous and this I believe accounts for the fact that the publication has not been more widely popular in the United States.

As I mention, I am convinced that endoscopic sinus surgery will probably revolutionize current surgical approaches in the future.

Fig. 45.1: Letter to Mr Norman Silbertrust at Karl Storz Endoscopy America, Inc, dated April 20, 1984, detailing the need for specially designed instrumentation for endoscopic surgery of the nose and sinuses.

re-establish ventilation and enhance mucociliary clearance from the paranasal sinuses, was reflected in the acronym FESS that would be adopted rapidly into the permanent surgical lexicon of otolaryngology.[29–31]

The introduction of the technique of FESS and its early refinements to the American audience enabled a number of unmet needs to be addressed within the nascent discipline of rhinology. For the field to flourish, advances in operative instrumentation, radiographic imaging, and the education of both residents in training and practicing otolaryngologists would be required.

The surgical goals envisioned for surgery of the nose and sinuses would require specialized instrumentation that is complementary to the endoscope. A collaborative effort with Karl Storz Endoscopy was initiated, resulting in the development of surgical tools for a procedure whose name had not yet been coined (Fig. 45.1). Small telescopes with a variety of viewing angles require similarly angled hand instruments for tissue removal. Angled suction and through-cutting is instruments that allow access to the lateral nasal wall, skull base, and frontal recess were developed in conjunction with the senior author and his European counterparts to reflect surgical needs and the growing body of basic science research that supports mucosal preservation, removal of osteitic bone, and enhancement of the natural drainage pathways by complete surgical dissection in the absence of mucosal stripping. These through-cutting handheld instruments, curved probes and angled forceps provided the basis for all instrumentation in endoscopic sinus surgery and its later expansion into endoscopic surgery of the orbit and skull base. In later years, the introduction of powered instruments (microdebrider, drills) and scope cleaning devices would further the visualization and the ability to preserve mucosa by which surgeons could address the nose and paranasal sinuses.

Appropriate radiographic imaging studies that reflect the improved understanding of mucociliary clearance pathways became a fundamental requirement for performing safe and complete endoscopic sinus surgery. Plain films that assess the frontal and maxillary sinuses became rapidly outdated as the paradigm for treating CRS shifted from external approaches with mucosal destruction to endoscopic methods that facilitated normal mucociliary flow. Zinreich's work with Kennedy was instrumental in developing and promulgating the use of coronal plane CT scan as the standard view for delineating the anatomy of the lateral nasal wall.[32] Adoption of the coronal view rapidly became the standard of care for surgeons addressing sinus disease; however, the importance of reviewing axial and sagittal planes cannot be overstated in the modern radiographic evaluation for paranasal sinus surgery.

Appropriate education in the theory and techniques of this new method of performing sinus surgery was critical to its widespread adoption. The first postgraduate course for instruction in endoscopic sinus surgery was held in the United States in 1985, codifying the surgical method and sharing this technique through cadaver dissection, an approach which remains a critical component of teaching in rhinology.[33] Although residency education and cadaver training courses remain integral to rhinology education, the future of clinical and academic rhinology is largely based on the ongoing development and rapid growth of fellowship training.

INDICATIONS FOR ENDOSCOPIC SINUS SURGERY

The absolute indications for FESS remain somewhat rare, and in some cases, controversial. Absolute indications for surgical intervention in sinus disease include purulent complications involving the orbit or intracranial space, expansile mucoceles, invasive fungal rhinosinusitis, and neoplasms. Modern techniques greatly favor endoscopic techniques for the vast majority of paranasal sinus disease; however, when considering the acute management of suppurative complications, frontal osteomyelitis,

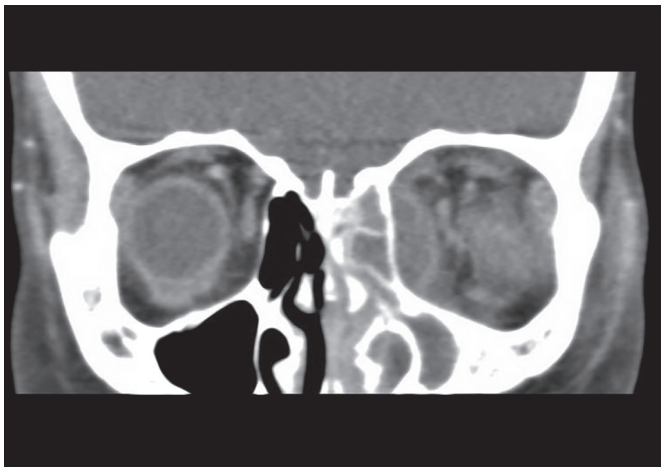


Fig. 45.2: A left subperiosteal orbital abscess is depicted with inflammatory changes in the adjacent ethmoid sinuses.
Courtesy: Kevin Welch, MD, Loyola University, Chicago, IL, USA.

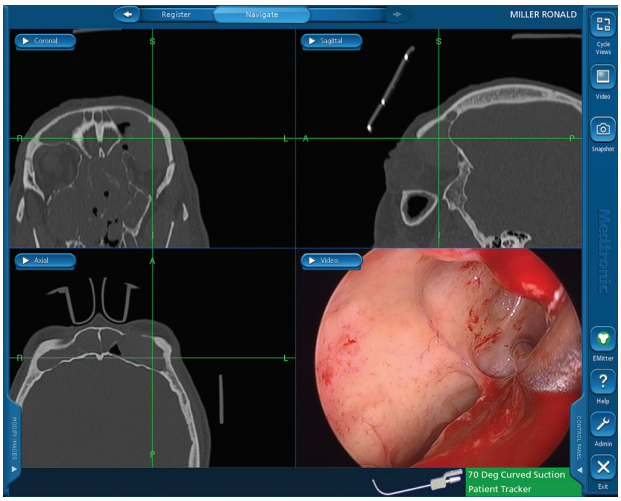


Fig. 45.3: Obstruction of the frontal sinus drainage pathway resulted in expansile changes in the associated bony boundaries of the frontal sinus with extension of a frontal sinus mucocele into the left orbit. The image guidance instrument demonstrates that surgical access has been gained into the lateral extent of the mucocele, allowing the cavity to drain into the nose via an enhanced pathway.
Courtesy: Calvin Wei, MD, Mount Sinai and Lennox Hill Hospitals, New York, NY, USA.

and unfavorable anatomy, external approaches retain a position of surgical relevance. In our institution, suppurative complications of frontal sinusitis may be treated urgently with trephination, drainage of the abscess, and irrigation of the frontal sinus along with antibiotics modified on the basis of culture, and in the presence of severe acute inflammation, endoscopic drainage may be delayed.

More controversial is the absolute indication for surgery in orbital complications of sinusitis. Subperiosteal orbital abscesses are uncommon complications of ethmoid sinusitis (Fig. 45.2). The need for medical management and continuous inpatient monitoring of this disease process is emphasized by all investigators[34]; however, the absolute indications for surgery are less certain. Large case series of subperiosteal abscesses secondary to sinusitis[35,36] as well as retrospective reviews of the literature[37] have identified several features that favor surgical therapy. Abscesses that are not medially located within the orbit, those with volume >0.5 mL or dimensions of width >4.5 mm and length >17 mm, or any associated with loss of visual acuity, proptosis >5 mm, intraocular pressure >20 mm Hg, or the onset of ophthalmoplegia should be addressed surgically.[34–38] In general, a failure to improve or clinical deterioration within 48 hours of the initiation of medical therapy represents an additional absolute indication for surgical intervention.[36,37]

Relative indications for sinus surgery, which in the modern era is synonymous with endoscopic sinus surgery, are those conditions that improve maximally with surgical techniques and remain less responsive, if at all, to medical management. Mucoceles represent a class of paranasal sinus disease in which anatomic abnormalities result in an obstructive process that can be remedied through endoscopic surgery directed toward the obstruction (Fig. 45.3). Wide marsupialization of the mucocele and attentive postoperative debridements, along with appropriate medical therapy, provide uniformly high success rates in the treatment of these largely obstructive processes.

While mucoceles are the most manifest of the inflammatory paranasal disorders for which surgery is indicated, for the remainder of the spectrum of rhinosinusitis the relationship between anatomic variations and sinonasal inflammation remains controversial. Recurrent acute rhinosinusitis (RARS) is a particularly vexing condition, as this most likely represents hyper-reactivity of the sinonasal mucosa, a variable or subtle immunodeficiency, or repeated exposures to environments or infectious agents that are troublesome for a particular patient. FESS should be broached with caution in RARS, and probably not at all unless the patient has some persistent inflammation between episodes, as patients will still probably experience repeated acute infections. The one potential advantage of surgery in this situation is that it may allow greater delivery of topical medical therapy to the involved sites and improved levels of baseline control of nasal inflammation. On the other hand, if there is an environmental or allergic component, surgery will open up virgin mucosa to the same environmental factors that be a factor in the patient's RARS.

A similar degree of prudence should be exerted when considering FESS for the patient with facial pain and pressure or headache. In a population of patients undergoing CT scan for indications other than disease related to the sinuses, between 10% and 50% of scans demonstrated radiographic abnormalities consistent with sinusitis.[39,40] There remains an intersection between the population of patients with headaches and those with asymptomatic radiographic findings. Unlike acute sinusitis, patients with chronically inflamed paranasal sinus mucosa do not experience marked pain. Normal sinonasal mucosa is more sensitive to pain derived from ostial obstruction than is chronically thickened mucosa. Episodes of barosinusitis during flying, or scuba diving and acute sinusitis can be associated with more marked pain symptoms than in CRS, and is a good indication for surgery or balloon dilatation. On the other hand, there is no clear association demonstrated between weather changes, headache, and sinusitis. Appropriate diagnostic studies should be considered in the longstanding CRS patient with new development of severe pain, as this can indicate dural inflammation, neural involvement, neoplasm, or an infectious complication of rhinosinusitis. The rhinologist must discriminate between these patient subsets to improve the satisfaction with surgery and avoid subjecting the vast majority of patients who have vascular variant headaches to surgical intervention. Thorough endoscopic examination as well as adjunctive consultations with a neurologist and, occasionally, pain management specialists can be helpful in appropriately addressing the patient with facial pain and pressure in the absence of paranasal sinus findings.

While medical management is an essential component of the management of all inflammatory conditions of the nose and sinuses, there are a few processes in which relative indications for surgery predominate and current trends favor surgical intervention earlier in the disease process. CRS with nasal polyposis can be better controlled after an initial and complete operation to remove the inflammatory polyps, widely ventilate the paranasal sinuses and improve the penetration of topical medical therapy. Similarly, allergic fungal rhinosinusitis (AFRS) represents a subset of CRS with nasal polyposis for which medical therapy is greatly enhanced by surgery. Though immunomodulation with corticosteroids and/or mold allergen desensitization therapy is fundamental to the management of AFRS, wide surgical ventilation of the paranasal sinuses and removal of all eosinophilic mucin is the critical component for successful management, along with complete removal of the bony intracellular partitions and long-term endoscopic surveillance.[41]

The most common indication for FESS is the persistence of symptoms of CRS despite appropriate courses of medical therapy. Though there is a lack of uniformity among various medical treatment protocols for CRS, there is some consensus regarding the minimum of medical care. The majority of treating physicians reported prescribing oral antibiotics, oral steroids, and intranasal corticosteroid sprays, with over 90% of survey respondents recommending oral antibiotics for average durations approaching 4 weeks in combination with intranasal corticosteroids.[42] Rhinologists are more likely to use oral corticosteroids than are other otolaryngologists, with mean peak prednisone doses over 50 mg.[42,43] Mucolytics, topical decongestants, allergy testing, surfactants, and large volume irrigations, sometimes incorporating high-dose topical steroids, are helpful adjuncts to the aforementioned medical strategies. There also exist a variety of interventions that are used infrequently or rarely and for which there is relatively little evidence of efficacy, including antifungal sprays, nebulized antibiotics, or intravenous antibiotics as a routine component of medical management in the patient with CRS. Optimization of the patient's risk factors for CRS is always considered prior to proposing surgery. Often, this will include allergy testing and management of atopic conditions, eliminating exposure to cigarette smoke and other environmental hazards, enhanced medical control of reactive airway disease, as well as a battery of immunologic tests in select refractory cases. Patients experiencing ongoing symptoms of CRS despite diligent medical evaluation and treatment are most likely to appreciate significant improvements following FESS and are the ideal candidates for whom surgery is indicated.

PREOPERATIVE COUNSELING FOR ENDOSCOPIC SINUS SURGERY

The goals for and role of endoscopic sinus surgery in the overall management of CRS are fundamentally different from the commonly understood functions of operative procedures for most other disease processes. As such, it is incumbent upon the otolaryngologist to educate the patient properly regarding surgery and perioperative care. Appropriate management of expectations is of critical importance when addressing a process of ongoing inflammation, as the patient's cooperation in preoperative preparation and postoperative office-based procedures are requirements for a successful surgical result.

Treatment of CRS is overwhelmingly medical, with surgery reserved for a minority of patients who fail to respond appropriately to oral corticosteroids, intranasal corticosteroids, oral antibiotics, and control of allergic inflammation. Considered broadly, endoscopic sinus surgery is typically not curative for CRS, but rather plays an adjunctive role in the global management of sinonasal inflammation. Preoperative counseling that emphasizes the long-term strategy for management of CRS enables patients to have an understanding of treatment goals as well as the need for ongoing medical management following successful surgery. Surgeons should communicate to their patients that the primary treatment of CRS is medical and not surgical.

Surgery augments medical regimens by the removing inflammatory tissue, facilitating proper drainage from the paranasal sinuses, and allowing penetration of topical medical therapy into the affected sinuses. Recent studies suggest an increasingly important role for surgery as a route of medication delivery, as the paranasal sinuses are directly accessed by intranasal sprays and irrigations only after proper surgical access has been achieved.[44] Conversely, one significant disadvantage of surgical intervention is that, if the underlying predisposing cause for the rhinosinusitis was environmental and this is not controlled, surgical intervention opens up additional virgin mucosa to the same environmental factors. Unlike most other surgical procedures, patients play an active role in modulation of the operative site during the postoperative period. The operative site is evaluated by the surgeon on a weekly basis and debrided as necessary until the endoscopic examination of the mucosa stabilizes. During this period, the patient is treated with oral corticosteroids, irrigations, topical corticosteroids, and, as necessary, office-based debridements. Meticulous postoperative care is an absolute requirement for a successful result. The persistent and careful removal of residual bone fragments, mucus, clots, and early synechiae decreases the burden of bacteria and fungus within the operative field, preserves the enhanced drainage pathways, and reduces overall sinonasal inflammation.[45] We believe that proper counseling prior to surgery can improve patient compliance with medical therapy in the pre- and postoperative periods, which is integral to the overall success of endoscopic sinus surgery.

GENERAL PRINCIPLES OF FESS

Our practice and understanding of the role of FESS continues to evolve. Following the introduction of FESS in 1985, there has been a steady progression of basic science and clinical outcomes knowledge that guides the present techniques of FESS. Though Naumann had originally delineated the ostiomeatal complex in 1965, the area was not widely accessible to physicians as the anatomic knowledge predated the wide introduction of imaging techniques and viewing modalities that would later reshape the field of rhinology.[46] When the ostiomeatal complex became clinically accessible at the dawn of the endoscopic era and CT imaging of the sinuses, the pendulum swung to an overemphasis of the importance of this region in the pathogenesis of CRS. The notion of CRS as largely an obstructive phenomenon predominated the field for many of the early years, and vestiges of this notion still persists in some quarters. No longer is it accepted that CRS is a simple process of ostial obstruction that results in bacterial infection of the associated sinus. Although surgery directed to improving ventilation and drainage through the ostiomeatal complex remains an important component of treating CRS, the role of anatomic variation and obstructive phenomena have been relegated to a supporting position. CRS is broadly recognized as a spectrum of signs and symptoms that arise from a persistent inflammatory process of paranasal sinus mucosa and bone.[47] As such, the management of CRS is directed to the etiologic agents of inflammation (Table 45.1), largely through medical therapy to control infection, reduce allergic responses, and restore normal mucociliary flow. When surgery is indicated, the technique of FESS is employed and mucosa is maximally preserved. While controversy exists regarding methods of performing sinus surgery, the formerly held notions supporting the stripping and complete removal of "condemned mucosa" has long been relegated to history. Discussed elsewhere in this text, balloon catheter dilation of sinus ostia and surgery of the transition spaces within the nose are surgical techniques that result in less surgical trauma and less mucosa scarring that traditional FESS. However, these minimally invasive operations do not allow for the removal of involved bone, and its associated inflammation.[48] It is clear that CRS is not just an issue of sinus obstruction. Moving forward, however, it is likely that the management CRS will migrate toward more minimally invasive procedures in combination with topical anti-inflammatory therapy. Hybrid procedures that incorporate balloon catheter technology for dilation of some paranasal sinuses in combination with traditional endoscopic techniques for removal of diseased bone and associated mucosa have been suggested to offer low revision rates in treatment of CRS, though methodologic issues in assessing the success of this approach remain.[49]

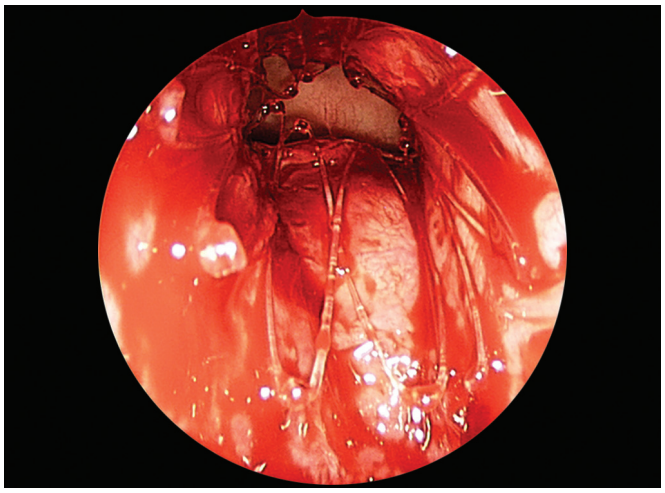


Fig. 45.4: A drug eluting implant placed within a Draf 2A frontal sinusotomy exerts a centrifugal force against the surrounding tissue and releases mometasone into the surrounding tissues over 30 days before degrading over the following several weeks after drug elution is complete.

Our current practice of FESS places great importance on the preservation of mucosa and the removal of osteitic bone while endeavoring to appropriately ventilate the associated paranasal sinuses. When mucosa is completely stripped, the epithelium that eventually regenerates in a traumatized location will possess a significantly reduced population of ciliated cells with compromised mucociliary clearance.[50] Surgically exposed bone experiences a greater degree of inflammation and frequently this bone becomes osteitic, undergoes neo-osteogenesis, and may sometimes be associated with chronic pain and pressure. Preservation of mucosa is a fundamental step in avoiding a cascade of inflammatory responses within the bone that requires long-term medical management and possibly surgical revision. When osteitic bone is noted in revision surgery, its complete removal is recommended to reduce the inflammatory burden and the associated implications with persistent mucosal disease and scarring. The extent of FESS in CRS is generally directed to perform complete operations that address one sinus beyond the disease process noted on preoperative CT scan or the inflammation present at the time of surgery. Complete uncinectomy is performed in every operation, as the failure to remove the entire uncinate process has been associated with persistent inflammation, maxillary sinus obstruction, and the need for revision surgery.

Future developments in the evolution of our specialty may support more minimally invasive techniques, especially with the introduction of drug eluting implants and other topical therapeutic interventions that can be delivered into the paranasal sinuses with lesser degrees of anatomic disruption.[51] At present, well-controlled investigations into a clinically available, bioabsorbable implant that elutes mometasone directly into the postoperative ethmoidectomy defect have demonstrated successful reduction of postoperative synechiae, mucosal inflammation, early polyp formation, and middle turbinate lateralization[52–54] (Fig. 45.4).

OUTCOMES RESEARCH IN FESS

For nearly three decades, surgical practice and the medical literature has clearly established the role of FESS in the management of CRS. As our knowledge base expands, a critical analysis of outcomes research allows surgeons to better counsel patients with CRS regarding the expectations for FESS. Outcome data have become available for a wide array of subjects related to CRS and its surgical management. Review of the outcome data for FESS as it related to QOL scores, particular symptoms of CRS, and various surgical techniques will allow surgeons to better understand the expected impact on patient satisfaction, which in CRS is the ultimate indicator of successful management.

Outcomes of FESS in the Management of CRS

While only a minority of patients with CRS will eventually undergo FESS, the technique is well established as the gold standard for surgical intervention in inflammatory disease of the paranasal sinuses. Outcomes assessments have become fundamental tools in the evaluation of surgical procedures. In disease states such as CRS, where the goal is improved control of an ongoing inflammatory process, an understanding of treatment success from a patient's perspective has become a fundamental tool in the assessment of management strategies. Numerous outcomes studies have established FESS as both a safe and a highly successful intervention that, when combined with appropriate postoperative care, provides durable improvements in sinonasal symptoms and overall health. While level 1 evidence supporting FESS in CRS is not as robust in numbers, there is an abundance of published level 2 and 3 evidence that supports the previously described role for FESS in the management of CRS in adult patients.[55]

It is now generally accepted that rates for symptomatic improvements following FESS should be attainable in the

vast majority of patients with CRS.[56] Some of the largest early studies showed symptomatic improvements, in the absence of validated surveys, between 80% and 89% of patients with an average follow-up of 17 months.[57] The senior author prospectively followed 120 patients and reported symptomatic improvement in 97.5% an average of 18 months after FESS in conjunction with appropriate medical therapy.[58] Use of validated questionnaires in prospective studies has become a fundamental component of outcomes assessment in CRS.[59] Metson and Gliklich demonstrated significant improvements in symptoms and health as well as reductions in medication usage in 88% of patients meeting criteria to undergo surgery for CRS, based upon prospectively obtained validated questionnaires.[60] Similar reports of improvement after FESS with SNOT-20 symptom scores are reported as early as 3 months and persist or improve at 12 months following surgery.[61] The senior author has shown these subjectively reported improvements after FESS to remarkably durable. With nearly 8 years of postoperative follow-up, 98.4% of patients experienced continued symptomatic relief, although 18% of patients, most of whom had had prior surgical interventions elsewhere, required revision surgery during this follow up period.[45] Longer-term studies of FESS have demonstrated overall improvements in QOL assessments based on patient responses to validated surveys. Khalid et al. found patient's overall health status to remain significantly improved at 3 years after undergoing FESS and appropriate medical therapy for medically refractory CRS.[62] It is expected that postoperative patients, with appropriate medical management, will achieve QOL scores that are equivalent to general population counterparts without CRS.[62]

While the overall expectations remain high for improvements in QOL after FESS, several patient features have been suggested to decrease overall improvements in evaluated symptom domains. Smith et al. found primary FESS patients to experience significantly greater improvements than revision FESS patients on overall QOL inventories.[63] Furthermore, there is evidence that aspirin intolerance and depression may be predictive of poorer overall QOL outcomes.[64] Despite this, severity of depression has been shown to significantly improve after FESS.[65] The use of cigarettes remains an interesting and mildly controversial subject, with regard to outcome data. Though the revision rate for endoscopic sinus surgery is known to be elevated,[45] there are outcome data that suggest no or limited difference in QOL scores between smokers and nonsmokers undergoing FESS for CRS.[66] There are significant differences, however, in the postoperative endoscopy scores when light smokers are compared to heavy smokers.[66] All patients who smoke cigarettes should be counseled toward cessation as a primary intervention in improving their sinonasal symptoms. It is the practice of the senior author to avoid elective, nonurgent sinus surgery on active smokers, given our findings that suggest patients with more extensive inflammatory disease are especially prone to require revision operations when they continue to smoke.[45] An understanding of some of the preoperative features that portend reduced QOL outcomes will allow surgeons to properly counsel patient regarding appropriate postoperative expectations.

Outcomes for Medical Therapy versus Surgery in the Management of CRS

Medical therapy and surgery are both appropriate treatment strategies for long-term management of CRS, and are complementary in their objectives. Recent literature indicates that patient-based outcomes are significantly improved in the patient population undergoing combination therapy. Patients undergoing FESS for CRS after failing initial medical therapy reported superior QOL improvements, decreased absenteeism from work/school, as well as reduced use of antibiotics and oral corticosteroids over first 6 months as compared to the cohort selecting ongoing medical management.[67] A 12-month follow-up of this study population allows greater understanding of the outcomes for FESS when compared to surgical management for medically refractory CRS. Not only did the surgical cohort report a significantly greater improvement in QOL scores than did the medically managed group, but one third of the medically managed patients crossed over to the surgical arm after medical therapy failed to improve their symptoms. Both the surgical group and the cross-over group experienced significantly greater QOL improvements than did the medically managed group.[68] The demonstrated efficacy of surgery in providing significant improvements in QOL, especially after demonstrating the inability of medical therapy alone to achieve the desired results, is a powerful argument for the role of FESS as an integral adjuvant component in the CRS treatment strategies.

Outcomes for Olfaction after FESS

Hyposmia is a common and challenging symptom to improve in patients with CRS. There are multiple and often coexisting mechanisms for olfactory impairment, including mechanical obstruction and inflammatory damage

directly to the olfactory neuroepithelium. Recently, several authors have demonstrated that both local and systemic eosinophilia correlates with greater levels of olfactory dysfunction, though the precise mechanism of sensory loss remains incompletely understood.[69,70] While the pathogensis of olfactory loss remains incompletely understood, our appreciation for the benefits of FESS in particular populations of patients with CRS has been better elucidated by recent outcomes studies.

For olfactory function alone, surgery is a powerful adjunct when compared to medical therapy alone. A matched, nonrandomized study comparing medical therapy alone to combined therapy with FESS followed by intranasal corticosteroid sprays, found the surgical group to experience significantly improved olfactory function in CRS with nasal polyposis.[71] Though surgical intervention in CRS has been demonstrated, repeatedly, over the past few decades to successfully improve the symptoms of CRS, specific examinations of the effects of FESS on olfaction have been less encouraging.

A prospective trial of 111 patients undergoing FESS for CRS demonstrated the surprising finding that patients with more severe olfactory dysfunction experienced a significant and sustained improvement in performance on standardized tests of olfaction, whereas those with lesser degrees of hyposmia did not.[72] These findings support improved olfactory outcomes in anosmic patients with obstructing polyps, while those without obstructive disease are more likely to have sustained additional injury to the olfactory neuroepithelium for which surgery alone is not reparative. Complementing this study is a prospective work that reviewed the degree of olfactory cleft opacification in 52 patients with CRS with nasal polyps who later underwent FESS. It was shown that patients with lesser degrees of inflammatory disease of the anterior olfactory cleft improved to a greater degree than did those with more severe mucosal inflammation on preoperative CT scan.[73]

Despite this, overall results for olfaction after FESS remain somewhat troubling. Pade prospectively evaluated 206 patients with CRS with nasal polyps and reported subjectively appreciated olfactory improvements in only 23%.[74] Objective data for patients in a similar prospective trials of CRS patients including populations with and without nasal polyps found only cautiously optimistic improvements for this symptom. Performance on olfactory discrimination tests 5 years after primary surgery showed improvements in only 53%.[75] Patients undergoing revision FESS demonstrate similar rates of improvement in olfaction as those reported in studies of primary FESS operations. A prospective analysis of hyposmic patients undergoing revision FESS demonstrated rates of improvement on postoperative objective olfactory testing at 47.8% between 12 and 24 months after surgery.[76]

The irregularity with which any prognostication can be made regarding expected olfactory outcomes continues to bedevil those who counsel patients regarding hyposmia as a result of CRS. Jiang prospectively evaluated 70 patients with CRS and failed to demonstrate any significant difference in either the objective or subjective olfactory function outcomes.[77] The group did, however, show a correlation between severity of changes on CT scan and olfaction testing, supporting previous authors that demonstrated more severe inflammation in patients with worse olfactory outcomes.[77] Despite this correlation, there are no more specific data that allow surgeons to reliably counsel patients on features that portend positive or negative olfactory results after surgery. The extent of sinonasal inflammation, degree of nasal airway obstruction, coexisting diagnosis of allergic rhinitis, or the presence of nasal polyps in this population have not been shown to be predictive of olfactory improvement following FESS.[78]

These examinations of olfactory function have parsed patient populations most likely to improve with surgery and medical management as well as the expected degree of improvement. A better understanding of olfactory outcomes following FESS allows for proper counseling of CRS patients considering surgery. Multiple features of olfactory impairment, including improvement on oral steroids, age, duration of inflammatory disease, number of prior operations, and degree of nasal polyposis, must make surgeons cautious when prognosticating long-term improvement in hyposmia for many patients with CRS. In general, postoperative olfactory outcomes are better in those populations with anosmia and nasal polyposis and somewhat diminished for those with hyposmia and nonpolypoid inflammatory disease. More severe radiographic changes preoperatively, and specifically those that involve the anterior olfactory cleft, are associated with worse olfactory outcomes. There does not appear to be a significant difference in olfactory outcomes between primary and revision operations. Preoperative counseling should take into consideration the available outcome data regarding olfaction to properly manage surgical goals and patient expectations.

Outcomes for Specific Surgical Maneuvers in FESS

There is a paucity of literature related to outcomes of specific maneuvers during FESS. There are, however, a few operative techniques among the many components of FESS procedures for which some outcome data have been produced. Management of the middle turbinate, extended frontal sinus operations, and the creation of an enormous maxillary sinus antrostomy are surgical maneuvers rhinologists have to consider in refractory disease.

Outcomes in Determining the Anatomic Extent of Maxillary Antrostomy

The maxillary sinus is, arguably, the most commonly addressed sinus by surgeons performing FESS. Despite the frequency with which this sinus undergoes surgical intervention, substantial differences persist regarding the degree of opening necessary to achieve improved results. Key components of the decision-making process in this operation relate to the effects of antrostomy on maxillary sinus nitric oxide concentrations and adverse effects of nasal airflow on the newly exposed sinus mucosa, and the ability to introduce topical therapies into the maxillary sinus.

Nitric oxide is produced in the paranasal sinuses and is thought to contribute to the normal function of these spaces both by its role in ciliary function as well as through its antibacterial properties. Basic science investigations into the relationship of maxillary antrostomy size and nitric oxide concentrations do demonstrate a decrease in levels with larger antrostomies, yet clinical outcomes have not been correlated with diminished nitric oxide levels. Despite the basic science demonstration that nitric oxide concentrations decrease with an antrostomy >5×5 mm, there is a lack of clinical outcome data linking lower nitric oxide levels to chronic maxillary sinusitis.[79] Albu and Tomescu evaluated prospectively the relationship between small (<6 mm) and large (>16 mm) maxillary antrostomies, yet no significant correlation was demonstrated between the improvement in a patient's symptoms of CRS and the resultant antrostomy size.[80] An extensive meta-analysis of the available literature addressing nitric oxide levels within the paranasal sinuses failed to demonstrate any negative clinical outcomes of a large maxillary antrostomy as a result of diminished nitric oxide concentrations.[81]

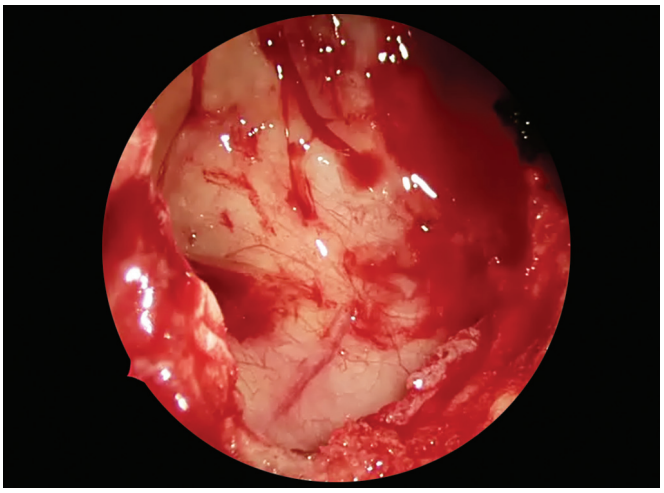
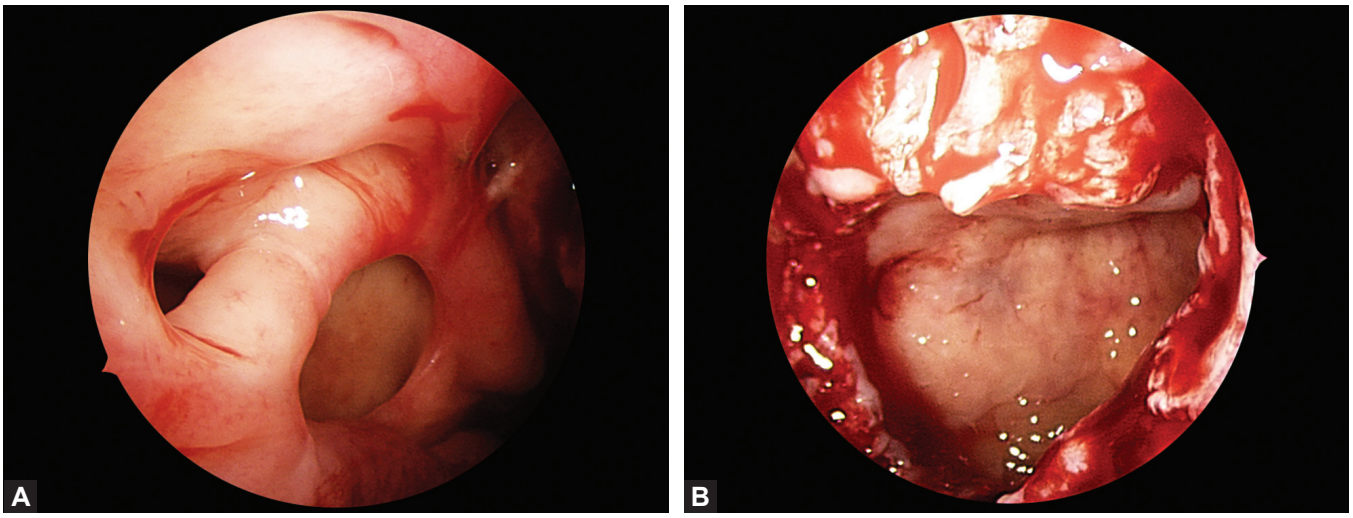


Fig. 45.5: Mega-antrostomy/modified maxillary antrostomy. The endoscopic modified medial maxillectomy can be used in the salvage of a chronically infected though otherwise patent maxillary sinus. This extended operation allows for maximum irrigation, improved penetration of topical therapy, and results in a form of "marsupialization" of the sinus that facilitates debridement in the office setting. Note the continuity between the right maxillary sinus floor and the nasal floor after removal of the medial maxillary wall.

There is some agreement on one population for whom a very aggressive maxillary antrostomy has been shown to be associated with improved outcomes: chronic maxillary sinusitis refractory to prior well-performed surgery and medical therapy. In these cases, endoscopic removal of the medial maxillary wall such that the antrostomy connects with the nasal floor has been demonstrated to be an effective technique.[82] This dramatically larger opening of the maxillary sinus facilitates office-based debridement, improves penetration of topical medical therapy, and allows greater access for irrigation and removal of retained mucous. In populations with impaired mucociliary clearance this procedure offers the benefit of an enlarged drainage pathway without the need for mucociliary flow against gravity toward the natural ostium (Fig. 45.5). In prospectively evaluated cystic fibrosis patients, this procedure significantly improved both sinonasal symptom scores and endoscopic scores 1 year following surgery.[83] Cho and Hwang reported symptomatic improvement in 100%, and complete resolution of symptoms in 74% of retrospectively reviewed patients treated for medically and surgically recalcitrant maxillary sinusitis.[84] Similar overall outcomes for this operation have been reported by Schlosser's group; however, success rates were lower in the groups with cultures positive for *Pseudomonas aeruginosa* and worse still for those with *Staphylococcus aureus*.[85]



Figs. 45.6A and B: Although there are valid disagreements regarding the size of a maxillary antrostomy, the procedure should always incorporate the natural ostium at this most anterior extent to prevent complications related to recirculation of the mucociliary flow from the maxillary sinus. Part (A) demonstrates a right maxillary antrostomy with synechiae separating the right natural ostium from the surgical antrostomy with resultant recirculation. Part (B) demonstrates a more idealized left maxillary antrostomy with incorporation of the natural ostium at the anterior extent of the surgical dissection. Note the pear shaped antrostomy with the apex anterosuperiorly.

The negative effects of nasal airflow on maxillary sinus mucosa have been more definitively demonstrated than those postulated for a reduced nitric oxide concentration. Animal studies clearly depict a slowing or cessation of mucociliary clearance in the presence of maxillary sinus airflow.[86] The combination of these effects may be a factor in biofilm formation within the maxillary sinus, accounting for a portion of residual and refractory disease in patients despite widely patent antrostomies. When the posterior limits of the maxillary sinus protrude medially, large antrostomies can create an "air scoop" with resultant drying of the maxillary sinus mucosa. This anatomic configuration should be recognized preoperatively to allow either minimal opening of the maxillary sinus or an extensive opening back to the pterygoid plates, as both of these surgical approaches would limit airflow that is drying to the maxillary mucosa. Avoiding this airflow would prevent the subsequent ciliary stasis and possible promotion of biofilm formation despite a patent maxillary antrostomy. Though there is a paucity of strict clinical outcome data, there is sufficient information to enable surgical decision making with regard to the size of a maxillary antrostomy.

Surgeons must have clear understanding of their goals for a particular patient when evaluating the existing outcome data and determining the desired size of an antrostomy. Larger antrostomies should be favored in cases of allergic fungal rhinosinusitis and in fungal ball of the maxillary sinus, as postoperative surveillance and removal of material from the maxillary sinus are anticipated. Similarly, when treatment goals include penetration of topical medical therapy into the maxillary sinuses, larger antrostomies have been shown to allow greater postoperative penetration of irrigated solutions.[87]

Regardless of the selected antrostomy size, the uncinate process should always be removed completely during surgery. This structure is involved early in CRS and, when retained following surgery, the remnant uncinate bone and associated mucosa acts as a persistent source of inflammation and obstruction to normal mucociliary flow from the maxillary sinus.[88] The natural ostium should be directly visualized during dissection and this requires the use of 45° or 70° angled endoscopes. Surgery and subsequent postoperative care should endeavor to maintain a generally pear-shaped antrostomy, regardless of gross size, that includes the natural ostium at its most anterior extent and remains free of synechiae[89] (Figs. 45.6A and B).

Outcomes for Extended Frontal Sinus Operations for Inflammatory Disease

Over the past 20 years, there has been a dramatic increase in both the frequency and the extent to which surgery is performed for frontal sinus disease. The introduction of trans-septal frontal sinusotomy (TSFS) broadened the

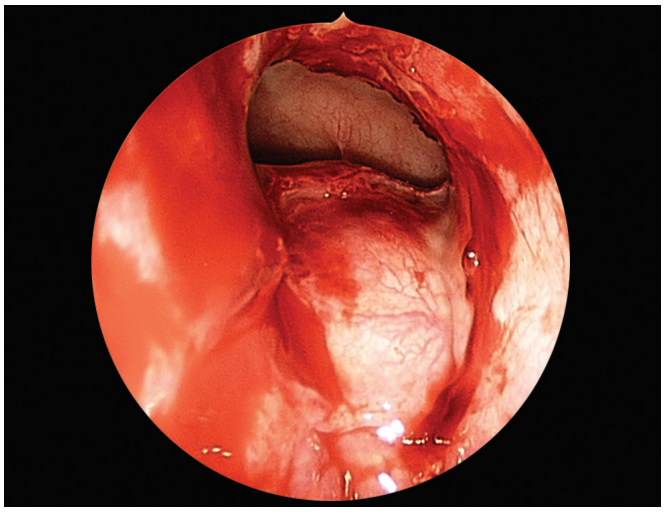


Fig. 45.7: Draf 2A operative site. In the vast majority of primary and revision FESS, removal of all partitions within the frontal sinus drainage pathway and meticulous preservation of the associated mucosa of the medial orbital wall, skull base and middle turbinate, provides a successful surgical intervention for the frontal sinus.

range of conditions amenable to endoscopic procedures while the availability of image guidance and novel instrumentation has increased the total number of frontal sinus operations.[90] Outcome data are now available that have helped shape the approach to the frontal sinus when extended operations may be considered.

In the vast majority of surgical patients including both primary and revision surgery, a formal endoscopic frontal sinusotomy, or Draf 2A procedure is successful (Fig. 45.7). A review of 717 such operations at a tertiary referral center found > 92% were effectively managed without extended frontal sinus procedures.[91] There are, however, generally agreed upon indications for which TSFS is accepted: severe osteoneogenesis within the frontal recess, traumatic injury to the frontal sinus drainage pathway, resection of sinonasal neoplasms, complex frontal recess cells, failed frontal sinus obliteration procedures, mucoceles, and frontal anatomy associated with a narrowed or osteitic drainage pathway.[92] While patency of the frontal sinusotomy is critical, there is emerging research that the postoperative frontal ostium size correlates with persistence of symptoms, and larger sinusotomies may offer improved symptom control.[93] A review of the outcome data for TSFS operations indicates a high degree of success, with at least one author offering this more extensive operation as a primary surgical intervention for certain subsets of patients with CRS.

Wormald demonstrated a success rate of 93% among prospectively enrolled revision patients with recalcitrant frontal sinusitis undergoing TSFS.[94] Similarly, improvement in symptoms of CRS has been reported in as many as 98% of patients undergoing TSFS.[95] A meta-analysis of the literature found an overall patency rate of 95.9% for TSFS at an average follow-up interval of 28.5 months in the 394 patients for whom endoscopic postoperative results were reported, with similar complication rates to those reported in the literature for traditional FESS procedures.[96] The favorable outcomes of TSFS in a difficult patient population has prompted some authors to investigate the utility of this extended frontal sinus operation as a primary surgical intervention. In one study, the presence of asthma, polyposis, frontal ostia < 4 mm, and Lund-MacKay radiographic scores > 16 were identified as risk factors for failure of a standard frontal sinusotomy and a primary TSFS may be considered in these patients.[97] TSFS affords additional access for instrumentation of the frontal sinus, removal of inflammatory disease burden, particularly when the pathology is a lateral within the sinus and increased penetration of postoperative topical medical therapy. However, the vast majority of patients with CRS, including patients with a previous failed frontal sinusotomy, will respond to a meticulously performed Draf 2A procedure (Fig. 45.8).

Outcomes in Middle Turbinate Management

Debate regarding management of the middle turbinate during surgery prompted several prospective and retrospective investigations. Development of outcome data for middle turbinate surgery in FESS has provided surgeons with more solid data upon which surgical decisions can be based. Brescia et al. retrospectively reviewed their experience with 48 patients undergoing FESS for CRS with nasal polyposis and did not identify a statistically significant difference in nasal obstruction or endoscopic score between the group that underwent middle turbinate resection and the group for which the turbinates were preserved.[98] Prospective studies comparing middle turbinate resection with middle turbinate preservation have been undertaken with similar results. Byun and Lee showed that there was more extensive inflammatory disease in the group undergoing middle turbinate resection, and a difference persisted postoperatively, with worse endoscopic

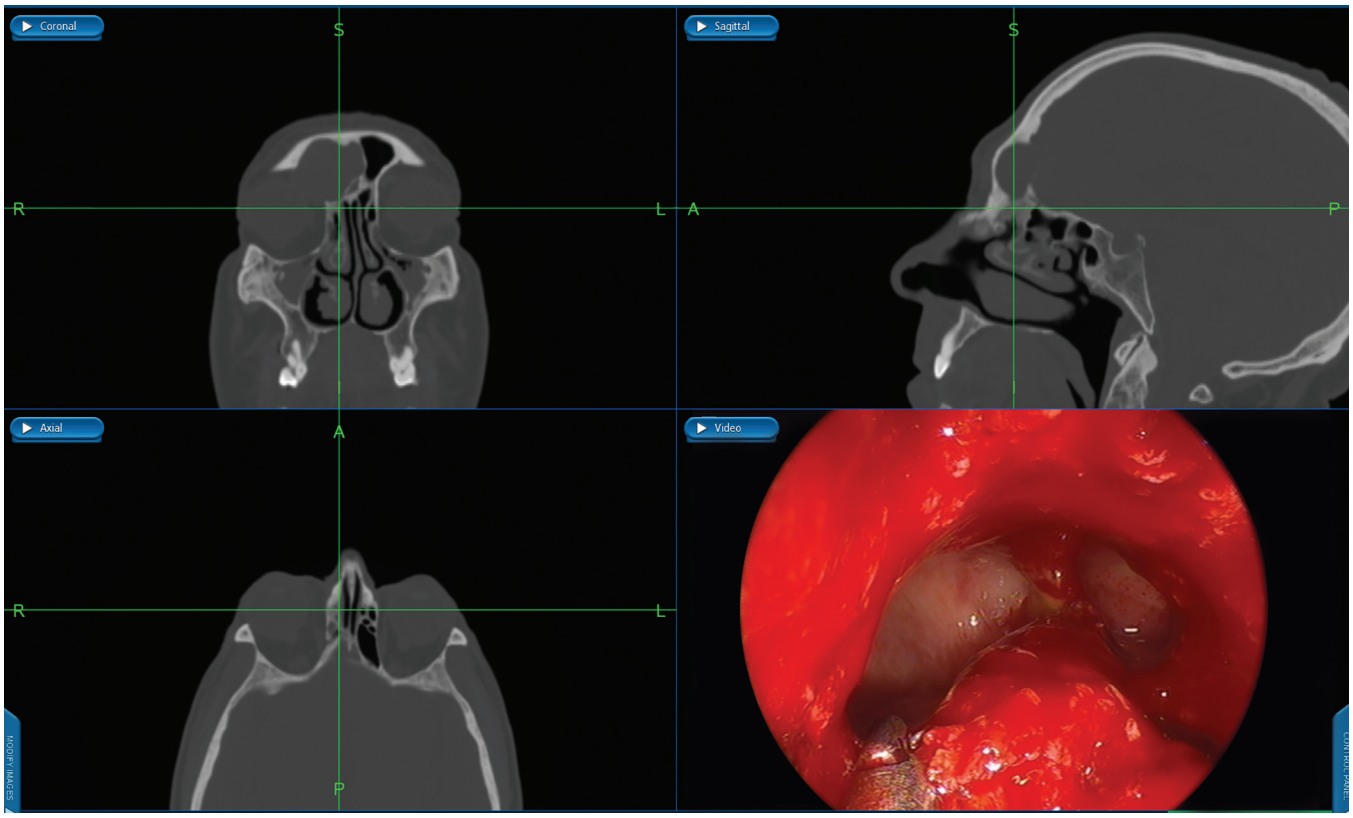


Fig. 45.8: In revision cases, a transseptal, frontal sinusotomy is recommended for opening of a frontal sinus that is involved with more severe osteitis, inflammatory mucosa, or scarring from prior frontal sinus surgery. A frontal sinus mucocele with significant osteitis of the drainage pathway is a typical case for which a Draf 3 procedure would be performed to allow wide ventilation and drainage of the involved sinus as well as access for postoperative surveillance and augmented penetration of topical medical therapy.
Courtesy: Kevin Welch, MD, Loyola University, Chicago, IL, USA.

scores in these patients at 12 months.[99] Subjective assessment with Sino-Nasal Outcome Test 20 and a visual analogue scale did show differences between the groups 1 year following surgery.[99]

Conversely, Soler et al.'s prospective study demonstrated greater improvements in the endoscopic examination for those patients undergoing middle turbinate resection, though subjective QOL measures did not differ significantly between these groups.[100] The difference in endoscopic findings may indicate greater severity of the baseline inflammatory process, differences in the type of postoperative topical medical therapy, or that the absence of middle turbinates in the postoperative cavity represents a loss of some natural protection to an environmental feature that provokes inflammation.

Though recent literature has destigmatized middle turbinate resection with regards to outcome data, the decision to resect middle turbinates should be undertaken with additional caution. It is the senior author's practice to preserve the middle turbinate unless it is diseased. If middle turbinate bone is exposed during the surgical procedure, the exposed bone is resected, even if it may lead to the turbinate becoming somewhat poorly suspended. Middle turbinates that have become lateralized or altered by prior surgical interventions may be resected when their retention prevents completion of the planned operation, especially if the bone is osteitic (Fig. 45.9). Middle turbinate lateralization is a common cause of failure after primary FESS, with an incidence between 11% and 78% reported by revision surgeons in tertiary care settings.[101,88]

Prophylactic surgical techniques that facilitate both preservation of the middle turbinate and a reduced risk of lateralization have been in wide use for many years. Suture techniques[102] and controlled placement of a temporary or permanent synechiae[103] between the middle turbinate and the nasal septum optimize middle meatal access both during surgery and in the office for postoperative endoscopic debridements (Fig. 45.10). Outcome studies of middle

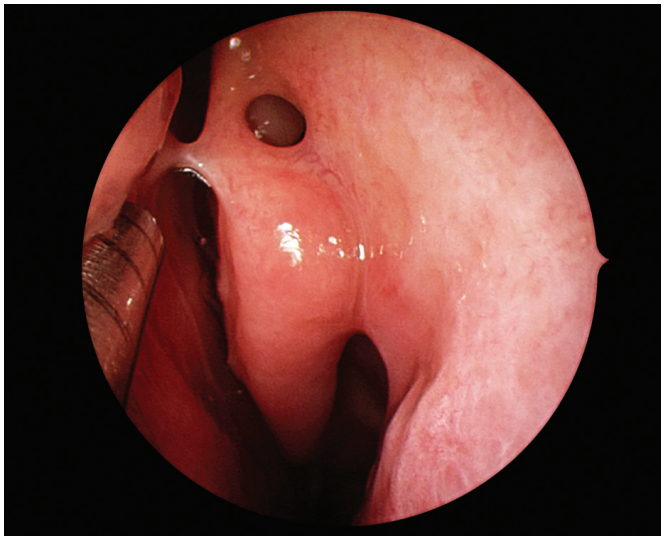


Fig. 45.9: Lateralization of the middle turbinates is one of the most common reasons for revision sinus surgery. Middle turbinates that have been destabilized during sinus surgery, or improperly medialized, can adopt a position that approximates the lateral nasal sidewall. This lateral orientation both hinders normal postoperative care and can obstruct the frontal sinus drainage pathway.

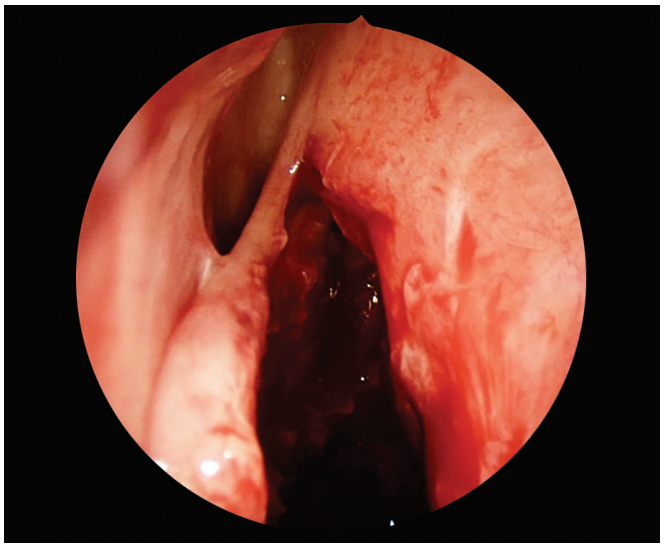


Fig. 45.10: Middle turbinate preservation is the favored technique of the senior author, preserving this important anatomic landmark and limiting the removal of normal tissue from the nose and sinuses. Immediate intraoperative appearance of middle turbinate lateralization with suture technique of patient in Figure 45.6.

turbinate medialization techniques demonstrate a high degree of success in preventing middle meatal cicatricial complications,[104] and despite concerns regarding narrowing of access to the olfactory cleft, these maneuvers do not appear to impair olfaction after FESS.[105]

Severe polypoid disease, osteitic bone, or abnormal positioning that hinders postoperative care or the penetration of topical medical therapy are several common reasons for resection. The middle turbinate provides an exceptional landmark for general surgical navigation and, even in cases when resection is planned, the use of this landmark during the operation can facilitate the procedure and perhaps resection should be delayed until the conclusion of surgery. When resecting the middle turbinate, avoidance of common iatrogenic complications is paramount. The vertical lamella should be removed such that lateralization is not likely to occur. In cases with narrow frontal sinus drainage pathways or insubstantial rigidity of the remnant vertical lamella, the middle turbinate should be removed up to the skull base. Visualization with angled endoscopes and the use of curved frontal sinus through-cutting instruments are necessary to remove the vertical component, prevent intracranial entry, and avoid leaving denuded bone in this critical region of the operative cavity. Removal of the horizontal component of the middle turbinate can be complicated by bleeding, as a branch of the sphenopalatine artery enters the middle turbinate in this location posteroinferiorly. Proper use of cautery at the middle turbinate remnant along the lateral nasal wall as well as gentle postoperative debridement at this site will be required. Outcome data indicate that subjective results are not impaired by middle turbinate resection; however, surgeons should remain thoughtful in their approach to this structure, removing the turbinate only when it is felt that preservation would adversely affect their treatment strategy.

CONCLUSION

A better understanding of future expectations for endoscopic sinus surgery for CRS can be obtained by a more complete awareness of the history of this unique operative technique. The field of rhinology has experienced a rapid evolution, and this is certain to continue as basic science research unlocks some of the fundamental questions regarding the pathogenesis of CRS that remain. The evolution in surgical techniques will probably continue toward more minimally invasive surgical techniques, such as balloon dilation combined with anti-inflammatory topical therapies. Currently, FESS offers minimally invasive techniques for maximal surgical intervention within the nose, paranasal sinuses, and skull base. Since CRS is really a

syndrome of diseases, treatment in any one case needs to be carefully individualized, based in part on predisposing factors and environmental exposures. FESS will continue to evolve in concert with new scientific discoveries as the platform for surgical intervention and medical management of CRS.

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CHAPTER

Training for Sinonasal Surgery: Past, Present and Future

46

Rachel Kaye, Marc J Gibber, Marvin P Fried

INTRODUCTION

To properly understand the history of training techniques used for sinus surgery, it is imperative to first have a strong understanding of the history of treatment of sinus disorders. Up until the development of endoscopic equipment in the mid to late twentieth century, training techniques were limited due to the difficulty and danger posed by this very complex region. Because of this, training was largely based on the literature and description of procedures. Beyond this, there was little more than the "see one, do one, teach one" approach, which combined with cadaveric training when available, was the predominant form of training throughout the nineteenth and early twentieth century.

The beginning of modern endoscopy dates back the early twentieth century during which time endoscopic surgery was mostly restricted by the limitations of the endoscopes themselves; by their optical capacity (the Nitze system of a succession of glass lenses)[1] and illumination (mostly containing flame or electric bulbs). The rapid development and superior quality of endoscopy in the 1960s and 1970s (i.e. the Hopkins rod system[1] and Karl Storz angled endoscopes[2]) produced the culture and standardization of endoscopic sinus surgery (ESS) that is prevalent today. It also allowed for a much greater ability to teach sinonasal anatomy and procedures to trainees and students.

ENDOSCOPIC SINUS SURGERY

Endoscopic sinus surgery was first widely introduced in the 1970s to 1980s and has since been established as the standard of care for operative treatment of the sinuses and nasal cavity.[2–5] This technique provides the surgeon with excellent visualization, supplemented by an array of instruments that permit access to the depths of the sinuses, and to the base of the skull.

The use of computer-based image guidance systems adds to these capabilities by providing unprecedented navigational support to reach the pathology while delineating the surrounding anatomy that is not at pathologic risk. The applications of endoscopic procedures have expanded widely as safety and efficacy have been documented.[6–8] Tumor resection at the cranial base can be safe and effective. The growing application of the endoscopic approach to the pituitary for adenoma removal has diminished the morbidity and hastened the recovery of an expanding number of patients. It has also opened the technology to an entire specialty that previously had no exposure to the technique. Surgery of the orbit can be facilitated by improved optics (endoscopes) and anatomical depiction (navigation and tracking) of the critical anatomy.

Although the concept of ESS is quite straightforward, skillfully performing the procedure safely can be quite challenging.[9] The relevant anatomy is highly complex and compact, with the added concern of having critical structures such as the brain, orbital contents, and carotid artery closely juxtaposed and therefore at surgical risk.[10,11] Thus, the acquisition of surgical proficiency in ESS is of utmost importance not only because of the difficulty in manipulating the instruments and endoscopes but also because of the complicated anatomy with propensity for significant individual variation and the potential for disastrous complications. The advances made in the field of ESS

occurred due to multiple developments, including greater comprehension of anatomic structures, advanced endoscopic surgical techniques, precision endoscopes and cameras, CT and MRI guidance systems, and unique instrumentation, however complications still arise.[12,13]

The overall incidence of complications from ESS range from 4% to 17%[14] and the push is continuously toward improving patient safety. In addition, the surgeon must navigate and manipulate in this environment with both dominant and nondominant hands simultaneously, while coordinating movements indirectly with the aid of a television monitor. Well-developed hand-eye coordination is an obvious prerequisite. Emphasis is therefore placed on the quality and quantity of training that an endoscopic surgeon must have prior to his/her independent performance on any procedure.

NEED FOR TRAINING

Currently, training of residents in ESS is predicated on direct observation of procedures in the operating room. As residents progress in their training, they are given more of an active role in the operating room, ultimately becoming the major participant. The technical acumen required for basic ESS procedures is not achieved, for the most part, until the later half of a resident's training. The learning curve is significant with a decline in major complications with increased exposure and case volume.[15] Stankiewicz[16,17] was one of the first to describe a significant learning curve as he reported a sharp decline in his major and total complication rates when comparing his first 90 cases to his second series of 90 cases. His major complications (hemorrhage, CSF leak, and blindness) decreased from 5% in his first 90 cases to 0.7% in his subsequent 90 cases. Furthermore, his overall complication rate decreased from 29% to 2.2% when comparing these two series of patients. Similarly, Marks[18] reported his complication rates with his own first 393 cases and found a significant difference in minor complication (synechiae, ecchymosis, stenosis, epiphora) rates between the first and second half of his series (8.5% vs. 2.5%). With the increase in the complexity of microdissection equipment and the ever-increasing demand to broaden the indications of ESS, there is a real need to make residents more familiar with the technical skills of ESS at an earlier stage in training. This has necessitated the supplementation of skills training with video training tapes, cadaver or animal dissection, and simulators [ranging from low-fidelity to virtual reality (VR)]. It comes as no surprise that with the continued technological advancements of today; computer-assisted devices have already had significant success in augmenting the education and training of surgical residents in several fields.[19–22]

HOW TRAINING IS ASSESSED?

Surgical skills training should be predicated on standard and well-tested methods of instruction. However, in general, such a universal curriculum in surgery remains elusive. Cadavers have been used by some institutions to provide the first surgical experience for residents learning ESS. Stankiewicz has long been a proponent of a rigorous curriculum using cadaveric dissection prior to performing the first sinus surgery.[11] Furthermore, there have been efforts to validate the utility of training prior to performing ESS. Keerl reported that complications were reduced when surgeons underwent a multimedia learning program before performing sinus surgery, demonstrating that those surgeons who participated in the learning program had fewer dural and orbital complications.[23]

CADAVERS

Akin to temporal bone dissection, for which cadaveric courses have been successfully used, ESS is landmark based and thus a fundamental dynamic anatomical knowledge is essential.[24] Furthermore, cadaveric training offers a safe environment without risk to patient safety and a bloodless surgical field. The transition to training on cadavers was reliable and necessary as the new technology became available. Currently, training courses are a reputable part of otolaryngology head and neck surgical training.[25] The combination of proper training, cadaveric course participation, and supervision is considered to be a formula for the execution of safe surgical procedures by trainee.[26,27] In fact, a recent study reported that cadaveric sinus dissection improves both subjective and objective skills for all training levels,[14] while an international multicenter study found that such dissection courses are both well received and considered valuable by surgical trainees.[28] Sinus laboratory settings are well perceived by trainees and increase their comfort.[29] However, a significant drawback to cadaver training is the insufficient availability of specimens and high costs, curtailing the accessibility of cadaver training for all.[30]

TRAINING COURSES

Surgical skill courses are increasing in popularity in parallel with the movement of surgical education away from the traditional model of apprenticeship.[30] This progression has been, in part, driven by the field of endoscopic surgery. Conventional otolaryngology training programs are predicated on a finite number of procedural cases, which could produce haphazard and unpredictable learning.[30] The maintenance and acquisition of surgical skills requires repeat practice at regular intervals, something that may not be provided for in the standard clinical training. As such, supplementary training courses are in high demand and are looked for as a means to propel one's anatomical knowledge and surgical skills. Such workshops provide the trainee with opportunities to practice good techniques, eliminate poor technique, and receive timely feedback that further cements the training.[31] Training courses may introduce new skills or reinforce an acquired one. Courses have been standardized such that guidelines and recommendations exist.[30] The "ideal" course provides fixed learning objectives, senior faculty members, a combination of short presentations and technical skills stations, with further reinforcement often occurring in small peer groups. A recent international study showed that ESS dissection courses were both widely accepted and considered beneficial by the trainees. Furthermore, when participants were questioned about the best way of gaining anatomical knowledge, most (66%) considered ESS dissection courses as the primary way to obtain and also to improve their knowledge.[28] Furthermore, minimally invasive training was not found to inhibit adequate training.[31]

CREDENTIALING COMPETENCY IN RESIDENCY AND BEYOND

The Accreditation Council for Graduate Medical Education (ACGME) currently assesses residents through the use of case log numbers that are meant to be indicators of resident experience, but do not necessarily confer resident competence. Although the highest minimum number of key indicator procedures required lies within rhinology at 40 ethmoidectomies (as of 2013), simply completing a finite number of surgical procedures does not necessarily confirm competence especially when taking into account patient variability and the individual resident's learning curve. To that end, the ACGME has incorporated 16 milestones to be included in the Next Accreditation System annual program review, in effect July 1, 2014[32] The milestones identify target levels of competence, which for rhinology includes completing ESS procedures only with oversight (as apposed to guidance), and identification of "nasal endoscopic pathological findings in the previously operated patient.[33]" Thus, the ACGME has evolved to standardize a graduation requirement of not just experience, but also competency; this lends itself the interesting question of just how competency will be (and should be) evaluated.

In contrast to the direct oversight over otorhinolaryngology residency programs by the ACGME, there does not currently exist an authority or agency responsible for quality assurance in rhinology fellowships. With the increase of subspecialization within otolaryngology training, an additional year or multiple years of training in the field of rhinology and skull base surgery, beyond the standard residency training has become more popular. From the late 1940s through the first half of the 1950s a group of physicians led by Dr Maurice Cottle was instrumental in establishing the American Rhinological Society (ARS), which was a society dedicated to pathology, physiology, and aesthetic qualities of the nose.[34] The creation and subsequent work of the ARS created a home base for those focused on this anatomic region, and was instrumental in the further development of dedicated training in rhinology. As endoscopic techniques and abilities improved in the 1980s and 1990s, so too did the interest of otolaryngologists looking to focus primarily on this area. Individual year long fellowships started to be offered in the late 1980s; however, the application process only became formally organized in 2006 with a centralized match process under the auspices of the ARS.

As interest in this subspecialty continues to grow, the registered fellowship applicants and programs have also increased dramatically. However, to date the goals and educational experiences of rhinology fellows are not completely defined, and so an inherent disparity between different fellowship experiences is a very real hazard. In 2009, Tabaee et al. published the responses of the past 6 years of fellows to a survey to which 66% responded and overall showed a favorable response (graded on a Likert scale) when questioned whether the fellowship experience met stated goals and whether fellows felt comfortable performing rhinologic surgery. However, this study also highlighted the need for a continuous examination of the subspecialty training, given the inherent differences

between training programs and a lack of assessment of core competencies following training.[35] Later, a similar-minded survey was conducted under the purview of the American Rhinologic Society (ARS) that surveyed all fellowship graduates between 1990 and 2009 and corroborated many of the data from the previous study. They had a 55.4% response rate and found that the overall fellowship experience was rated positively in all respondents (on a Likert scale). They also found that the average number of rhinologic procedures performed during fellowship was more than 200 in 34 (58.6%), 151–200 in 16 (27.6%), 101–150 in 7 (12.1%), and less than 100 in 1 (1.7%) and that surgical caseload was deemed "just right" by 94.7% of respondents. However, this study did make note that case load alone is not an adequate assessment of quality education and called for further reviews and discussions toward a programmatic education within this fellowship.[36] As the future of credentialing continues to evolve, educators must decide what methods will best assess and address the competency of graduating residents and fellows, keeping in mind these methods should be well-studied and validated.

SIMULATOR TRAINING AND APPROXIMATING REAL SURGERY

Stricter regulations with regard to hands-on training has created combined with the technological revolution of the twenty-first century has brought about a new and exciting approach to medical education and training. Specifically, the ability to create highly realistic three-dimensional surgical simulators has opened a new avenue by which surgeons can be trained. High-fidelity virtual reality (VR) simulators have long had an impact on improving the skill level of military and commercial pilots, and they hold similar promise for the medical field. Based on the lessons from aviation training over the past three decades, computer-assisted devices have had significant success in augmenting the education and training of surgical residents in several fields.[19,37,38] VR simulation has already played an introductory role in the training of residents for laparoscopic, gastrointestinal, plastic, ophthalmologic, dermatologic, and urologic procedures.[39–45]

The field of otolaryngology has been at the forefront of simulator training specifically in the areas of temporal bone and ESS. Both low-fidelity and high-fidelity simulators have been proposed. One type of low-fidelity simulator was described by Wais et al. and involved

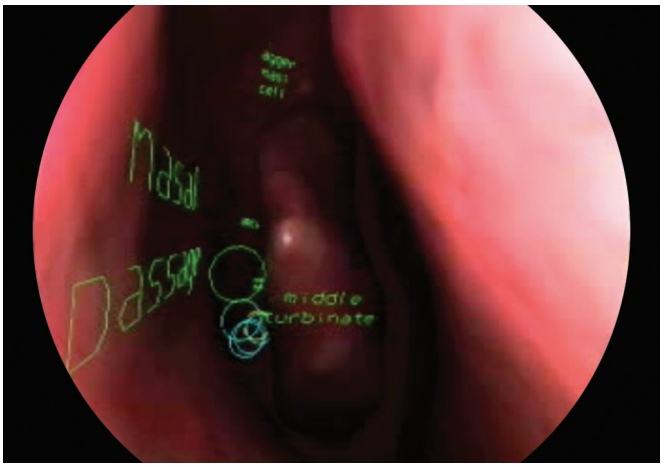

Fig. 46.1: Endoscopic view of ES3 during the navigation task showing targets (hoops for the trainee to navigate through) and virtual anatomy instruction, labeled nasal passage, middle turbinate, and agger nasi cell.

inexpensive and commercially available materials that set out to simulate navigation (through rings), tool localization (touching numbered stickers), and maxillary antrostomy (remove a foam square).[46] Although this is a very inexpensive model with ingenuity that could be easily reproduced, the simulated tasks and view do not replicate endoscopic sinus anatomy and the haptic feedback is limited by the material used and may not be similar to operative experience. Despite these setbacks, they were able to show that trainees were able to improve essential basic endoscopic sinus surgical skills when tested on a cadaveric model.[47] Although low-fidelity simulators are potentially more widely available (due to cost), they do not replicate the operating room experience with the visual cues and haptic feedback that exist within high-fidelity simulators; while endoscopic navigation can be taught well, combining anatomical knowledge and task dexterity to produce a surgical outcome may best be addressed by high-fidelity simulators.

The group led by Fried et al. conducted multiple studies using a simulator (ES3) created by Lockheed-Martin (Figs. 46.1 to 46.4). This particular simulator employed virtual anatomy and instruments, both visual and haptic (force) feedback, voice commands, phased instruction, and performance monitoring to create a virtual reality environment that can be potentially be utilized to teach otolaryngology residents.[48–51] The ES3 is a procedural simulator that trains and assesses the performance of an entire task (such as an ethmoidectomy, which requires complex endoscope navigation, ambidexterity, and surgical precision). Users of the ES3 perform ESS on a virtual

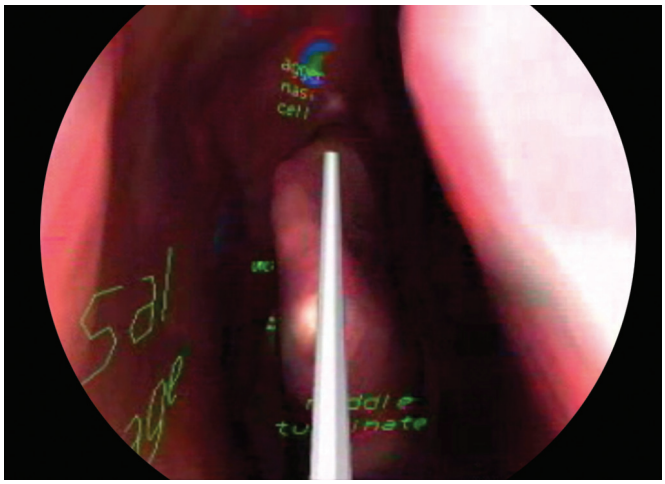

Fig. 46.2: Endoscopic view of ES3 during the injection task showing targets (bulls-eye target) for the trainee to inject with the virtual needle seen in the center of the screen. The virtual anatomy prompts are present, highlighting the nasal passage, middle turbinate, agger nasi cell, and the uncinate process.

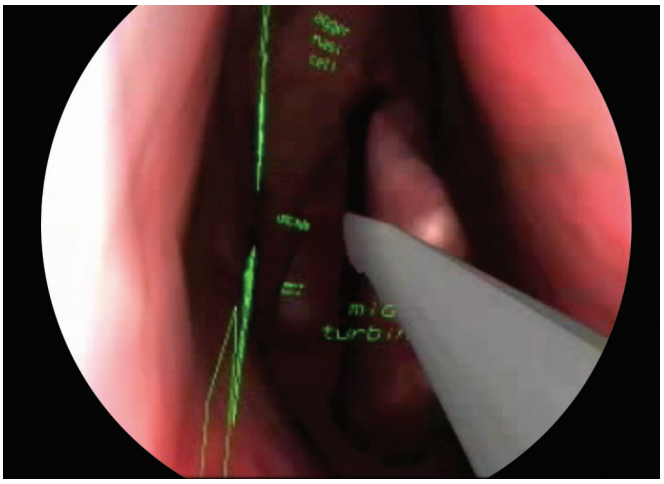

Fig. 46.3: Endoscopic view of ES3 during dissection task showing Freer tool used to medialize the middle turbinate. The simulator provides haptic feedback during real-time dissection tasks.

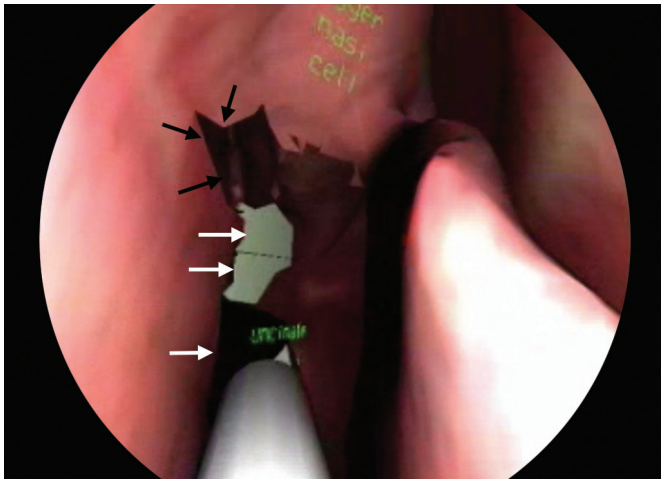

Fig. 46.4: Endoscopic view of ES3 during dissection task showing microdebrider tool used to remove the uncinate process. In addition to haptic feedback, the ES3 also provides for an accurate anatomical depiction of virtual surgery, here showing the resected tissue (black arrows) and bony spurs (white arrows).

Fig. 46.5: Operating room configuration of typical ESS at our institution. The surgical instructor (attending) coaches the trainee (resident) as the trainee uses an endoscope and operating tool while viewing the endoscopic screen.

patient with an interface consisting of a mannequin outfitted with a multipurpose tool and endoscope that closely resembles the operative experience (Figs. 46.5 and 46.6). The tool delivers haptic feedback to the user and the virtual instructor guides the user by stating mistakes, errors, and misses while the system records overall and task-specific completion scores for each performance in real time.

The road toward validation of a surgical simulator is an arduous one and can include face/content, discriminant, construct, concurrent, and predictive validity. The group led by Fried et al. was able to show that the ES3 provided a reliable assessment of factors that are important to the acquisition of minimally invasive surgical skills, demonstrating construct validity.[52] They were then able to complete the construct validity assessment of the ES3 by demonstrating its discriminant capabilities; the simulator established expert surgeon benchmark performance criteria and furthermore shows that the ES3 can consistently train novice subjects to attain that performance level.[53] The group was able to perform a study, which showed

Fig. 46.6: ES3 simulator showing the endoscope and multiuse tool within the mannequin, as well as the apparatus utilizing screen guidance in a similar fashion to the operating room.

simulator training improves resident technical skills so that each individual attains a proficiency level, despite the existence of an inherent range of individual abilities. This proficiency level translates to at least equal, if not superior, actual real-time operative performance compared with that of current conventional training and its associated finite repetition of live surgical procedures. This vital study was one of the first published that showed objective improvement in operating room performance by those that train on simulators.[54]

BARRIERS TO SIMULATOR ADOPTION

One of the main prerequisites of surgical simulators as a training tool is confirmed construct and predictive validity.[55] Validity studies must remain rigorous and with a large sample size in order to justify utilizing simulators during residency credentialing; this is often difficult to attain within subspecialties given the inherent small number of residents. Furthermore, although virtual reality and high-fidelity simulation has many diverse advantages, the major drawbacks are high cost and software development. This translates into a wide range of availability between training institutions. Low-fidelity simulators can also benefit anatomic and procedural knowledge while maintaining a wider availability; however, the anatomic knowledge and interface does not completely correlate with the visual and force feedback that one experiences during surgery. Despite their differences, both types of simulation seek to provide an alternative to early experience on live patients for novices in order to improve patient safety.

THE FUTURE OF SURGICAL SIMULATION

As the technology becomes cheaper and more accessible, simulation and virtual training will assume a larger role in the training arsenal especially in the fields of minimally invasive and endoscopic surgery. A required or suggested simulation-based training curriculum would possibly drive down costs due to increased demand and production. Simulation-training curricula are gaining interest, and in 2012, Zevin et al. demonstrated a consensus-based methodology to design and implement a simulation-based training curriculum with input from international surgeons that were considered experts in surgical education.[56] As we move toward standardizing these curricula, the process toward validation and implementation could be streamlined thereby increasing simulator accessibility throughout institutions.

The ACGME is now redefining how to assess surgical competency, especially in the new age of work-hour restrictions. This has already made an interesting turn of events within the field of general surgery, as the American Board of Surgery now requires the Fundamentals of Laparoscopic Surgery course (includes simulation exercises) for certification.[57] It is not unforeseeable that simulators could be used as a credentialing tool due to their potential to produce defined and validated metrics of technical performance that pose no risk to patient safety. Furthermore, several high-fidelity simulators (including the ES3) have the ability to load a patient's CT images, thereby creating an individualized virtual environment that fosters surgical planning for even the expert surgeon. This creates a virtual model of each individual patient and allows the surgeon to hone surgical technique to the unique anatomy presented by the patient. As we move more toward individualized medicine, surgical simulation is certainly a wonderful asset. As technology continues to evolve, surgical simulation will continue to gain a greater role in the training of rhinologic procedures.

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CHAPTER

47

Innovations in Optics and Instrumentation

Arjuna B Kuperan, Jean Anderson Eloy, Roy R Casiano

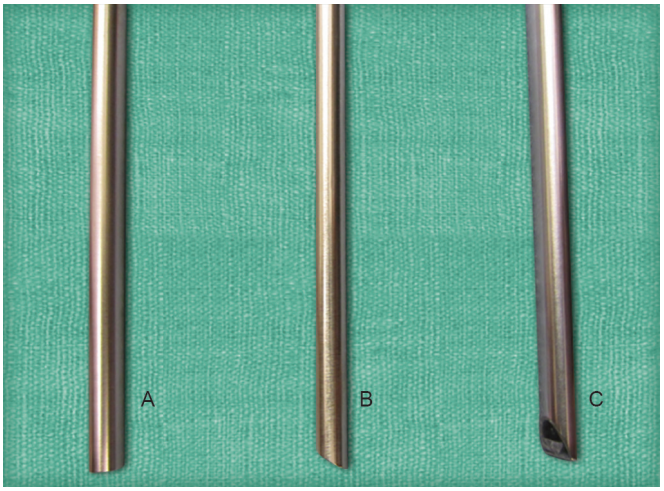
INTRODUCTION

The development of new instruments for use in the endoscopic management of sinus and skull base pathology has grown exponentially over the past few decades. From its inception, we have witnessed endoscopic sinus and skull base surgery (ESSBS) continually expand the limits of its domain due in part to the technologic advances the discipline has championed. This chapter serves to describe and analyze the current instrumentation, latest advances, and future developments in sinus and anterior skull base surgery.

OPTICS

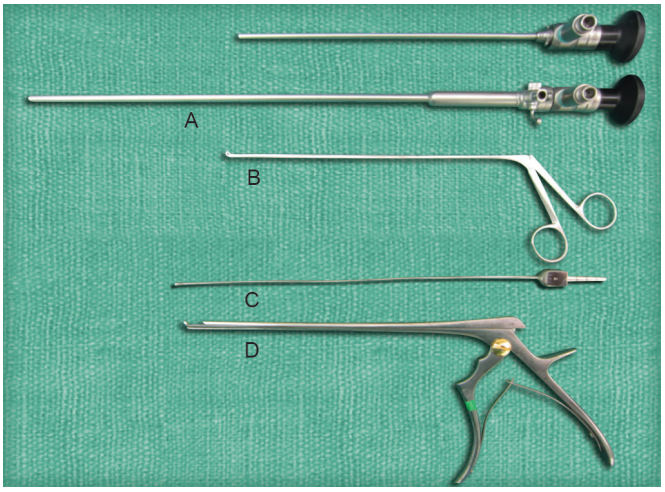
The rigid endoscope is the most essential element of ESSBS. It allows the surgeon to visualize with unparalleled clarity the surgical field and execute precise maneuvers. Historically, the first nasal endoscope was used by Hirschmann in 1901 to view the maxillary sinus through the oral cavity.[1] From this experience, the development and patenting of the rod lens system by Harold Hopkins led to a rigid endoscope with a much narrowed diameter as a result of using glass rods rather than lenses in the instrument shaft. Hopkins later joined with Karl Storz to develop endoscopes that incorporated the rod lens system with fiberoptic light transmission.[1,2] The Hopkins rod endoscope is the primary scope system in use today. The scopes vary from 2.7 to 4.0mm depending on pediatric or adult use, respectively.

The rigid endoscopes allow angled visualization based on the prism used in each device. Commonly used endoscopes are the 0-, 30-, and 70-degree telescopes (Figs. 47.1A to C), as well as the 45-degree telescope that is less commonly used. Traditionally, surgery was performed with direct visualization through the endoscope eyepiece. However, further technologic advances including the high-definition video camera adaptation, monitor, and recording devices have ushered in significant improvements (Fig. 47.2). First, viewing the image on the screen allows for manipulation of the image size without compromising clarity. In addition, the ability to teach and instruct residents and students is made much easier with use of the monitor. The ability to record high-definition videos and images has paved the way for creating high-quality surgical technique guides and publications that



Figs. 47.1A to C: The (A) 0-degree endoscope, (B) 30-degree endoscope, and (C) 70-degree endoscope are the three most commonly used for endoscopic sinus and skull base surgery.

Fig. 47.2: The endoscopic tower consists of a high-definition monitor, digital video and still photograph recorder, and light source.



Figs. 47.3A to D: (A) The extended length endoscope with irrigating sheath is seen in comparison to shorter sinus endoscope. (B) Cupped up-biting skull base forceps. (C) Long malleable PMT suction with graded control hole. (D) Up-biting Kerrisonrongeur.

continue to push the field forward. Lastly, the incorporation of the video camera with the endoscope allows the surgeon more distance from the patient thus improving his or her comfort that can make a significant difference especially in longer procedures.

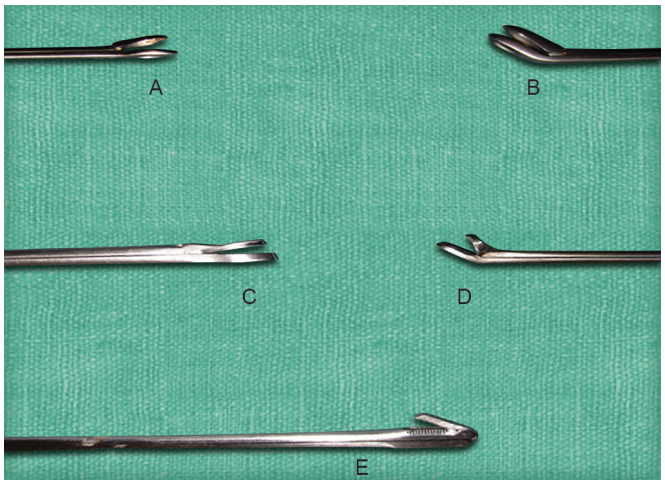
The 0-degree telescope allows for an excellent initial straight-on view of the surgical field. Structures that lie directly in its view include the septum, middle and inferior turbinates, ethmoid sinuses, and sphenoid sinus. It is more difficult to view around corners or peer into more obtusely positioned cavities like the maxillary, frontal, and lateral sphenoid recess. The major disadvantage of the 0-degree telescope is that it does not allow for a dynamic view of the surgical field; the view the endoscope provides is only changed by anterior or posterior and medial or lateral movement of the actual device.

The advantage of using angled telescopes like the 30- and 70-degree variants is that it allows for a dynamic view of the surgical field with rotation of the beveled lens allowing for greater visualization of the area of interest. For example, the maxillary sinus is better visualized with a 30- or 70-degree telescope by turning the bevel of the lens toward the cavity than it can be by using a 0-degree telescope from a similar vantage point. Furthermore, endoscopic approaches to the frontal sinus and anterior skull base must be done with an angled endoscope, preferably the 45- and 70-degree endoscope, because they allow for optimal visualization of these areas. Placing the endoscope below the instrument allows the surgeon to see the surgical field clearly while avoiding instrument contact interference or "fencing."

One challenging aspect of ESSBS is keeping the lens of the endoscope, which is the key to visualization, clean. Blood and other debris can contaminate the lens and obscure the image. Aside from routine removal of the endoscope from the nasal cavity for cleaning, there are sheaths available that irrigate the lens via a foot pedal (Figs. 47.3A to D). These devices obviate the need for manual cleaning and disruption of the endoscopic view. The sheaths are variable in different sizes and can add significant circumference to the endoscope making manipulation, especially with other instruments, more cumbersome. The irrigation from the device can also obscure the surgical field requiring suctioning for removal; for the single surgeon operating this may be an impediment. However, they can be particularly useful in three- or four-handed technique endoscopic skull base procedures where one surgeon is using two hands and can suction the irrigation run-off.

Usually the light source input is located 180-degree from the beveled lens surface; however, there are endoscopes available where the light input is on the same side. This is of benefit in endoscopic skull base surgery (ESBS) with three and fourhanded techniques in which the light cable is physically limiting. Rigid endoscopes with a rotatable lens are available that allow visualization from 0- to 90-degrees with the same device; the only negative aspect to these instruments is the decrease in clarity and light transmission resulting from the rotating lens design.

The endoscopes used in ESBS (Fig. 47.3A to D) are longer than those used in traditional endoscopic sinus



Figs. 47.4A to E: The Blakesley forceps are either straight (A) or up-biting (B). The through-cut forceps are either straight (C) or up-biting (D). The back-biting through-cut (E) can be rotated to achieve the desired direction.

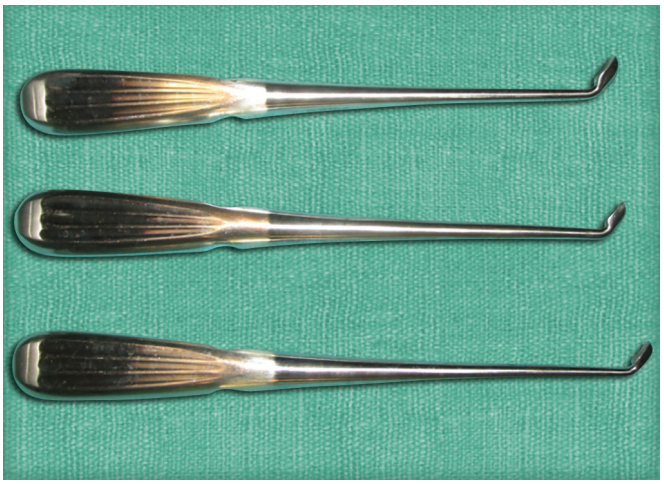


Fig. 47.5: The cervical spine curettes come in different sizes and can be used to remove the bone of the nasofrontal beak or sphenoid rostrum, in lieu of a drill.

surgery (ESS). These endoscopes are usually fitted with an irrigating sheath attachment to lessen the need for withdrawal of the scope for cleaning, especially when using high-speed drills. In addition the longer endoscope allows the camera head, and camera holder's hand, to be a greater distance from the region of instrument access. This added space allows for increased maneuverability when using three and fourhanded techniques.

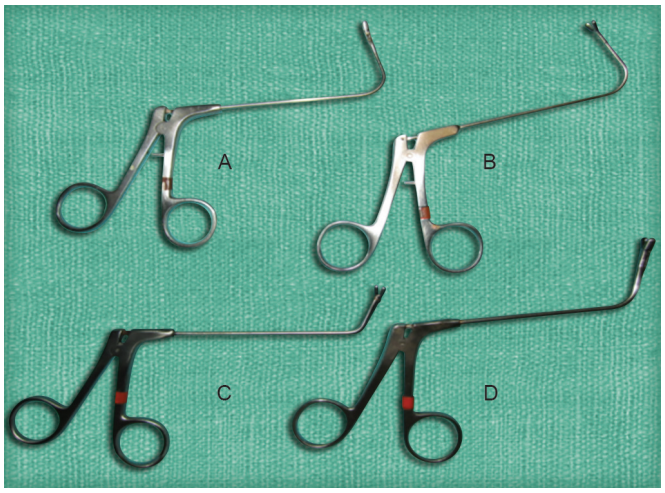
COLD STEEL INSTRUMENTATION

The workhorses of ESS include the through-cut and non-cutting forceps (Figs. 47.4A to E). The non-cutting forceps are available in different sizes and angles including 0-, 45-, and 90-degree. The non-cutting instruments are primarily used for removing already loose or detached fragments of tissue. These can inadvertently strip or tear mucosa and must be used with caution with adherent tissue. The through-cut forceps are available in straight and 45-degree versions, as well as a 90-degree punch. These are available in different orientations like the down-biting, side-biting, and back-biting variants as well as a single multi-purpose instrument in which the head can be rotated to achieve the desired positions. Through-cutting forceps and punches are best used to sharply and precisely cut mucosa, cartilage, or bone resulting in minimal mucosal stripping.

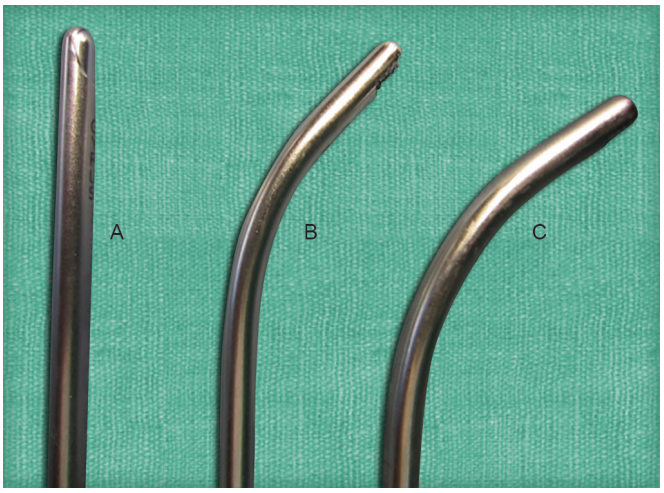
Further traditional instruments for endoscopic, endonasal surgery include elevators and probes. Cottle and Freer elevators are certainly not unique to endoscopic endonasal surgery and were in use long before the advent of the rigid endoscope. The improved visualization with the endoscope, especially posteriorly in the nasal cavity, allows for the more efficacious use of the Cottle and Freer elevators when performing a septoplasty for surgical access or septal deviation. The ball tip probes include the maxillary and frontal sinus seekers. Probes are essential tools of sinus surgery as they allow for gentle identification of sinus ostia with minimal risk of iatrogenic trauma.

Various curettes may be used in order to remove bone of the frontal sinus ostium as well as the thick bone of the sphenoid rostrum. Frontal sinus curettes with an acute angle curvature are useful in exposing the frontal recess and removing suprabullar or agger nasi cells. Cervical spine curettes prove very useful in extended frontal sinus procedures when removing the nasofrontal beak, in lieu of a high-speed drill, where there is osteoneogenic bone (Fig. 47.5). The cervical spine curettes cause less trauma to the bone and may result in decreased frontal sinus stenosis from less osteogenic bone formation. Care must be taken to avoid upward and posterior movements with the curette to avoid inadvertent skull base penetration.

Due to the superior and anterior location of the frontal sinus, and its close proximity to the skull base, delicate giraffe instruments were developed (Figs. 47.6A to D). These noncutting forceps allow for removal of soft tissue and loose bone fragments along the frontal sinus outflow tract and anterior skull base. A through-cutting giraffe also exists for fine bony and mucosal cuts and is paramount in preventing postsurgical frontal recess or ostium stenosis. The instruments open in a side-to-side or front-to-back fashion depending on the orientation of the tissue being



Figs. 47.6A to D: The giraffe forceps come in a vertical side-to-side or front-to-back opening (A and B), as well as a horizontal front-to-back and side-to-side variants (C and D).



Figs. 47.7A to C: The straight (A), curved 40-degree (B), and curved 60-degree (C) microdebriders are used to efficiently suction and microdebride soft tissue and bone.

removed. The cup can be 2 or 3 mm and the angle of the instrument ranges from 45- to 110-degree.

The ESBS instruments are generally longer than those used in ESS (Figs. 47.3A to D). The instruments much reach to the skull base and beyond for intracranial dissection. The suction is longer with a graded control hole allowing for greater variability in vacuum forces. The instruments are also smaller at the tip allowing for finer and gentle grasping of tissues. The Kerrison Rongeur is also a useful instrument for removal of bone at the skull base, particularly the sella turcica of the sphenoid sinus. Finally, adaptation of neurosurgical microinstruments additionally allows for soft tissue dissection within the intracranial cavity

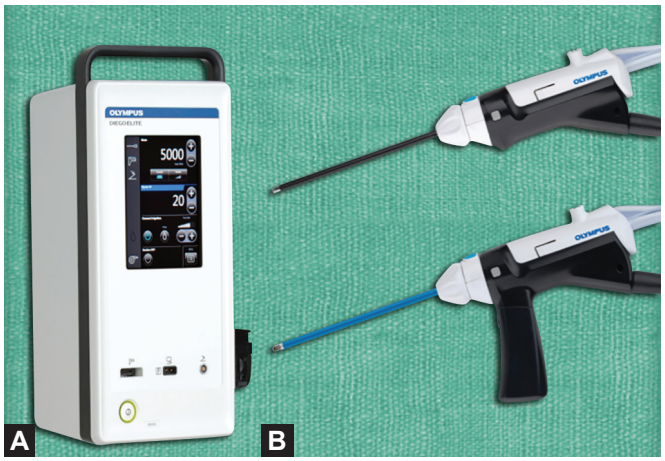
POWERED INSTRUMENTATION

The powered microdebrider, or tissue shaver, is a cornerstone of ESS. Its first endonasal use was documented in 1993 by Setliff and Parsons.[3] Since this initial description, the instrument has continued to gain popularity and notoriety among endoscopic sinus surgeons. The success of this instrument, and the expansion of endoscopic surgery to include the anterior skull base, prompted the development of irrigating drills for removing bone. The microdebriders and drills can be used in conjunction with the same hand piece that allows for rotation of the instrument head. The recent advent of the bipolar cautery function to the microdebrider tip also allows for controlled coagulation without changing instruments. There is much less diffuse thermal injury compared to the monopolar cautery and it is much safer to brain parenchyma if controlling bleeding at the skull base.

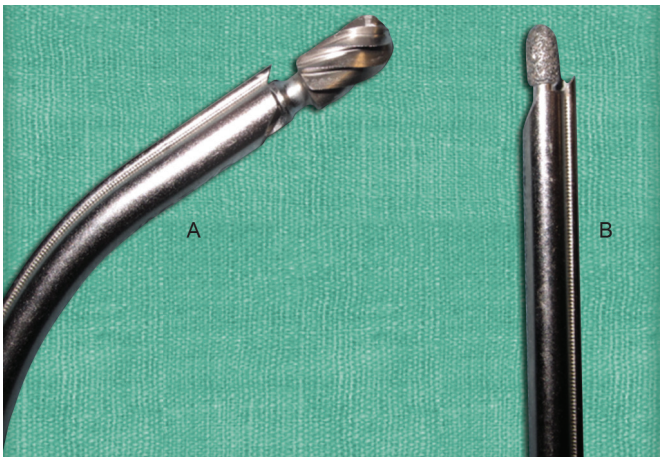
The microdebrider works by suctioning tissue into the tip of the instrument's shaft while a rotating serrated blade cuts the tissue. Different disposable cutting blades are available based on individual companies that make the microdebriders, including aggressive blades that more easily cut bone. A straight microdebrider blade is the mainstay for ethmoid and sphenoid sinus surgery, as well as inferior and middle turbinate surgery. The curved microdebrider is available in 15-, 30-, 40-, 60-, 75-, 90-, and 110-degree (Figs. 47.7A to C). The 60-degree blade is most commonly used for the maxillary sinus, frontal sinus, and exposing and preserving the mucosa of the fovea ethmoidalis, although other curvatures may be used as needed.

A new product called the Diego Elite (Olympus Gyrus ACMI, Southborough, MA) is a fusion of the microdebrider and either the suction monopolar or bipolar cautery (Figs. 47.8A and B). This device is likely to significantly reduce operative time because it negates the need to switch instruments for cauterization, which over the course of a long case, can be substantial. In addition, because the device can seamlessly cauterize, it may result in a less bloody operative field. The instrument is available in straight and various angled microdebrider attachments with the serrated and aggressive blades. The Diego Elite is poised to be a practical and efficacious addition to the ESSBS armamentarium.

A major advantage of the instrument is its ability to suction blood and debris from the surgical field and is



Figs. 47.8A and B: The Diego Elite (Olympus Gyrus ACMI, Southborough, MA) with the console and both the (A) microdebrider/monopolar and (B) microdebrider/bipolar instruments.



Figs. 47.9A and B: The 60-degree curved irrigating cutting barrel-burr (A) and the straight diamond irrigating bullet burr (B) are two examples of drill attachments that are used to remove bone of the nasal cavity and skull base.

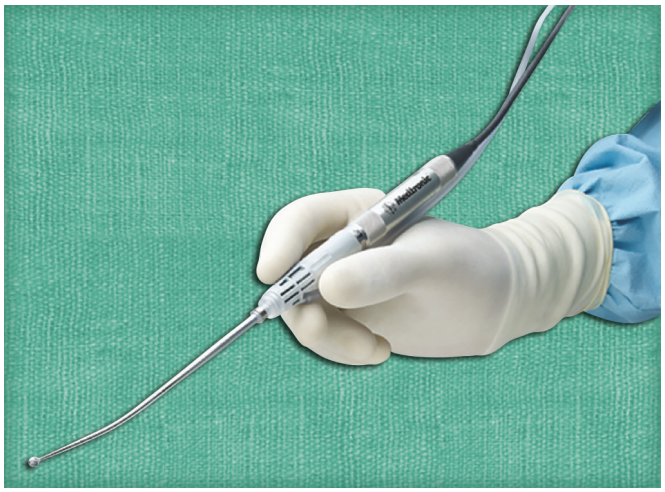
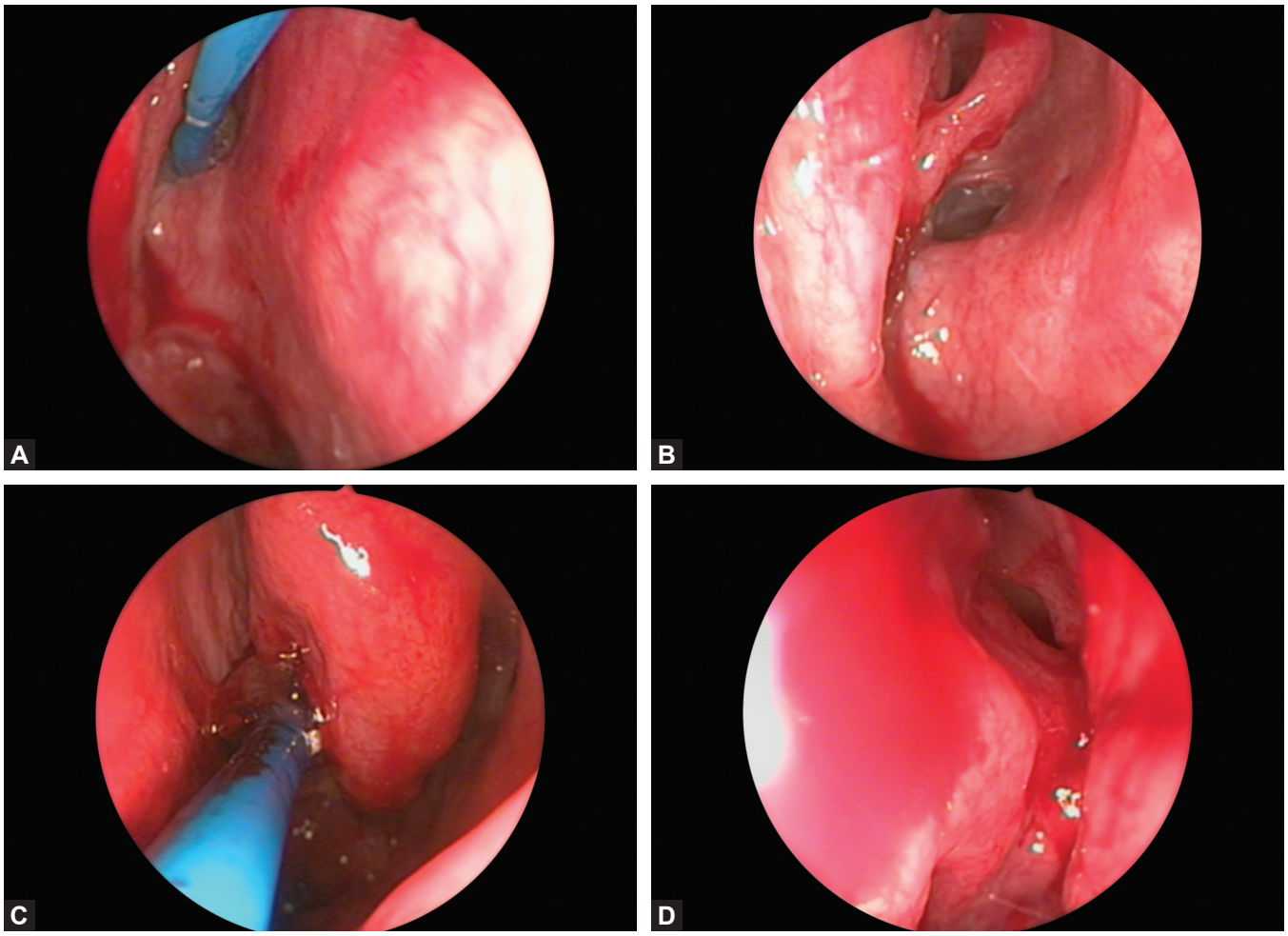


Fig. 47.10: The Medtronic Stylus (Medtronic, Jacksonville, FL) transnasal skull base drill with protected shaft and angled irrigating burr.

particularly advantageous to the endoscopic surgeon with only one free hand for instrumentation. The shaft of the instrument varies from 2 to 4 mm; the wider the shaft the less likely the instrument is to clog and require manual cleaning, ultimately prolonging operative time. Maintenance of strong suction and a sock in the suction canister to collect the shaved tissue contents is critical for cutting efficacy and pathologic analysis, respectively. The only significant negative attribute to this instrument is the rapidity of its action and the catastrophic damage that can occur in seconds. Detailed knowledge of the anatomy and preoperative review of the computed tomography (CT) scan is crucial to avoid iatrogenic injury to the skull base, orbit, and nondiseased mucosa. Cold steel instrumentation is slower at tissue removal but the risk of significant iatrogenic injury is lower; regardless of instrument choice, there is no substituting knowledge of technique and surgical landmarks.

Irrigating and suctioning drill attachments were developed for the removal of dense bone during endoscopic sinus and skull base procedures. Some applications include, but are not limited to, drilling the nasofrontal beak during a Draf III frontal sinusotomy, removal of the sphenoid rostrum, resection of the anterior skull base, dacryocystorhinostomy (DCR), and choanal atresia repair. Various irrigating shaped bits in cutting and diamond forms at angles from 0- to 70-degree are available including the barrel, shielded barrel, ball, bullet, taper, and DCR burrs (Figs. 47.9A and B). The location of drilling dictates the burr selection; e.g. a shielded barrel burr is excellent for removing the nasofrontal beak because it decreases the circumferential damage to the frontal sinus ostium that may result in osteoneogenic bone formation.

During ESBS a high-speed drill proves useful for efficient and controlled removal of bone. The drill attachments for the microdebrider system are excellent, but the revolutions per minute (RPM) do not exceed 15,000. The high-speed drill, in contrast, can attain RPM up to 60,000. The Medtronic Stylus (Medtronic, Jacksonville, FL) skull base drill has a long protective sheath and an irrigating angled tip with diamond and cutting burr attachments (Fig. 47.10). This instrument allows access to the clivus



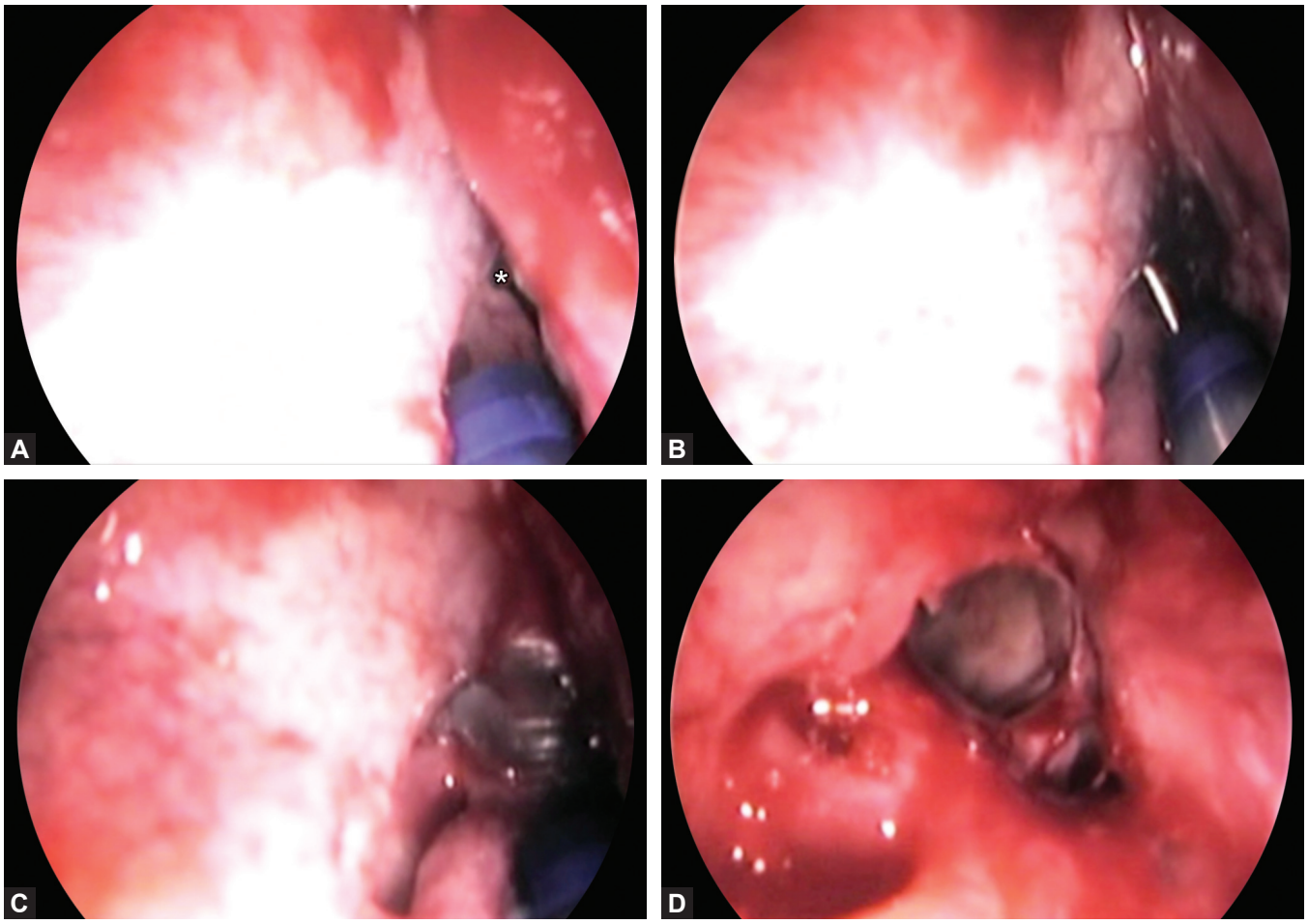
Figs. 47.11A to D: (A) The right sphenoid before dilation and (B) after dilation. (C) The left sphenoid before dilation and (D) after dilation.

and upper cervical spine, in addition to more traditional uses at the fovea ethmoidalis, planum sphenoidale, and sphenoid rostrum.

BALLOON SINUS DILATION

Lanza described the first balloon dilation of the frontal sinus in 1993 with the use of Fogarty catheters in post-functional endoscopic sinus surgery (FESS) patients to achieve temporary opening of the frontal sinus outflow tract.[4] The first sinus balloon catheter was approved by the FDA in 2005. Since then numerous studies have shown its efficacy in maintaining ostium patency and safety of the device in the short term and 2-year follow-up, with level 4 evidence consisting mostly of retrospective reviews.[5-8] However, the indications for when balloon sinus dilation is appropriate and its outcomes compared to traditional FESS are less clear.

The device is used to open the maxillary, sphenoid, and frontal sinuses. The mechanism of the balloon sinus catheter is different from previously designed devices for the coronary artery, e.g. in that it is semirigid and noncompliant and therefore is able to expand bony and soft tissue openings. The device consists of an introducer, guide wire, a catheter balloon, a pump, a pressure gauge (manometer), and a lavage catheter. The primary technique for using the device is the Seldinger technique that involves identification of the sinus ostium, cannulation with a guide wire, and passage of the balloon over it into the sinus with saline inflation. In this example, the right and left sphenoid sinuses are identified, cannulated, and opened with the saline filled balloon catheter (Figs. 47.11A to D). Another example shows the right frontal sinus outflow tract identified, cannulated, and opened with the balloon catheter (Figs. 47.12A to D). The sinus can be redilated as needed to achieve the desired opening.



Figs. 47.12A to D: (A) The right frontal recess denoted by the asterisk is cannulated with the guidewire (B) and then dilated with the saline filled balloon (C). The end result is a widely patent frontal sinus ostium and outflow tract (D).

Balloon sinus dilation was first introduced as a procedure to be done in the operating room as a primary surgery for sinus obstruction. The impetus for their popularity was due in part to maximal mucosal preservation since the device could open the sinus with minimal adjacent trauma. It has since evolved into use in the office for initial surgery or for revision dilations of stenotic ostia under only local anesthetic agents.[9] With the growing applicability and familiarity with balloon devices, their popularity has grown among sinus surgeons. However, despite their continued utilization there are few prospective studies to compare their efficacy with that of traditional FESS. A prospective randomized study by Plaza et al. compared Draf 1 frontal sinusotomy to balloon dilation with hybrid FESS (traditional ethmoidectomy with balloon dilation of the frontal sinus outflow tract). Visual analog scores, rhinosinusitis disability index scores, Lund–McKay scores, and olfactory thresholds were statistically improved in both groups. Lund-McKay scores for the frontal sinus were improved with statistical significance to nearly the same score in both groups. Frontal sinus patency and resolution of disease were marginally better in the balloon group though not statistically significant. The study, in the end, did not have sufficient data to prove equivalency between balloon dilation of the frontal sinus and Draf 1 sinusotomy.[10]

Balloon sinuplasty is a useful adjunct in the management of chronic rhinosinusitis (CRS). More prospective studies with randomization must be performed in order to truly assess its comparative utility with FESS. Clearly, patients with osteogenesis, significant polyposis, and high Lund-McKay scores are poor candidates for balloon procedures. As the data on balloon dilation grows so will our understanding of its most appropriate applications to CRS.

STENTS

Stents are most commonly used for the frontal sinus and more recently the ethmoid sinus cavity. Use of sinus stents dates back to 1905 when Ingals used a gold tube to maintain the patency of the frontal sinus.[11] Since then, different materials were used to similar ends with variable results. In a landmark animal model study by Neel et al., it was found that firm tubing caused increased osteoblastic activity and scar formation as compared to softer materials.[12] This discovery propelled stent development strongly in the direction of softer materials.

Stent placement in the frontal sinus may prevent stenosis by maintaining the patency of the outflow tract while allowing mucosal regeneration in cases where it has been stripped due to osteitic bone formation or tumor burden.[11] There are no strict indications for stent placement, but relative indications include stenosis after surgery, circumferential bone exposure, neo-ostium less than 5 mm, trauma to the outflow tract, and lateralization of the middle turbinate. In a study by Hoseman et al. they found the postoperative stenosis rate with a neo-ostium greater than 5 mm was 16% versus 33% with the same opening less than 5 mm.[13] The duration of stent placement remains controversial with studies recommending placement anywhere from 1 week to 5 years in cases of refractory chronic frontal sinusitis[14,15] Most commonly stents are used for weeks to months. It is important to note that bacterial biofilms were found on stents removed 1–4 weeks after surgery, although the prognostic significance of this is unclear.[16]

A variety of stent materials are described in the literature like rubber, gold, Silastic, and Dacron.[17] Some stents are dilated at one end to avoid extrusion from the sinus cavity rather than requiring suturing to stay in place. The newest developments include drug-eluting stents that administer steroids into the stented sinus cavity. A spacer stent with a reservoir to slowly disperse steroids topically exists for the frontal and ethmoid sinuses; however, the device is only FDA approved for administering saline despite initially promising results with triamcinolone.[18] Most recently, in 2012 the FDA approved the first drug-eluting nasal stent called the Propel stent (Intersect ENT, Menlo Park CA). It is a frontal sinus and ethmoid cavity expanding copolymer bioabsorbable mometasone furoate-releasing stent (Fig. 47.13). It releases 370 μg of the steroid locally for 30 days and then resorbs without requiring removal. Several large studies have proven the safety and efficacy of this stent and shown significant reductions in polyposis, adhesions, postoperative inflammation, and the need for postoperative oral steroids.[19-22]

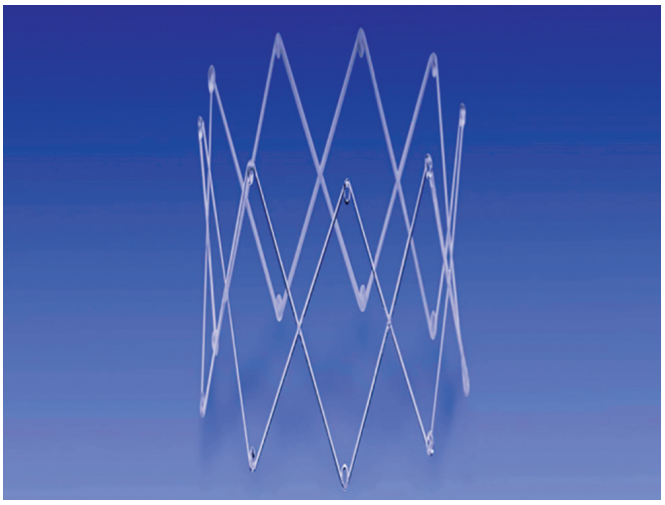


Fig. 47.13: The Propel nasal stent (Intersect ENT, Menlo Park, CA) is shown with small steroid-eluting reservoirs at the apex of each individual rhomboid.

The stent debate is far from over and will continue to evolve as further studies document the long-term efficacy and safety of these devices. Most rhinologists would agree that routine surveillance of stented sinus cavities is critical to maintain device position and functionality. In the interim, the decision to use structural or drug-eluting stents remains at the surgeon's discretion as there are currently no definitive indications or contraindications to their use.

THREE-DIMENSIONAL ENDOSCOPY

Most otolaryngologic and neurosurgical procedures are done with a three-dimensional (3D) view either with the unaided eyes or the microscope. ESS and ESBS have traditionally been limited by a monocular view. Surgeons, therefore, must rely on haptic feedback, monocular visual cues, and knowledge of the anatomy. The key limitation of high-definition two-dimensional (2D) endoscopy is the lack of depth perception as defined by vertical disparities, convergence, and stereopsis. Obtaining separate views from different angles allows the visual cortex to superimpose the images and create stereopsis, or a 3D picture. Until the advent of the latest 3D endoscopy technology images were of poor resolution and often caused the user to experience eye fatigue in addition to nausea or headaches. The newest generation of 3D stereoendoscopes utilizes a microscopic

array of video lenses, like an arthropod's compound eye, to generate multiple images that are processed into a 3D image on a stereoscopic monitor and viewed with polarized glasses. [23]

This new 3D stereoendoscope technology developed by Visionsense Ltd. (Orangeburg, NY) has spawned a rebirth in enthusiasm for its use in ESSBS. Numerous studies from cadaveric comparative dissections between 2D and 3D endoscopy to prospective randomized trials have validated the improved spatial representation with 3D images. No otolaryngology or neurosurgery studies have shown a decrease in operative time, complications, or length of hospital stay with 3D stereoendoscopy.[24-28] Some limitations of the 3D technology include a reduced field of view up to a 52% reduction as determined in a controlled lab setting.[29] Furthermore, image sharpness is more significantly affected by minimal lens debris along with insufficient light in tight nasal passages and central darkness. The adverse user side effects like nausea, headaches, and eye fatigue were not experienced in any of the studies highlighting a significant improvement from the older technology.[26,27,30]

Based on current trends in the literature, it is clear that use of 3D endoscopy is preferential toward ESBS. Only one noncadaveric study used the 3D technology for ESS and this was in select more complex cases.[26] As 3D endoscopy gains popularity, more studies will continue to explore if it improves patient outcomes assessed by various measures. Improvements in this new video lens array will also continue to improve image quality, especially with angled endoscopes, and further expand its utility.

ROBOTIC SKULL BASE SURGERY

The only FDA-approved robotic system for otolaryngology is the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA). The use of this device is well documented in head and neck surgery for transoral robotic surgery (TORS) as well as transaxillary robotic surgery for thyroid and parathyroid disorders.[31-33] The da Vinci robot has not been used clinically for strictly transnasal sinus or skull base surgery largely due to the limitations the system has with providing access through the narrow nasal corridor.

In 2007, Hanna et al. described a transantral use of the da Vinci robot to access the sella turcica, planum sphenoidale, and cribriform plate through bilateral superior vestibular incisions in cadavers. This approach provided good access but presented the added morbidity of transmaxillary dissection.[34] TORS for skull base tumors was later described in cadaveric studies for resection of lower and middle clivus lesions, as well as the infratemporal fossa (ITF).[35] Difficulty accessing structures cephalad to the hard palate was circumvented in cadaveric studies by both cervical–transoral robotic surgery (C-TORS) that includes the addition of transcervical ports lateral to the submandibular gland, as well as suprahyoid transcervical ports for access to the ITF.[36,37] A cadaveric study proved an invasive posterior hard palate resection with TORS allows for transnasal or transoral placement of the endoscope with transoral instrumentation and exposure of the skull base from the crista galli to C1.[38] Further studies combined use of the extended endonasal approach(EEA) with TORS to achieve resection of a clival chordoma and an adenoid cystic carcinoma extending from the nasopharynx into the clivus and ITF. The endoscopic approach was performed first for exposure superior to the eustachian tube, and the soft palate was then retracted superiorly with a rubber catheter to facilitate TORS gross total resection.[39]

At present, there is still no strict TORS due in part to the limitations of the robotic arm size and instrument attachments for the da Vinci system. One critical limitation is the lack of a robotic drill instrument for bony resection of the skull base. There are currently several robotic prototypes in design specifically for endonasal use; however, they are still in development.[40,41] Some of these prototypes are trying specifically to include either optical or electromagnetic navigation that the current robotic system does not afford. Designing a system that is applicable entirely through the nose would be a major step forward in robotic sinus and skull base surgery. Furthermore, the development of haptic feedback technology is particularly paramount when operating near the critical neurovascular structures at the skull base interface.

CONCLUSION

ESBS has experienced tremendous growth and development over the past 30 years due to significant contributions from pioneers in the field. Since the development of the rod lens system, one technological advancement after another has continually kept the field on the cutting edge. Further studies must be conducted to fully validate the efficacy of the tools we use like balloon sinus catheters and nasal stents to ensure that patients continue to receive the best possible surgical and medical treatments for their specific pathology. With new advances like 3D endoscopy and robotic surgery, there must be a systematic methodology to determine if the new technology truly provides superior treatment before

mainstream adaptation ensues. Amidst the changing landscape of ESBS, there is one constant; a fundamental and dynamic understanding of the anatomy is the key to unlock the potential of the field's constant innovations.

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CHAPTER

48

Surgical Radiology and Image Guidance Surgery

Jeremiah A Alt, Richard R Orlandi

INTRODUCTION

Radiological imaging is paramount in performing safe endoscopic sinus surgery (ESS); therefore, mastery in ordering appropriate imaging to assess disease processes and reading radiographic studies with its corresponding anatomy is a prerequisite for the sinus surgeon. Studying and analyzing preoperative imaging arms the surgeon with the anatomical knowledge to successfully navigate the nasal cavity and paranasal sinuses, reducing the risk of potential catastrophic complications. Following key anatomical landmarks in a thoughtful, careful, and precise manner can significantly reduce complications. However, minor and major complications can and still do occur due to various factors including anatomical variants, altered anatomy due to previous surgery, severe polyposis, and decreased visibility from bleeding. In these instances, image guidance has become more widely used. Nonetheless, the surgeons' familiarity with each patient's unique anatomy and pathology, gleaned from preoperative imaging, may be one of the most important variables in reducing the risk associated with ESS and will be discussed herein.

IMAGING IN SINONASAL PATHOLOGY: IMAGING MODALITIES

Standard Roentgenographs (Plain Film Radiography)

Röntgen discovered the X-ray over 100 years ago. His contribution advanced the fields of both physics and medicine, and was awarded the Nobel Prize. Since the initial discovery, the X-ray has been widely used in medicine. The X-ray was particularly well adapted and successfully used in the evaluation of the maxillofacial skeleton. The four standard views used to display sinonasal anatomy are the Waters' view, Towne's view, lateral view, and submentovertex views. These views are adequate in displaying the maxillary sinus, a general outline of the frontal sinus, and views of the mid-sagittal sphenoid sinus. However, these views are inadequate at visualizing the inferior third of the frontal sinus, ethmoid skull base, and posterior ethmoid sinuses. In addition, inflammatory disease, polyposis, and anatomic variations are inadequately assessed with the X-ray. In summary, although plain films have been used in the past to assess sinonasal anatomy, this modality inadequately assesses the anatomical complexities needed for modern ESS.

Computed Tomography

The advent of high-resolution thin-cut multiplanar computed tomography (CT) has dramatically improved the assessment of the complex detail of the sinonasal anatomy. Traditional imaging in the axial and coronal planes was a dramatic improvement over X-ray-based plain films. However, anatomic relationships especially within the frontal recess and skull base were not always definitive despite these multiplanar views. The advent of tri-planar imaging with the inclusion of the sagittal plane allowed detailed radiologic assessment of the frontal recess.[1-4] For these reasons, plain films and multiplanar imaging have largely been replaced by tri-planar CT imaging due to the improved bony detail and discrimination. Of the three

views, the coronal images can be considered the most useful for surgical planning as they closely resemble the surgeons' endoscopic surgical view. However, certain aspects of sinonasal anatomy are ideally visualized with axial and sagittal images. Contrast is usually not needed for inflammatory sinonasal disease. New low-dose CTs may be advantageous to reduce radiation exposure.[5] Ultimately, tri-planar CT imaging is a critical tool for the sinus surgeon to obtain, as it designates and represents a roadmap for safe ESS.

Magnetic Resonance

As the boundaries of endoscopic sinonasal surgery have progressed, magnetic resonance imaging (MRI) has increasingly become more important in assessing patients with sinonasal neoplasms, aggressive inflammatory conditions, and intracranial processes. Tri-planar MRI imaging provides the radiologist and surgeon with detailed anatomic information by differentiating proteinaceous fluid from solid material. When evaluating the skull base, the MRI is particularly useful as it can differentiate between scar tissue, mucoceles, encephaloceles, trapped secretions, or sinonasal neoplasms. MRI has also been deemed more useful in characterizing aggressive lesions and evaluating perineural spread.

IMAGING IN INFLAMMATORY DISEASE

Sinusitis

Historically, plain films were the mainstay of diagnosing and evaluating the sinusitis following failure of medical management. Plain films are unable to show detailed bony anatomy and inflammatory pattern in detail due to overlapping of structures and lack of resolution, making the evaluation of key areas including the ostiomeatal complex, ethmoid sinuses, middle meatus, and sphenoid sinus somewhat limited. It is now common that all uncomplicated sinusitis is evaluated with a CT scan.

To eliminate the effects of reversible mucosal thickening, patients undergoing CT for evaluation of chronic sinus disease are best-scanned 4–6 weeks after medical therapy and not during an acute infection. Although the MRI has a rather limited role in evaluating uncomplicated sinusitis, it has a significant potential in evaluating complicated sinusitis including patients with meningitis, thrombophlebitis, subdural empyemas, intracranial, or intraorbital abscesses.

Mucoceles

The CT scan excels in assessing mucoceles, allowing assessment of bony remodeling and dehiscence. MRI can be complicated with variable signal intensity, such that the T1 and T2 signals may be hyperintense or hypointense depending on the level of desiccation. One caveat to this is the utility of MRI in distinguishing intracranial and intraorbital structures from the mucocele. A mucopyocele (infected mucocele), on the other hand, can be delineated by a contrast-enhanced MRI that typically demonstrates enhancement.

SINONASAL NEOPLASMS

The CT and MRI complement each other when evaluating sinonasal neoplasms. The CT is more sensitive in defining the bony confines and boundaries evident by surrounding osseous destruction, and is particularly useful at the skull base and/or orbital walls. MRI, on the other hand, offers improved soft tissue detail with improved sensitivity in evaluating extra-sinus extension. Extra-sinus extension dictates downstream management, thereby, determining, e.g. if the neoplasm can be resected endoscopically. Differentiation between inflammatory changes and the neoplastic mass is also facilitated by MRI. Our intent is not to review imaging modalities for every sinonasal neoplasm. We present a selected list of the most common, or those neoplasms with unique imaging characteristics.

BENIGN SINONASAL NEOPLASMS

Fibro-osseous Lesions

Fibro-osseous lesions such as fibrous dysplasia, osteomas, aneurysmal bone cysts, and osteoblastoma of the sinonasal structures are best characterized with CT imaging, as it defines the exact extent of the lesion. The proportion of both the osseous and fibrous component of the disease will dictate its appearance on imaging, such that the fibrous components appear more radiolucent, while those lesions of equal proportion have a ground-glass appearance. Cortical osteomas produce complete signal void on all MRI sequences, and are indistinguishable from the surrounding air, making the diagnosis more difficult. In addition, fibrous dysplasia can have an aggressive appearance on MRI and be mistaken for a malignant tumor. In this situation, the CT scan should be obtained to help confirm the diagnosis.

Inverted Papilloma

Inverted papillomas, also known as schneiderian papillomas, are one of the most common benign lesions of the nasal cavity and paranasal sinuses. Although benign, they commonly destroy bone and 13% of the time they are associated with squamous cell carcinoma (SCC).[6] Inverted papillomas are most likely to be located in the lateral nasal wall involving the ostiomeatal complex and maxillary sinus followed by ethmoid, sphenoid, and frontal sinuses. Imaging is important for surgical planning and for evaluating deeper invasion, which is characteristic of malignant transformation. Inverted papilloma enhances with contrast on CT imaging and is most commonly seen occupying the lateral nasal wall. If malignant transformation is a concern, MRI is often used to further delineate the involvement of the extrasinonasal cavity.

Juvenile Angiofibroma

Juvenile angiofibroma is an uncommon neoplasm with a pathognomonic site of origin at the level of the pterygopalatine fossa. It almost exclusively occurs in the second decade of life and nearly always affects boys. Benign and slow growing, blood supply is obtained from a variety of vessels, the most common being the internal maxillary artery. The lesion may spread through various pathways of the skull base foramina and fissures. At early onset, the angiofibroma may extend through the sphenopalatine foramen into the nasopharynx. Through bony erosion, some tumors may reach the anterior or middle cranial fossa and extend into the cavernous sinuses via the sphenoid sinus. Hypervascularized lesion emanating from behind the middle turbinate strongly suggests the diagnosis of juvenile angiofibroma and can be further confirmed with CT or MRI scanning that highlights three major features: the area of origin located at the level of the pterygopalatine fossa, the hypervascular appearance after contrast enhancement (flow voids in the lesion), and the pattern of growth.

Meningioma

Meningiomas arise from meningothelial cells most common in the arachnoid villi. Usually meningiomas are diagnosed in the sixth to seventh decade of life and are more commonly seen in women. More than 90% are intracranial and can be multiple in patients with NF-2. Meningiomas are encapsulated and attached to the dura. They are classified as typical, atypical, or malignant. CT imaging shows a homogenous contrast-enhancing lesion with an associated dural base. Hyperostosis of the adjacent bone is seen in a large percentage of patients. On MRI, the lesion has a broad dural base and is isointense or hypointense when compared to normal brain with a characteristic dural tail.

Malignant Sinonasal Tumors

Patients with sinonasal malignancies present with symptoms similar to rhinosinusitis such as nasal obstruction, epistaxis, headaches, and facial pain. A CT scan with contrast is useful to determine the bony erosion and extent of the disease, while adjunct MRI is useful for neurovascular invasion or need for better soft tissue detail. Although a biopsy of the mass will ultimately delineate the pathology, preoperative imaging is very useful to help guide surgical planning and staging of sinonasal malignancies.

Sinonasal Squamous Cell Carcinoma

Sinonasal SCC is a malignant tumor from sinonasal mucosal epithelium, and accounts for 80% of sinonasal malignancies. It is the most common sinonasal epithelial tumor and is most commonly found in the maxillary sinus with a 30–50% 5-year survival rate.[7] Other sinonasal epithelial tumors, such as adenocarcinoma, adenoid cystic carcinoma, and esthesioneuroblastoma (ENB), are more commonly found in the ethmoidal air cells. SCC is a fast growing, aggressive tumor that commonly invades the maxillary inferolateral wall and surrounding structures such as the orbit; therefore, the CT scan is useful in determining the bony erosion and extent of the disease. On MRI, SCC is characterized by low-signal intensity on T2 scans, allowing differentiation between retained secretions, which are typically bright in signal intensity. Lastly, tumors originating in the maxillary sinus are more likely to present with hypesthesia of the infraorbital nerve (V2) with concern of perineural invasion that is evaluated by gadolinium MRI imaging. Imaging should be carefully evaluated to trace the branches of the trigeminal nerve (pterygopalatine fossa, foramen rotundum, foramen ovale, orbital fissures) to identify perineural spread.

Salivary Gland Tumors

Minor salivary gland tumors and melanoma are the next most common malignancies to affect the sinonasal cavity after SCCA. Minor salivary gland tumors represent a wide variety of histologic types, including adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma,

and undifferentiated carcinoma. Of these tumors, adenoid cystic carcinoma is the most common variety and has three major variant histologic growth patterns of ACC: cribriform, tubular, and solid. Its signal intensity may be high or low on MRI T2 scans, secondary to the degree of tubular or cribriform histologic pattern, as well as cystic spaces, necrosis, and tumor cell density.

Esthesioneuroblastoma

ENB is a rare malignant sinonasal tumor thought to arise from the olfactory epithelium[8] and usually seen high in the nasal cavity on imaging. ENB falls under a group of sinonasal neoplasms referred to as "small blue cell tumors" because histopathologically they show sheets of small round blue cells with sparse cytoplasm and hyperchromatic nuclei with unsuspecting nucleoli. Other "small blue cell tumors" include sinonasal melanoma, lymphoma, sarcoma, and various neuroendocrine tumors. Evaluation of ENBs proves similar to other neoplasm of the anterior skull base requiring imaging evaluation. Imaging studies include a chest X-ray to rule out pulmonary disease and a bone scan if symptoms suggest bone metastasis. CT proves helpful to assess bony destruction at the cribriform plate while MRI imaging will better delineate soft tissue intracranial extension. Similar to many other sinonasal malignancies, ENBs have low signal intensity on T2-weighted MRI images.

PREOPERATIVE CHECKLIST FOR SURGERY

When evaluating a CT preoperatively for ESS, several key anatomical associations need to be assessed. A good grasp of sinonasal anatomy is required; therefore, a general overview of the anatomy will be discussed to present important relationships that should be examined prior to ESS. However, this chapter is not meant to provide a detailed explanation of sinonasal anatomy. Those areas that should be systematically reviewed during surgical planning include but not limited to:

- Lateral nasal wall
- Ostiomeatal complex with its associated anatomy
- Anterior ethmoid cells
- Uncinate process attachment and relationship to lamina
- Ethmoid roof height, cribriform plate, and lateral lamella
- Maxillary infundibulum and presence of Haller cells
- Anterior ethmoid arteries and their relationship to the skull base
- Sphenoid sinus and relationship to neurovascular structures
- Sphenoethmoidal air cells (Onodi cells)
- Frontal recess and the associated frontal air cells
- Nasal septum

Lateral Nasal Wall

Understanding the anatomy of the lateral nasal sidewall with its associated anatomical structures, spaces, and sinus ostia is necessary prior to interpreting preoperative CT scans. Projecting from the lateral nasal sidewall are three conchae or turbinate bones. They are named in ascending sequential order according to their position on the lateral nasal wall. The turbinates in ascending order from inferior to superior are as follows: the inferior turbinate, middle turbinate, superior turbinate, and if present there is a fourth turbinate termed the supreme turbinate. Below each turbinate is a meatus or space; whereby its name is derived from the turbinate above. Each meatus receives unique drainage from corresponding paranasal sinuses.

The nasolacrimal duct empties into the inferior meatus, which sits below the inferior turbinate. Hasner's valve is the distal opening of the nasolacrimal duct that is covered by a small mucosal flap. The nasolacrimal duct is best identified on axial CT cuts and becomes the most anterior limit of dissection when opening the maxillary sinus. The middle meatus is located lateral to the middle turbinate and is the most complex and utmost important to the endoscopic sinus surgeon. The middle meatus accepts drainage from the frontal, maxillary, and the anterior ethmoid sinuses. Posteriorly, the superior meatus is below the superior turbinate, which accepts drainage from the posterior ethmoid air cells. The drainage continues medially into the sphenoethmoidal recess, which also accepts drainage from the sphenoid sinus.

Ostiomeatal Unit

The ostiomeatal unit (OMU) is a complex anatomic area within the middle meatus, which can be defined as the functional unit of the anterior ethmoid complex, thereby acting as the common drainage pathway of the frontal, anterior ethmoid, and maxillary sinuses.[9] The OMU includes the following structures:

- Anterior ethmoid cells
- Uncinate process

- Ethmoid bulla
- Maxillary infundibulum
- Hiatus semilunaris

Obstruction of the OMU is commonly the cornerstone seen in the pathophysiology of chronic rhinosinusitis (CRS), which is best observed on a coronal CT scan. Obstruction may be secondary to inflammation or anatomic variations of the OMU such as paradoxical middle turbinates, concha bullosa, Haller cells, agger nasi cells, or nasal septal deviation. This anatomic relationship is important as ESS specifically addresses the OMU as a functional unit by targeting diseased cells. This enables the return of normal mucociliary drainage within the OMU. The endoscopic surgeon should carefully evaluate the anatomic variations on preoperative imaging within the OMU to address the underlying disease process. The OMU can best be understood by reviewing the coronal CT images prior to ESS.

Anterior Ethmoid Cells

The ethmoid air cell system is highly variable and varies across individuals. The middle turbinate has several critical areas of attachment that further defines the ethmoid air cells. The middle turbinate's intraethmoidal attachment is commonly called the basal or ground lamella and attaches medially to the lamina papyracea. Posteriorly, the basal lamella curves superiorly and becomes oriented in a coronal plane and divides the ethmoid air cells into an anterior and posterior division. This anatomic barrier between the anterior and posterior air cells is best observed on an axial CT scan. Those air cells in front of the basal lamella are classified as anterior ethmoid air cells and drain into the middle meatus, while the posterior ethmoid sinuses are posterior to the basal lamella and drain into the superior meatus.

Uncinate Process

The uncinate process is a sickle-shaped bone that appears as a fold on the lateral nasal sidewall that extends from the inferior turbinate to its anterior–superior attachments at the skull base and lamina papyracea. The superior attachment of the uncinate process has a tremendous amount of variation and is best assessed with CT coronal views, as the location of its attachments has direct consequence on drainage patterns of the frontal sinus and dictates surgical approach. The uncinate process can also present with pneumatization occluding the infundibulum of the maxillary sinus.

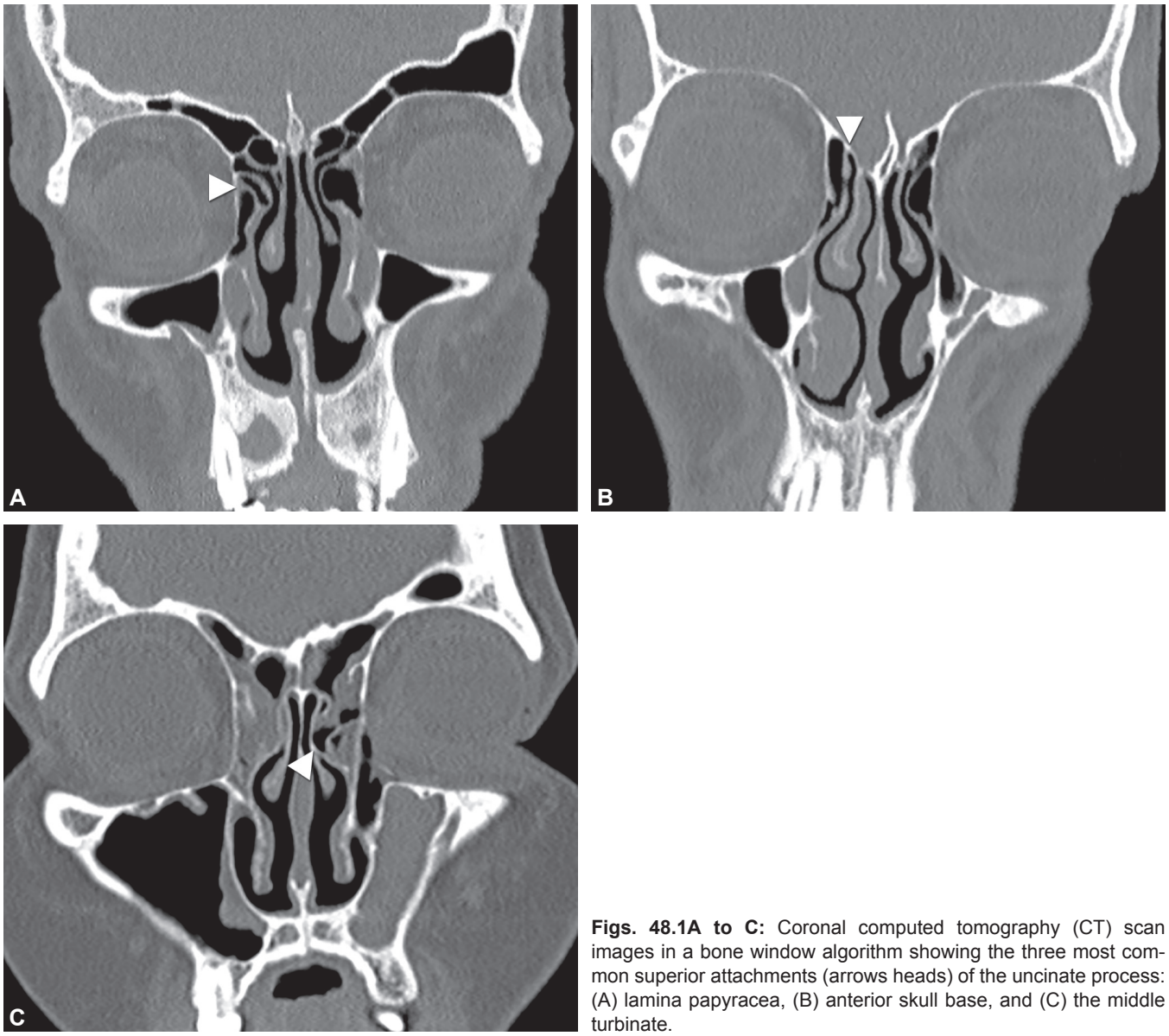
The superior attachment of the uncinate process is an important landmark when performing frontal recess surgery. Its superior attachment is highly variable and was originally classified with three distinct attachment sites including the lamina papyracea, skull base, or middle turbinate (Figs. 48.1A to C). A more descriptive classification was described by Landsberg and Friedman who classified the insertion into 6 different categories[10]:

- Types 1 and 2 inserted into the lamina papyracea
- Type 3 inserts into both the lamina papyracea and the junction of the middle turbinate with the cribriform plate
- Type 4 inserts at both the junction of the middle turbinate and the cribriform plate
- Type 5 attaches to the skull base
- Type 6 inserts on the middle turbinate

Of these subtypes type 1 and 2 are reported as being the most prevalent at 62.6%.[11]

Understanding the variations in the superior insertion of the uncinate process will enable the endoscopic surgeon to predict where the frontal sinus drainage will be located. When the uncinate process inserts into the lamina papyracea, the ethmoid infundibulum ends as a blind pouch named the recessus terminalis.[12] In this instance, the frontal sinus will drain medially into the middle meatus or the suprabullar recess. However, when the uncinate attaches to either the skull base or the middle turbinate, the frontal recess drains into the middle meatus through the ethmoid infundibulum.

The uncinate process can be atelectatic and/or intimately opposed to the lamina seen in conditions such as silent sinus syndrome or maxillary hypoplasia (Fig. 48.2A) or pushed medially as a result of nasal polyposis. If this space is not respected, the surgeon may inadvertently enter the orbital cavity. For instance, the distance between the uncinate process and the lamina papyracea can be as narrow as 0.1 mm.[13] Likewise, natural congenital dehiscence of the lamina is reported to be as high as 10% and should be avoided at the time of surgery. Temporally remote trauma can also cause lamina dehiscence (Fig. 48.2B), which can alter lateral nasal sidewall anatomy, which increases the potential for intraoperative injury while performing the uncinectomy. Therefore, careful dissection is required in these instances to prevent lamina penetration. This can be assessed intraoperatively, with external orbital pressure while visualizing the lamina endoscopically.



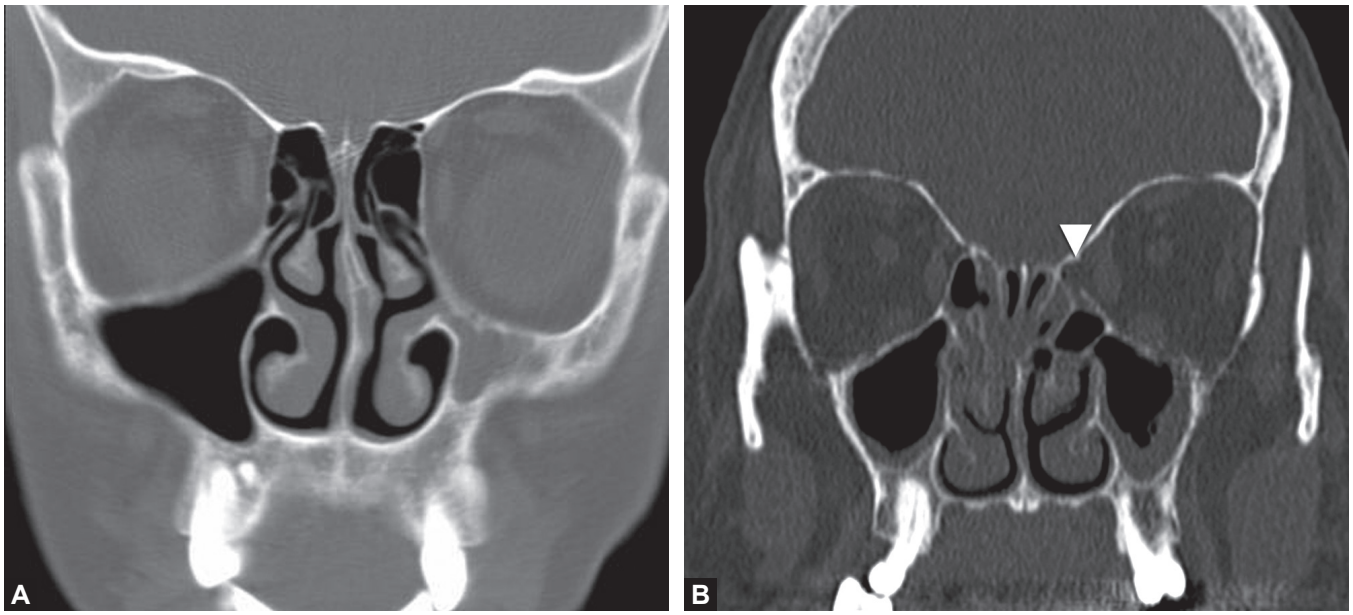
Figs. 48.1A to C: Coronal computed tomography (CT) scan images in a bone window algorithm showing the three most common superior attachments (arrows heads) of the uncinate process: (A) lamina papyracea, (B) anterior skull base, and (C) the middle turbinate.

Maxillary Infundibulum and Hiatus Semilunaris

The maxillary infundibulum is a three-dimensional space that is bounded by the lamina papyracea laterally, the uncinate process medially, and the ethmoid bulla posteriorly. The infundibulum can be likened to a hallway, which collects drainage from the frontal, ethmoid, and the maxillary sinus and subsequently directs the secretions medially to the hiatus semilunaris. The hiatus semilunaris, (exit) is a two-dimensional space that is defined by the free edge of the uncinate and the anterior face of the ethmoid bulla. The hiatus semilunaris can be seen with nasal endoscopy at the most posterior–inferior portion of the uncinate, is difficult to identify on coronal images, and is best seen on sagittal cuts. In contrast, the infundibular space cannot be visualized endoscopically unless the uncinate is removed, which is the first step to surgically access the natural maxillary ostium.

Ethmoid Roof Height

Iatrogenic injury to the skull base is a major complication that can occur during ESS. The height of the skull base



Figs. 48.2A and B: Coronal computed tomography (CT) scan images in a bone window algorithm demonstrating anatomic variations that need to be identified on operative imaging. (A) A left hypoplastic maxillary sinus with associated atelectatic uncinate process draped over the lamina papyracea. This resulted in obstruction of the maxillary sinus outflow and resultant maxillary opacification. (B) Prior maxillofacial trauma to the left orbit caused a dehiscence of the lamina papyracea (arrow heads), thereby altering the lateral nasal sidewall anatomy.

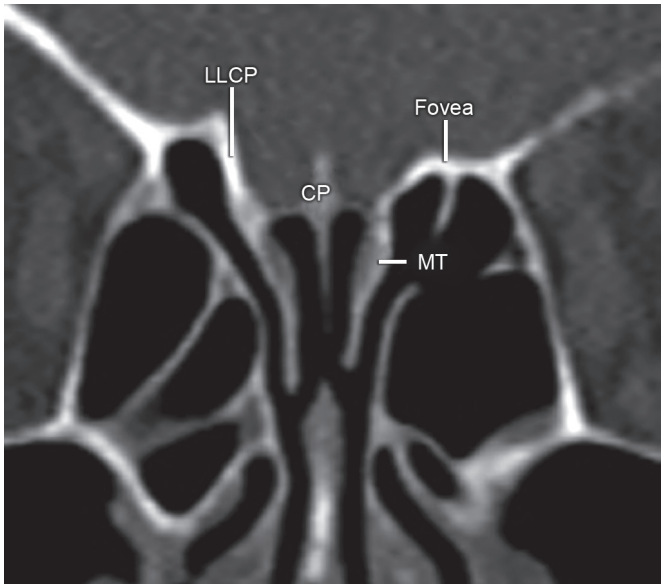
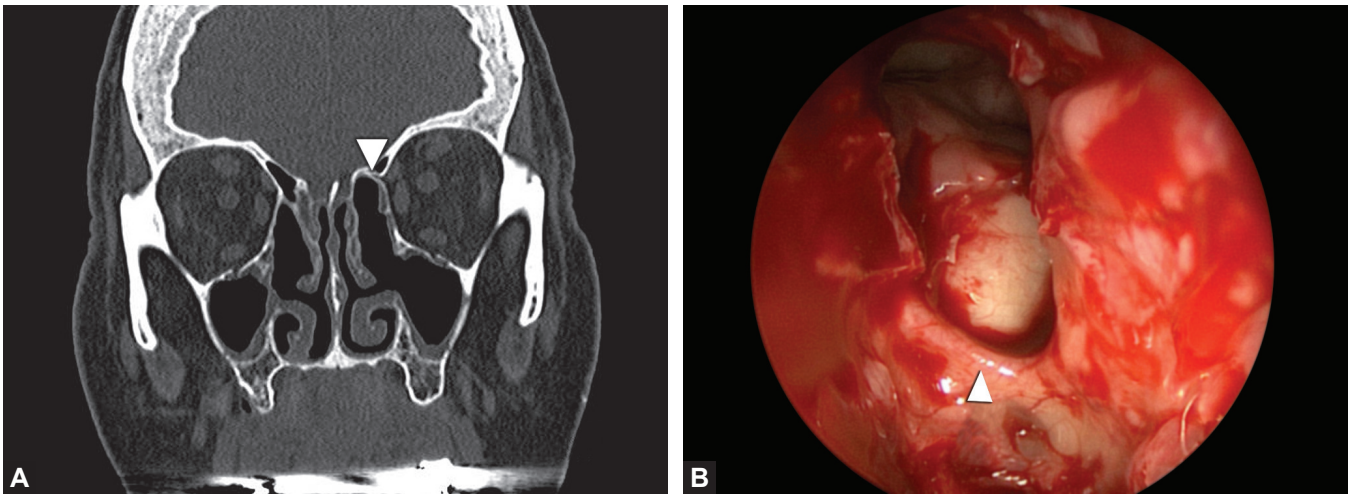


Fig. 48.3: Coronal computed tomography (CT) scan image in a bone window algorithm demonstrating the olfactory cleft and fossae. The length of the lateral lamella of the cribriform plate (LLCP) is depicted in this coronal image as measured according to Keros. Note the relationship of the LLCP with the insertion of the basal lamella of the middle turbinate (MT), as well as the fovea ethmoidalis (FE) laterally. The LLCP is commonly asymmetric, resulting in a deeper right ethmoid fovea as depicted. This asymmetric anatomical variation should be recognized on presurgical planning to prevent iatrogenic cerebrospinal fluid leaks.

can dramatically vary between patients. Evaluating the skull base preoperatively by determining if it is "low" can potentially help prevent this serious complication. Recognizing the relationship of the cribriform plate, fovea ethmoidalis, and the insertion of the middle turbinate should be assessed on coronal CT preoperative imaging. Historically skull base height has been assessed with the Keros classification, which helps identify a low cribriform plate. In 1962, Keros classified the olfactory fossa based on how low the cribriform plate sat in relationship to the ethmoid skull base. This relationship between the olfactory fossa and the ethmoid roof was classified into three types,[14] such that Keros type I is 1–3 mm deep, type II is 4–7 mm deep, and Keros Type III is ≥8 mm deep (Fig. 48.3). The lateral lamella of the cribriform plate (LLCP) extends superiorly from the cribriform plate and articulates with the roof of the ethmoid skull base, which is the medial extension of the frontal bone. The LLCP is the thinnest bone of the skull base and can be easily damaged. Therefore, investigations have tried to quantify the LLCP using CT imaging that has demonstrated significant asymmetry with the right LLCP being deeper than the left[14-16] with an average depth of 0–3.9 mm.[17] This is critical to assess with on preoperative imaging, as the more asymmetric ethmoid roof height—the higher incidence



Figs. 48.4A and B: Coronal computed tomography (CT) scan in a bone window algorithm at the level of the anterior ethmoid artery (AEA) as it exits through the anterior ethmoidal foramen. (A) A highly pneumatized ethmoid sinus is associated with a low hanging anterior ethmoid artery (arrow head) and should be noted on preoperative imaging to prevent inadvertent injury to the artery. (B) An endoscopic intraoperative visualization of a low AEA (arrow head) just posterior to the frontal recess.

of iatrogenic injury. The endoscopic surgeon should be aware that injury has been reported to be more common on the side with the lower ethmoid skull base.[16] CT images in the coronal plane can provide adequate information about the LLCP and its variations. While the Keros classification is useful in defining the LLCP and olfactory fossa, it is not useful for defining the overall general height of the skull base, which is critical when entering the posterior ethmoids through the basal lamella as inadvertent injury can occur. Measuring the height of the skull base from a horizontal midorbital line on a coronal sinus CT image is an objective useful technique to identify a low skull base. Using the maxillary sinus roof intraoperatively serves the same purpose, thereby decreasing inadvertent breach into the skull base causing a cerebrospinal fluid leak.[18-19]

Anterior Ethmoid Artery

The anterior ethmoid artery (AEA) is a critical structure for the endoscopic sinus surgeon to identify on preoperative imaging. The AEA and posterior ethmoidal arteries (PEA) are terminal branches of the ophthalmic artery that arise from the internal carotid artery. The anterior ethmoidal foramen transmits the AEA and nerve. It is usually found 20–24 mm posterior to the anterior lacrimal crest. In the same sagittal groove at the posterior aspect, the PEA travels through the posterior ethmoidal foramen. The average distance separating the anterior and posterior ethmoidal foramen is about 12 mm (range: 10–17 mm).[20] The optic foramen is located at an average distance of 12 mm (range: 8–16 mm) distal to the posterior ethmoidal foramen.[21] The above distances are important references that serve as important surgical landmarks. The AEA is primarily seen at the skull base, but in well-aerated ethmoid sinuses the AEA is commonly seen within a bony mesentery, several millimeters below the skull base in a coronal plane (Figs. 48.4A and B). When the AEA is within a bony mesentery, the risk of inadvertent injury is increased while operating near the roof of the anterior ethmoid cells. Injury to the artery can result in intraorbital bleeding with increased orbital pressure and loss of vision or intracranial bleeding.

Frontal Recess

Frontal sinus anatomy is formed by the superior pneumatization of the anterior ethmoid air cells in the fourth fetal month. A basic knowledge of the structural boundaries of the frontal sinus and its outflow tract is required for appreciating the complex anatomy when evaluating preoperative imaging. The frontal bone is composed of horizontal and vertical components, which comprise the orbital roof and forehead respectively. The vertical component is variably pneumatized in the majority of people, dividing the sinus into a thicker anterior table and a thinner posterior table.[22] The posterior table forms the anterior border of the cranial vault and is adjacent to the

underlying dura. The cribriform plate abuts the frontal sinus posteriorly and represents a critical location for injury during ESS. The nasofrontal outflow tract does not form a true duct but rather an hourglass-shaped space formed by the boundaries of this drainage pathway. General boundaries include the agger nasi cell anteriorly, the middle turbinate medially, the skull base posterior–superiorly, lamina papyracea laterally, and the ethmoid bulla posterior–inferiorly. The agger nasi cell is the first pneumatized cell located immediately anterior and superior to the attachment of the middle turbinate. The cell is found lateral to the middle turbinate, medial to the lacrimal bone, and posterior to the frontal process of the maxilla. The uncinate process and the agger nasi cell are the two key anatomical landmarks in ESS. The superior attachment of the uncinate process is affected by the pneumatization of the agger nasi cell, with or without involvement of the frontal ethmoidal air cells ultimately affecting the anatomical relationships within the frontal recess.

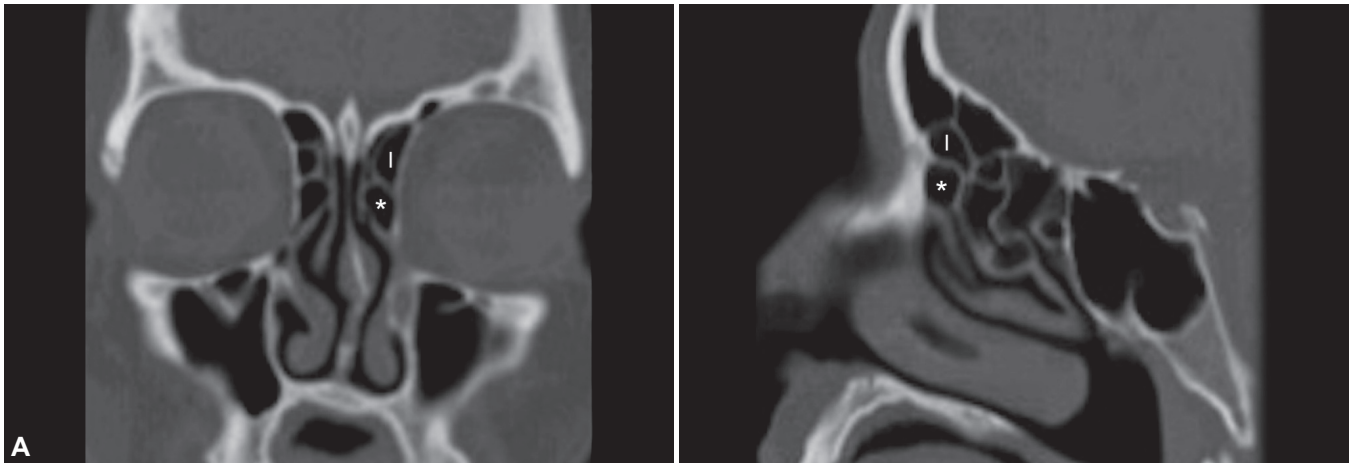
Frontal Cell Types

Understanding the agger nasi cell and its relationship with surrounding anatomical frontal recess anatomy is critical to performing endoscopic frontal sinus surgery. A large pneumatized agger nasi cell can narrow the frontal recess resulting in the uncinate attaching medially onto the middle turbinate. When a frontal ethmoid cell rests immediately superior to the agger nasi cell, this is termed a type one cell or a Kuhn type I frontal cell. When greater than one frontal ethmoid sits atop the agger nasi cell, this is termed a Kuhn type II configuration. When there is significant pneumatization of a frontal ethmoid cell and it extends beyond the frontal recess into the frontal sinus, this is termed a Kuhn type III cell. This configuration encroaches into the frontal sinus laterally, thereby narrowing the frontal sinus ostium. Another cell that is commonly overlooked is the intersinus septal cell or a medial frontal ethmoidal cell and can be visualized pushing into the frontal recess medially as its name suggests. An air cell that is isolated within the frontal sinus is called a type IV Kuhn cell (Figs. 48.5A to D).

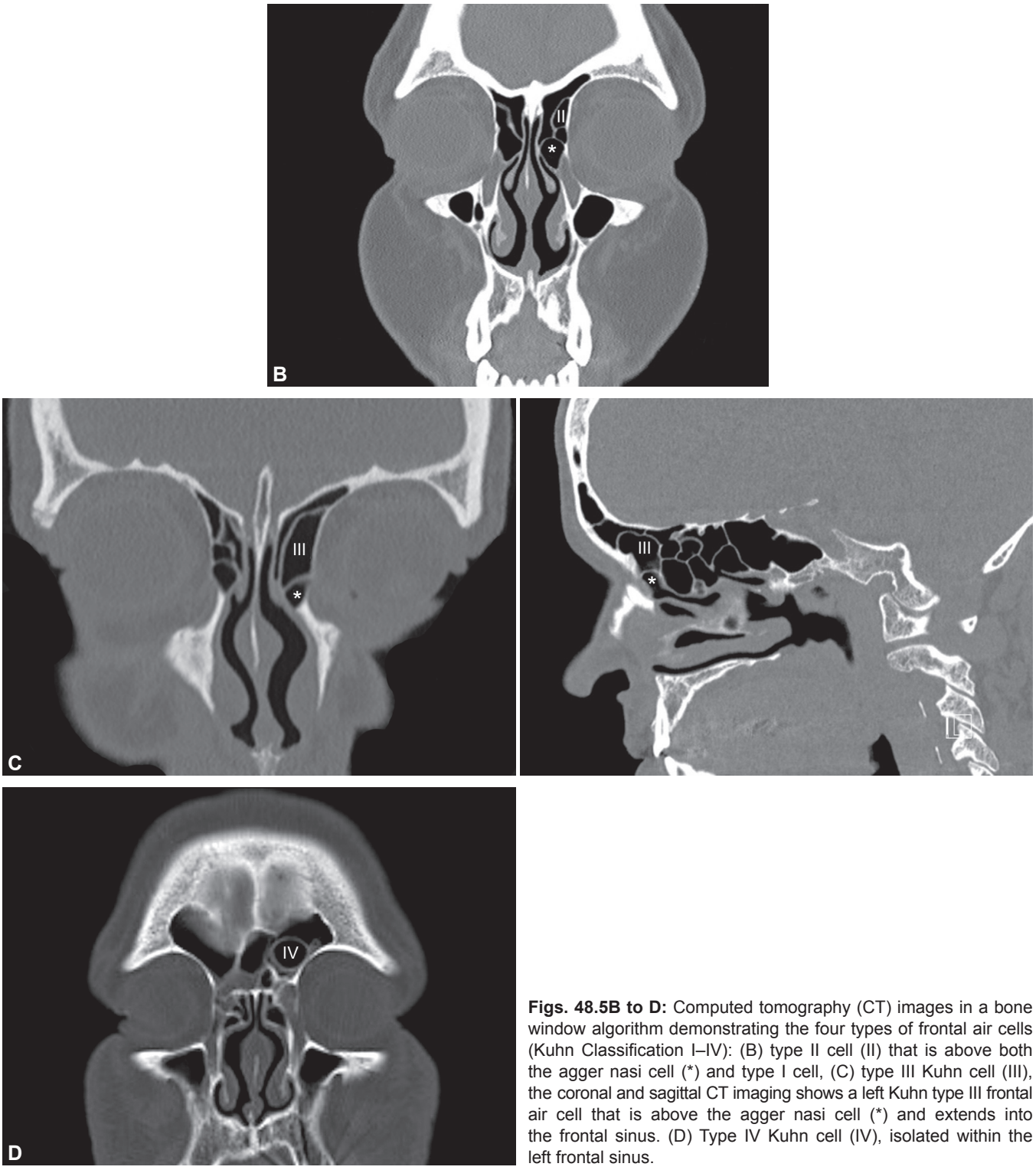
Sphenoid Sinus

Evaluating the integrity of the bony walls of the sphenoid sinus, the ethmoid sinus, and the optic nerve for possible dehiscence is a critical aspect of surgical planning. The sphenoid sinus is the most posterior sinus and is surrounded by critical neurovascular structures including the pituitary gland, the cavernous sinus, optic nerve, internal carotid artery, maxillary division of the trigeminal nerve, and the vidian nerve. As these neurovascular structures are just beyond the wall of the sphenoid sinus, there is an associated potential risk of severe adverse outcomes if damage to these structures occurs. Therefore, these structures and their relationship to the sphenoid sinus should be carefully evaluated prior to ESS.

The sphenoid ostium lies in the sphenoethmoidal recess and can be easily seen medially to the superior turbinate after the inferior one-third of the superior turbinate is removed. The sphenoid sinus ostium is 7 cm posterior at a 30° angle from the nasal spine in adults. The sphenoid



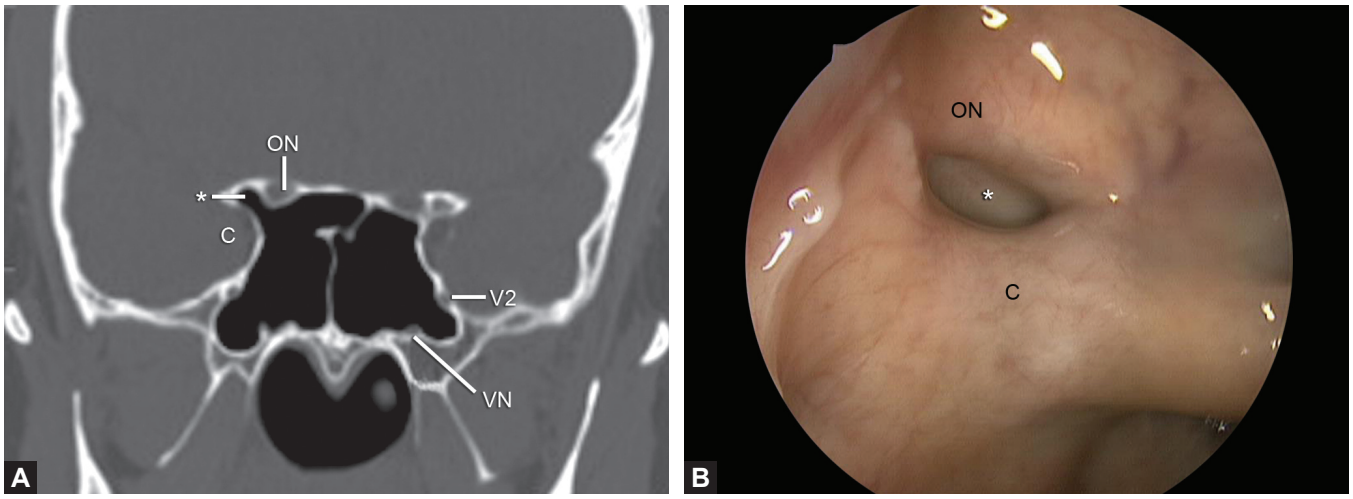
Figs. 48.5A: Computed tomography (CT) images in a bone window algorithm demonstrating the four types of frontal air cells (Kuhn Classification I–IV): (A) type I cell (I) directly above the agger nasi cell (*).



Figs. 48.5B to D: Computed tomography (CT) images in a bone window algorithm demonstrating the four types of frontal air cells (Kuhn Classification I–IV): (B) type II cell (II) that is above both the agger nasi cell (*) and type I cell, (C) type III Kuhn cell (III), the coronal and sagittal CT imaging shows a left Kuhn type III frontal air cell that is above the agger nasi cell (*) and extends into the frontal sinus. (D) Type IV Kuhn cell (IV), isolated within the left frontal sinus.

ostium can also be localized by measuring 1–1.5 cm above the superior aspect of the posterior choana between the nasal septum and the superior turbinate.

The roof of the sphenoid sinus is termed the planum sphenoidale and is posterior to the cribriform plate, a thicker contiguous flat bone that serves as an important



Figs. 48.6A and B: Coronal and axial computed tomography (CT) images in a bone window algorithm at the level of the sphenoid sinus. (A) In this cut, the bony impressions of the carotid artery (C) and optic nerve (ON) and the opticocarotid recess (*) are visible. The vidian nerve (VN) and the maxillary division of the trigeminal nerve (V2) can be seen inferior and laterally. (B) An example of the opticocarotid recess (*) and the bony protrusions of the carotid artery (C) and optic nerve (ON) seen intraoperatively using a zero degree endoscopic.

landmark for the sphenoid sinus and the optic nerve. It is bordered posteriorly by the optic chiasm and the superior aspect of the sella or the diaphragma sellae also known as the sellar diaphragm. Anteriorly it articulates with the planum ethmoidale. The junction of the sella and planum sphenoidale is called the tuberculum sellae. The posterolateral wall of the sphenoid sinus is made up of the lesser wing of the sphenoid. The lesser wing of sphenoid forms the anterior clinoid process, marking the location of the optic nerve superiorly and supracavernous internal carotid artery inferiorly.

The pituitary gland is housed within the sella turcica. Sphenoid sinus pneumatization can be classified into presellar, sellar, and postseller types and is best visualized with sagittal CT images. Pneumatization does not extend past a vertical plane posterior to the anterior clinoid process, in the presellar type. The sellar classification is associated with a well-pneumatized sphenoid, allowing straightforward surgical access to the sella turcica. In the conchal type, the sella is surrounded by bone, making surgical access to the pituitary more difficult. In a well-pneumatized sphenoid sinus, the floor of the sella turcica can be easily visualized medial to the bony prominences of the carotid and optic nerve.

The carotid and optic protuberances can be seen on the lateral nasal sidewall of the sphenoid sinus (Figs. 48.6A and B). The recess between the bony prominences of the optic and carotid artery is termed the opticocarotid recess. The vidian nerve is located in at the floor of the sphenoid sinus in an inferior–lateral position, and can be in a bony mesentery in highly pneumatized sphenoid. This is easily visualized on coronal imaging and should be noted if dissecting inferiorly while performing the sphenoidotomy. Just medial to the vidian is the palatovaginal canal also called the pharyngeal canal. It transmits the pharyngeal artery and nerve. Lateral to the sphenoid sinus and sella turcica is the cavernous sinus. The cavernous sinus contains vital neurovascular structures: oculomotor nerve (CN III), trochlear nerve (CN IV), two branches of the trigeminal nerve (CNV), the ophthalmic nerve (CN V1), the maxillary nerve (CNV2), and the abducens nerve (VI) that runs alongside the internal carotid artery.

Dehiscence of the neurovascular structures can be easily assessed on both axial and coronal CT views. The prevalence of carotid dehiscence ranges from 1.5% to 25%, while optic nerve dehiscence ranges from 3.6% to 12.5%.[23-25]

The sphenoid intersinus septum separates the left and right sphenoid sinus, has varied attachments, and can be pneumatized. It is critical to determine if the sphenoid intersinus septum attaches to either the carotid bony canal or the bony canal of the optic nerve. The sphenoid intersinus septum has been reported to insert onto the carotid canal in 37.5% of cases, and directly onto the optic nerve canal in 30.5% of cases.[25] This anatomical knowledge is critical to prevent inadvertent injury to these vital structures, which is best analyzed with a detailed preoperative analysis of both coronal and axial CT views.

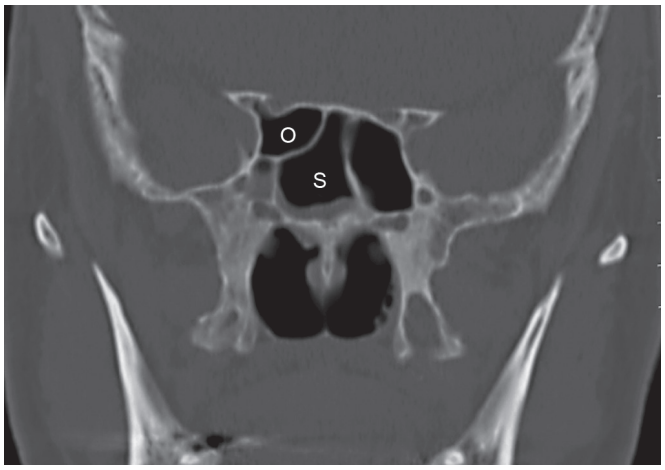


Fig. 48.7: Coronal computed tomography (CT) scan image in a bone window algorithm showing right sphenoethmoidal air cells (Onodi cells; O), which can be seen superior and lateral to the sphenoid sinus (S). The optic nerve and carotid artery are seen as bony protrusions in the sphenoethmoidal air cells, rather than along the lateral wall of the left sphenoid sinus.

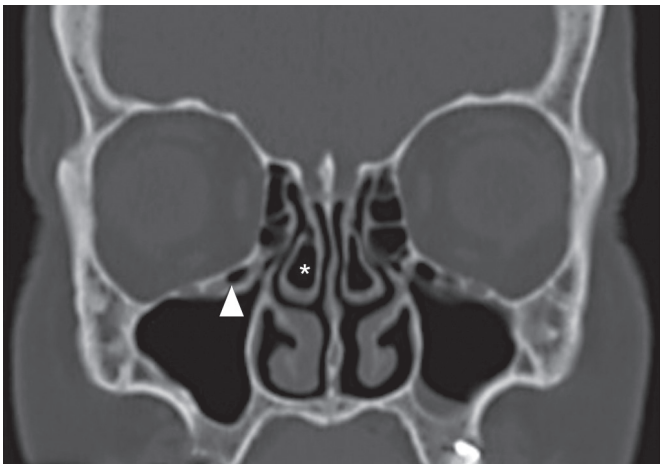


Fig. 48.8: Coronal computed tomography (CT) scan image in a bone window algorithm showing bilateral pneumatization in the head of the middle turbinates (*) also called concha bullosa. Infraorbital ethmoid air cells (Haller cells) are seen as pneumatized air cells off the inferior orbital floor (arrow head).

Sphenoethmoidal Air Cells (Onodi Cells)

The posterior most ethmoid air cell's relationship to the sphenoid sinus needs to be critically assessed as this cell can extend superiorly, posterior and laterally, thereby resulting in an intimate relationship with the optic nerve and carotid artery at its lateral wall. This anatomic variation was commonly designated as an Onodi cell, but is now more commonly referred to as a sphenoethmoidal cell that accurately reflects the anatomical position of this air cell. Especially perilous is when the optic nerve has no bony shell and is exposed within the Onodi cell; thereby increasing risk of injury. Onodi cells are present in 9% to 47.9%[26] of patients. This cell should be localized and opened intraoperatively to locate and define the posterior skull base during ESS. The sphenoethmoidal cell is best visualized on the coronal CT views, giving the appearance of a horizontal split of the sphenoid sinus. The angle at which the sphenoid sinus should be entered is also appreciated on sagittal reconstruction. However, all three views (coronal, sagittal and axial) should be reviewed to clarify that the origin of the cell is from the posterior ethmoids, rather than the sphenoid sinus that is medial and inferior (Fig. 48.7).

Concha Bullosa

Zuckerkandl coined the term concha bullosa when pneumatization of the middle turbinate was present. Pneumatization of the middle turbinate can narrow the OMC and can be involved in the pathophysiology sinus disease. Large concha bullosa function as large "balloons" in the middle meatus obstructing normal mucociliary drainage. The amount and location of the pneumatization varies with the most common location being the head of the middle turbinate (Fig. 48.8). This anatomic variation can easily be seen on both coronal and axial views and should be addressed during surgery.

Infraorbital Recess Cells (Haller Cells)

Infraorbital ethmoid air cells (Haller cells) are seen as pneumatized air cells that grow out of the inferior orbital floor at the roof of the maxillary sinus (Fig. 48.8). Infraorbital ethmoid cells are seen as distinctive air cells separate from the anterior ethmoid bulla. These cells are important to identify as they have the potential to narrow the ethmoid infundibulum and/or maxillary sinus infundibulum. The coronal CT is the best view for diagnosing these air cells.

Nasal Septal Deviation

Although commonly overlooked, it is important to assess the nasal septum prior to sinus surgery. Significant nasal septal deviation and septal spurs can prevent access to the sinuses during ESS. Surgical planning can be improved by using CT coronal and axial views of the nasal septum in conjunction with nasal endoscopy. In certain circumstances the septum may need to be addressed with

functional rhinoplasty due to severe septal deviation, very anterior caudal deflection, or dynamic valve collapse that can be addressed with concurrent ESS.

IMAGE GUIDANCE IN ENDOSCOPIC SINUS AND SKULL BASE SURGERY

History of Image Guidance

Image guidance has been referred to over the years by many terms: image-guided surgery (IGS), computer aided surgery, or surgical navigation. It began in the field of stereotactic intracranial surgery in the early 1900s with the development of a stereotactic apparatus for neurosurgical navigation. With the refinement of stereotactic frames in the 1950s, stereotactic surgery was being performed throughout the world, principally in performing thalamotomies for movement disorders. With the development of improved medical therapies, thalamotomies and stereotactic image guidance fell into disuse. CT's emergence in the 1970s and 1980s revived interest in stereotactic techniques. Software development in the 1980s combined CT data and stereotactic surgery, resulting in three-dimensional surgical targeting. In the early 1990s, the development of frameless stereotactic systems allowed probes and instruments to be tracked during procedures with the first such systems, developed for neurosurgery, used mechanical arms.

During this same period, interest in functional ESS exploded throughout the world. Naturally, the trajectories of ESS and IGS intersected. The initial experiments using IGS in the field of rhinology were performed by a group of surgeons in Aachen, Germany in the late 1980s using a passive articulated arm.[27] The Aachen group subsequently published their experience using this technology, finding that IGS was useful for intraoperative orientation and suggesting a 2% reduction in complication rate could be expected.[28] At about the same time Anon et al. published their report of computer-assisted ESS using this articulated arm, known as the Viewing Wand (ISG Technologies, Mississauga, Ontario, Canada).[29] The arm-based Viewing Wand had a detachable probe attached to its multiarticulated mechanical arm linked to an intraoperative computer with a high-resolution monitor. These authors found the IGS accuracy to be in the range of 2 mm and concluded the technology was generally useful. In 1995, Roth et al. added their experience with IGS using the Viewing Wand in 12 cases and found similar accuracy.[30] Importantly, they articulated several important deficiencies and outlined five goals that needed to be set in order for future systems to be adopted widely: (1) accuracy within 2–3 mm should be maintained, (2) the requirement for a second CT should be eliminated, (3) the computer should update for head movement, (4) suctions and dissection instruments should be tracked, and (5) the device must be easily operated by the surgeon in order to eliminate the technician. By the late 1990s, these goals had been reached through further advances in technology and clinical application and are minimum requirements for modern systems.

The Technological Basis of Image-Guided Surgery

At its core, IGS matches a large data set of radiologic spatial points—a patient's virtual anatomy—to the actual anatomy involved in a particular procedure. This alignment of the virtual anatomy and actual anatomy allows the surgeon to track an instrument's position in real-time relative to tri-planar imaging or three-dimensional formatted reconstruction.

All IGS systems incorporate a computer that is used to store the dataset, image processing software, a localization system, specialized instrumentation, and a monitor to display the radiographic images and the position of the tracked instrument. Early systems used arrays that were fixed in space, usually to the operating table, as a reference points. This setup then required the patient's head to be fixed to the table as well. These systems were quickly replaced by systems that used reference points on arrays that were attached to the patient's head, allowing the patient's head to move in space during the procedure while maintaining accurate navigation.

Navigating within the sinuses has also evolved. As mentioned above, the earliest systems used an articulated arm to localize the tip of the probe in space. Using technology analogous to proprioception, the arm was fixed to the operating table, as was the patient's head. The next generation of devices used optical imaging to determine the location of the patient and instruments in space. Infrared light emitting arrays attached to the patient's head and to instruments were localized by an infrared sensing camera. These active tracking systems were subsequently complemented with passive tracking systems, where the light was emitted and tracked by the same overhead device. Reflective materials were placed on the instruments and reference arrays in order to provide tracking, eliminating the cords, or batteries that the active

systems required. One drawback of the optical systems is that the line of sight between the instrument array and the detection camera must remain intact. This characteristic makes it impossible to track instruments that may move within the sinuses, such as bendable catheters and other devices.

In addition to optical systems, electromagnetic systems have been developed since the 1990s. These systems consist of an emitter and a detector that respond to changes in an electromagnetic field. By attaching emitters to instruments with known geometry, the location of the tip of a rigid instrument can be determined. As emitters become miniaturized, there is an increasing opportunity to place them into the tips of the instruments themselves. This advance allows the tracking of deformable instruments within the sinuses.

The Registration Process

The matching of the patient's anatomy to the radiologic dataset requires matching known points, a process known as registration. Registration is a stepwise process of moving from known points in three-dimensional space to unknown points. In early systems, registration was a complex and not entirely intuitive process. Along with the advances in technology over the last 25 years, there have been similar advances in the "user-friendliness" of these devices so that registration is brief and intuitive.

There are essentially two registration strategies. One is to use a small number of fixed points, either anatomic points (canthi, tragus, rhinion, etc.) or to use skin- or even bone-anchored fiducials that are placed prior to the CT scan. Skin and bone anchored fiducials are impractical for a number of reasons, not the least of which is that they necessitate an additional scan; therefore, are rarely used in rhinologic applications. Anatomic fiducial registration requires selecting known points on the radiographic images and then correlating the patient's anatomy to these same points.

The second strategy for registration, more commonly used today, is surface mapping registration. In this approach, hundreds of points are acquired from the patient's face, forming a virtual mask. The patient's facial surface mask is then fitted to another virtual mask created from the radiologic images, thus registering the patient to the radiologic images.

In both approaches, exactness in registration is critical in order to navigate accurately throughout the procedure. Accuracy of IGS is dependent on multiple factors including, quality of the dataset, stability of the fiducial points, number of fiducial points used during registration, and the three-dimensional spacing of the fiducial points around the target area.[31] Using points distributed throughout the surgical volume and along all three axes is critical in order to match the virtual and actual anatomy most accurately. Investigations evaluating the accuracy have found these systems to be within 2 mm with a mean degradation of 0.89 mm during the procedure.[32] While registration is typically quick and accurate, the accuracy should be routinely checked during the surgical case.[33] The most common source of inaccuracy is movement of the reference array during the procedure. It is easy to appreciate how just 1 mm of array movement can have important consequences for navigation accuracy at the skull base.

Practical Uses for Image-Guided Surgery

IGS is a powerful tool for confirming anatomic points during sinus and skull base surgery. By its nature, endoscopic surgery relies on no external landmarks. ESS entails a surgical dissection in an area surrounded by the orbit and brain, leaving little tolerance for positional error. Moreover, there are a limited number of anatomic landmarks available, some of which may be altered or destroyed by disease or previous surgery.

While IGS can be a tremendous asset in ESS, like any powerful tool it can be misused, with potentially disastrous consequences. The major danger of this technology is the potential for over-reliance. An accuracy of 1–2 mm in a surgical volume of hundreds of cubic centimeters is an entirely impressive accomplishment of engineering. Nevertheless, 1–2 mm is a large distance compared to the thickness of the LLCP, the lamina papyracea, or the thin bone covering the optic nerve. Additionally, 1–2 mm accuracy is a best-case scenario. IGS is a tool best used when complementing the surgeon's skill and knowledge, not as an attempt to replace them. Image guidance must always be utilized as an anatomy-*confirming* device, not an anatomy-seeking device.[34]

Image guidance is an expensive technology and must therefore be used in appropriate situations, where it is most likely to benefit the patient. Each surgeon's skill set will vary, as will the clinical situation of his/her patient. Overall, IGS is felt to be most valuable in cases where the anatomy is unusual or is particularly complex. Indications for use have been promulgated by the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) for over a decade and have remained constant:

"The AAO—HNS endorses the intraoperative use of computer-aided surgery in appropriately select cases to assist the surgeon in clarifying complex anatomy during sinus and skull base surgery. There is sufficient expert consensus opinion and literature evidence base to support this position. This technology is used at the discretion of the operating surgeon and is not experimental or investigational. Furthermore, the AAO—HNS is of the opinion that it is impossible to corroborate this with Level 1 evidence. These appropriate, specialty specific and surgically indicated procedural services should be reimbursed whether used by neurosurgeons or other qualified physicians regardless of the specialty. Examples of indications in which use of computer-aided surgery may be deemed appropriate include:

1. Revision sinus surgery
2. Distorted anatomy of development, postoperative or traumatic origin
3. Extensive sinonasal polyposis
4. Pathology involving the frontal, posterior ethmoid, and sphenoid sinuses
5. Disease abutting the skull base, orbit, optic nerve, or carotid artery
6. CSF rhinorrhea or conditions where there is a skull base defect
7. Benign and malignant sinonasal neoplasms."[34a]

As endoscopic skull base techniques have advanced beyond the sinuses into the orbit, pterygopalatine fossa, infratemporal fossa, and intracranially, IGS has played a critical role in fostering these minimally invasive advances. Undoubtedly, IGS is a valuable adjunct in endoscopic anterior skull base procedures extending beyond the sinuses.

Clinical Evidence for Image-Guided Surgery

The cost–benefit relationship of IGS has been a subject of interest nearly since its introduction in rhinology. Many substantial benefits can result from the use of image guidance in endoscopic sinus and skull base surgery. Rapid and accurate confirmation of the patient's anatomy may shorten surgery time, provide more thorough dissection within the sinuses, and potentially decrease complications from dissection beyond the surgical field. These potential benefits must be balanced by real and potential drawbacks. IGS systems are major capital expenditures and these expenses will naturally be passed on to patients. Gibbons et al. reviewed their experience before and after the availability of image guidance at the University of Alabama.[35] In their retrospective analysis, they found the times of surgery for these two groups were, in fact, not different. They did, however, find a small (2.6%) increase in charges for patients who underwent image guidance. Third party payer reimbursement for these charges can vary so that the true economic impact of image guidance is difficult to assess.

While there are potential benefits to offset these costs, the actual benefit of IGS has been difficult to fully assess. Complications in ESS are fortunately rare.[36] This infrequency makes demonstrating a reduction in the complication rate difficult, requiring large numbers of subjects in a clinical trial. Moreover, most experts would feel uncomfortable randomizing patients prospectively to an arm of a study where IGS was not used in cases where it would be otherwise indicated. For this reason, a prospective randomized trial of IGS will likely never be performed.[37]

Nevertheless, more recent larger scale analyses have drawn some firmer, though conflicting, conclusions. A recent systematic review and meta-analysis found that major and minor complications were more common in the non-IGS group.[38] In contrast, another meta-analysis found no reduction in complications or need for revision surgery with the use of IGS.[39] Taken as a whole the cumulative literature suggests that IGS has not been shown to decrease surgical complications or improve surgical outcomes. These evidence-based recommendations are based on limited literature with suboptimal research methodology. However, the utility and acceptance of IGS in ESS via expert opinion is supported by the available literature. Therefore in summary, the use of IGS in ESS is an option and should be based on clinical judgment and applied on a case-by-case basis.[36]

Recent and Future Advances

IGS continues to play an important role in sinus and anterior skull base surgery. The technology has evolved significantly over the last two decades in rhinology. In parallel, IGS has become routinely available as part of the endoscopic sinus surgeons' armamentarium.[40-41] While preoperative CT images are most commonly used, preoperative MRI images may be used as well, or even fused with the CT images. This technologic advance is especially useful for skull base neoplasm resections. Moreover,

intraoperative CT and MRI acquisition can be utilized to update the dataset. Early experience with these technologies appears to demonstrate a significant potential to impact outcomes.[42-43]

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CHAPTER

Primary Endoscopic Sinus Surgery for Chronic Rhinosinusitis

49

Bozena B Wrobel, Dale H Rice

Although Hirschmann first used a modified cystoscope in 1901 to examine the nasal cavity,[1] it was not until the advent of the rod lens endoscope by Harold Hopkins in the 1960s that the modern era of endoscopic sinus surgery (ESS) began.[2] The other major advances that allowed for the development of ESS included refinements in computed tomography, seminal research in sinonasal physiology, and the development of modern instrumentation. This chapter covers the principles and techniques of primary ESS. Chronic rhinosinusitis (CRS) is a common though poorly defined disease which is difficult to treat. As Poul Anderson said, "I have yet to see any problem, however complicated, which, when you look at it the in right way, did not become still more complicated." Suggested possible causes of CRS include repeated acute infections, allergic inflammation, nonallergic inflammation, anatomic variance, ciliary dysfunction, superantigens, fungi, and a variety of immune factors.

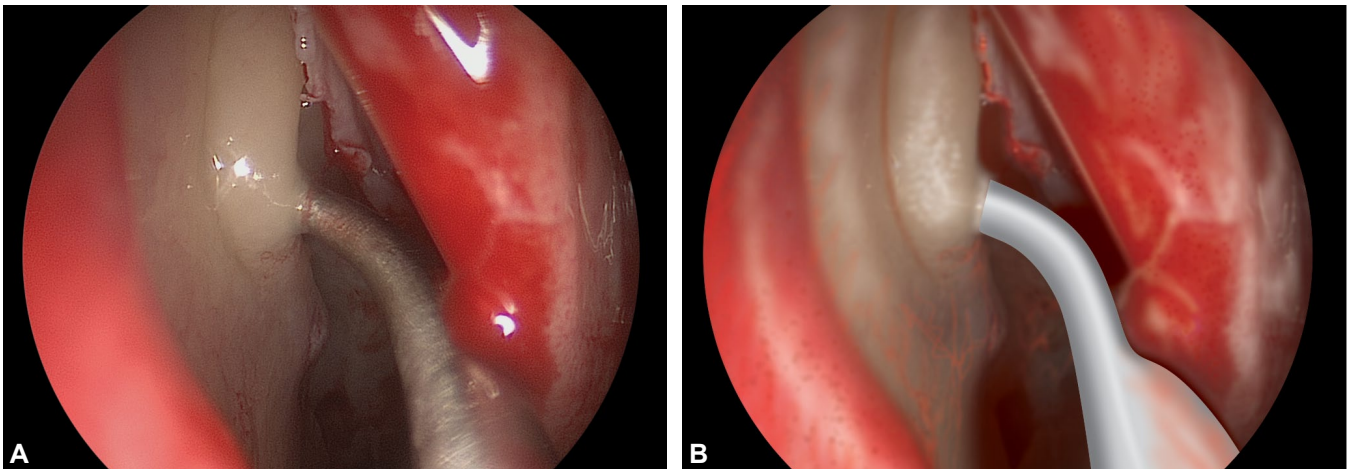
The basis of ESS is the assumption that obstruction of the paranasal sinus outflow tracts, including in the middle meatus area of the anterior ethmoid sinuses, secondarily block the maxillary, frontal and posterior ethmoid sinuses. The second assumption is that relief of this obstruction, particularly in the middle meatus, will allow improved physiology of the other paranasal sinuses and thus return to normal function. It is assumed in the vast majority of cases that the mucosal disease itself is reversible. A more modern concept is that one of the primary benefits of ESS is the creation of widely patent outflow tracts that allow for delivery of topical therapy in the postoperative setting. Although sinus disease is complicated in terms of its polymicrobial bacteriology, multiple possible causes of chronic inflammation, and numerous possible anatomic variations, there are two basic approaches based on two basic types of chronic disease: classic ostiomeatal complex disease and pansinusitis.

CLASSIC OSTIOMEATAL COMPLEX DISEASE

The classic ostiomeatal complex disease involves the anterior ethmoid sinuses, often the maxillary sinus and less frequently the frontal sinus. Generally, the posterior ethmoid and sphenoid sinuses are spared. While surgery can be done under local or general anesthesia, most commonly, in this country, general anesthesia is used. The authors prefer the use of laryngeal mask anesthesia over intubation. This largely reduces the frequent sore throat patients have from intubation, potential for laryngeal trauma and the risk of the patient bucking on the tube with associated bleeding at the end of the procedure.

Prior to starting the procedure, the CT scan should be carefully reviewed including disease pattern and surgical anatomy. A preoperative checklist of normal and variant sinonasal anatomy is reviewed including the integrity of the lamina papyracea and skull base, the thickness and slope of the ethmoid roof, depth of the cribriform plate, location and possible dehiscence of the anterior ethmoidal and internal carotid arteries, and common anatomic variants (i.e. infraorbital and sphenoethmoid cells).

Careful consideration is given to performance of nasal septoplasty. Indications include relieving nasal airway obstruction symptoms, and improving access both during the surgery and for postoperative care. Local anesthesia is

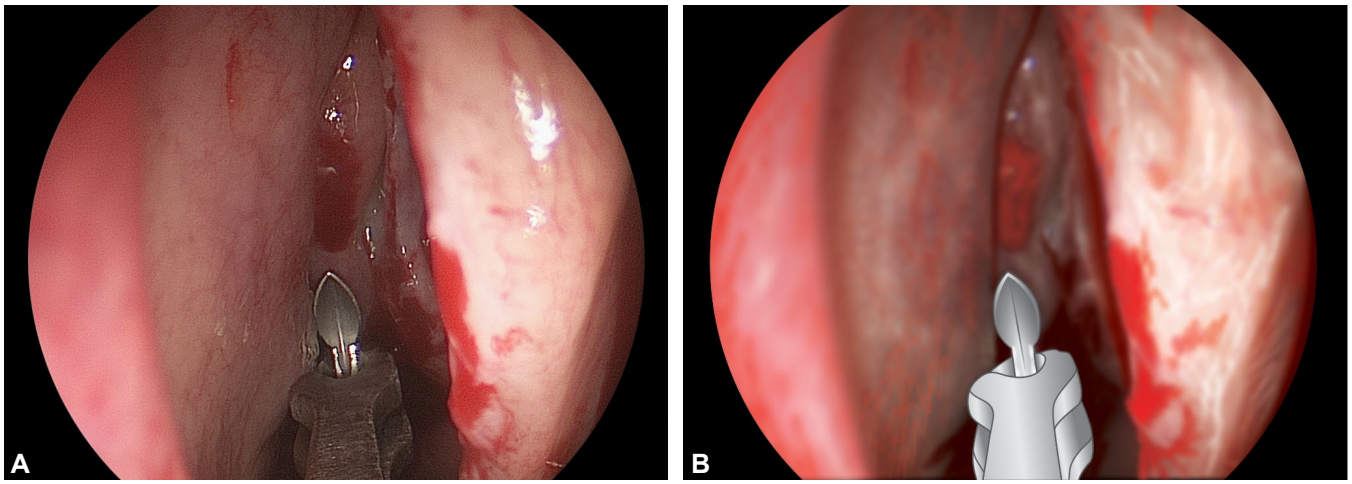


Figs. 49.1A and B: Sinus seeker behind uncinate process.

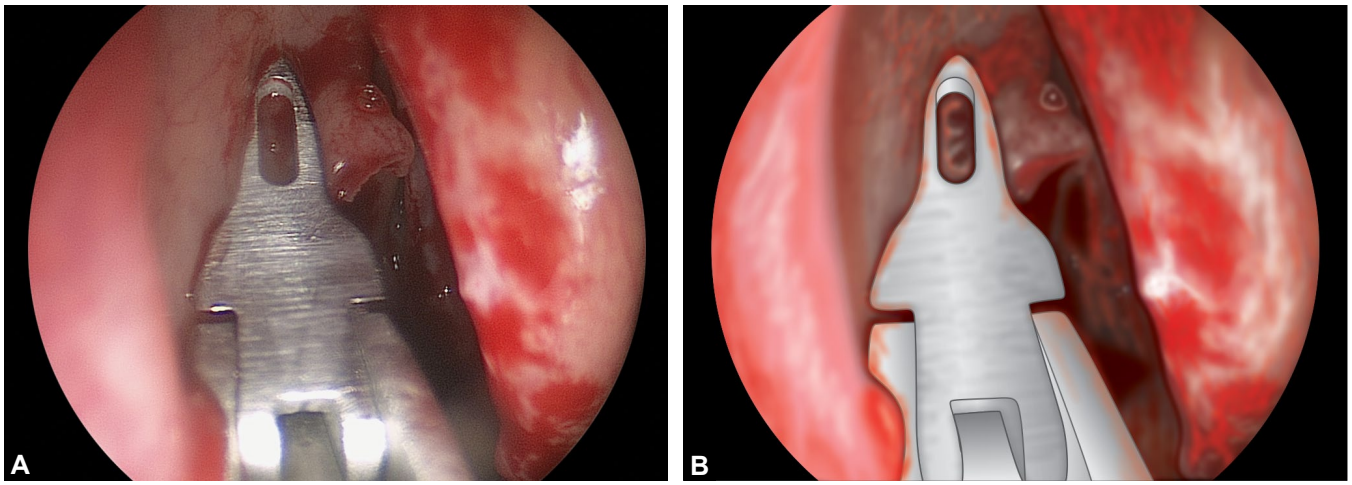
administered at the onset of ESS. One percent xylocaine with 1:100,000 of epinephrine is infiltrated into the submucosal plane of key areas including the nasal septum, the middle turbinate, the sphenopalatine foramen, and the lateral nasal wall in the area of the uncinate process. A greater palatine block may also be performed transorally in patients with severe polyposis. Decongestant (i.e. oxymetazoline, or xylocaine with epinephrine) soaked pledgets are then placed into the middle meatus and between the septum and the lateral wall, anterior to the middle turbinate. At least 5 minutes is allowed to elapse. During this time, the medications have time to take effect and the rise in blood pressure caused by the epinephrine injection will have subsided. It is preferable to have hypotensive anesthesia throughout the procedure.

ESS is started by inspecting the entire nasal cavity with a 0° endoscope. Assuming relatively normal anatomy, the procedure is started by removing the uncinate process. This can be done in a variety of ways. One common method is to make an incision at the base of the uncinate process with a sickle knife, Freer or Cottle elevator. The uncinate is then medialized and removed with straight Blakesley forceps. Others prefer to use a ball-tipped seeker (Figs. 49.1A and B) to fracture the uncinate anteriorly and then remove it with a microdebrider. Regardless of the method used, one needs to ensure a complete resection of the entire width and height of the uncinate process. Care additionally needs to be given to avoid over resection as the base of the uncinate is quite close to orbital contents. The width of the uncinate is approximately 5 mm. Proximity to the orbit is a particularly important consideration in patients with maxillary sinus atelectasis and hypoplasia where the uncinate process may be lateralized and adherent to the orbit. In these patients, a retrograde uncinectomy is preferable. This is performed by gentle anterior deflection of the uncinate process by a ball-tipped seeker followed by resection with a side biting forceps in a posterior to anterior direction (Figs. 49.2 and 49.3).

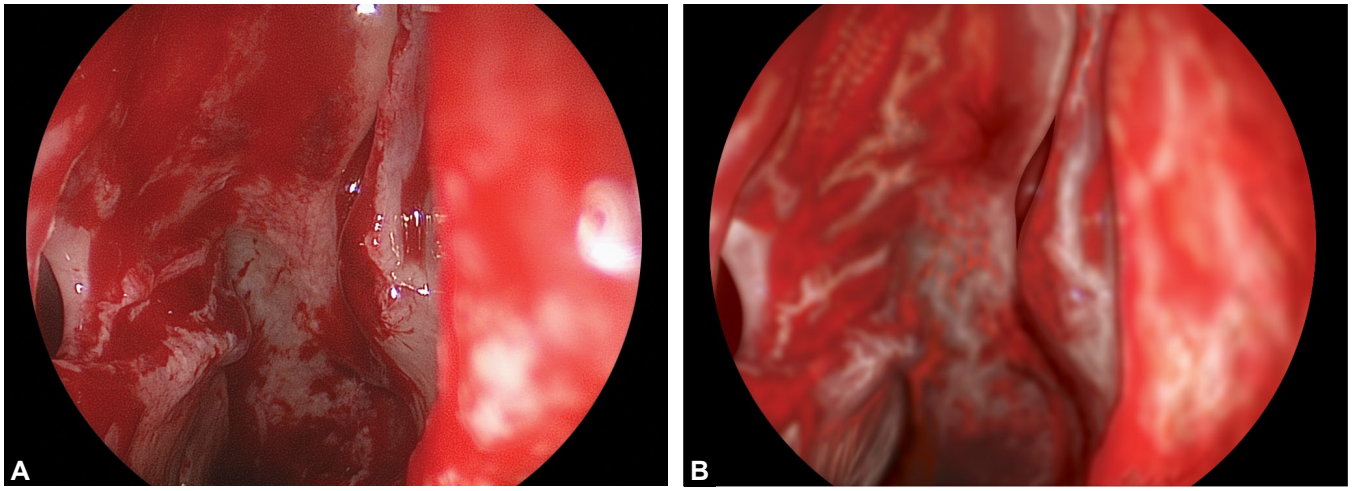
The next step following uncinectomy is to visualize the natural ostium of the maxillary sinus that lies posterior to the uncinate but anterior to the bulla ethmoidalis. The ostium lies within the hiatus semilunaris in proximity to the bulla. This may be seen with a 0° endoscope (Figs. 49.4A and B) but often a 30° (Figs. 49.5A and B) or 45° endoscope will be necessary. If the ostium cannot be visualized, one can palpate the fontanel area just superior to the inferior turbinate with a curved olive tip suction or ball-tipped seeker. The maxillary sinus ostium may be enlarged, particularly if work needs to be done within the maxillary sinus cavity. The ostium can be enlarged anteriorly using backbiting forceps. One should be careful to not go more anterior then the attachment of the uncinate process as you risk injuring the nasolacrimal duct that lies about 1 cm anterior. The ostium can also be enlarged posteriorly using thru-cutting forceps.[3] The posterior dissection is quite safe. There is no clear consensus as to the ideal size of the maxillary ostium, but 1 cm should be adequate. For many years, the senior author has done nothing to the maxillary ostium, regardless of size, if it can be easily visualized following the uncinectomy and no work needs to be done within the sinus. However, it is important that the natural maxillary ostium be identified and included in this antrostomy to avoid the risk of mucus recirculation. For the same reason, should one identify an accessory



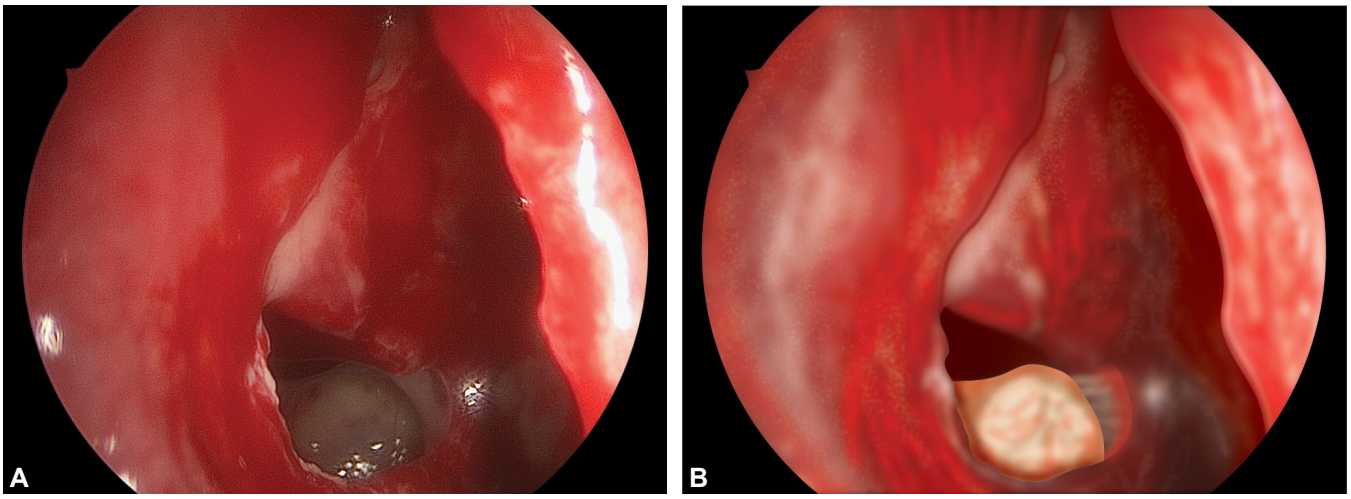
Figs. 49.2A and B: Pediatric backbiter resecting uncinated process.



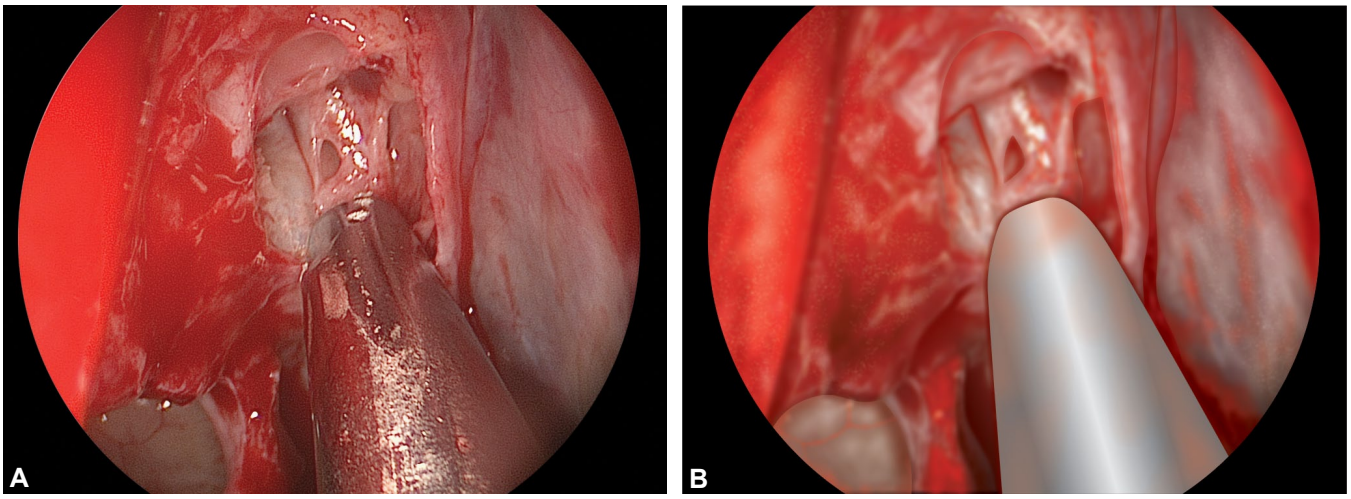
Figs. 49.3A and B: Completing the resection of the uncinated process.



Figs. 49.4A and B: Maxillary ostium viewed with a 0° endoscope.



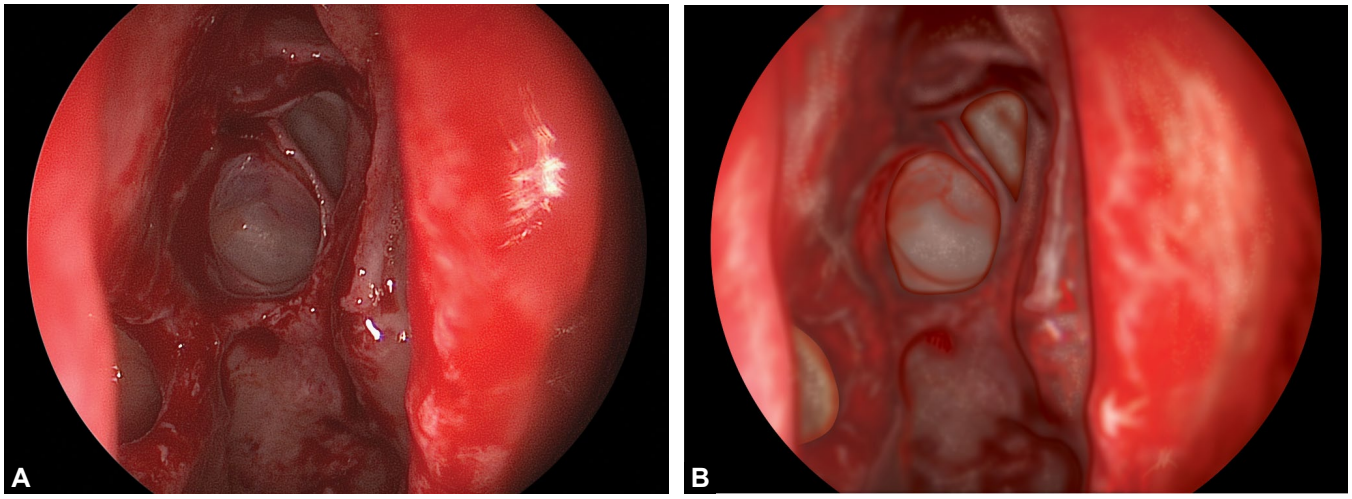
Figs. 49.5A and B: Maxillary ostium viewed with a 30° endoscope.



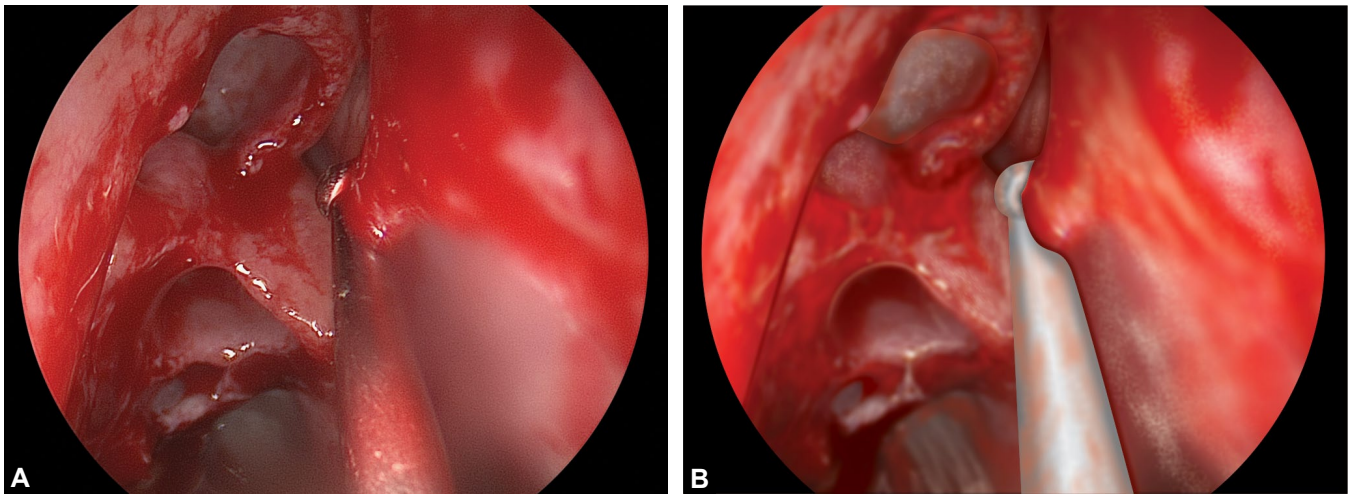
Figs. 49.6A and B: Resection of bulla ethmoidalis with microdebrider.

ostium posterior to the natural ostium, the two should be converted into one by removing the intervening mucosal bridge.

The next step is to complete the anterior ethmoidectomy by opening the bulla ethmoidalis and removing it (Figs. 49.6A and B) and all other anterior ethmoid air cells (Figs. 49.7A and B) to the level of the basal lamella. Throughout this chapter, straight and upbiting thru-cutting and Blakesely forceps will be mentioned frequently. In most of these instances, the procedure being discussed could be performed with a microdebrider as well. A lengthy discussion of the advantages and disadvantages of powered instrumentation is beyond the scope of this chapter. In brief, microdebriders allow for efficient clearance of polypoid tissue, mucosa and thin bone. The lack of mucosal stripping, active suctioning of blood and consistently sharp cutting surface are distinct advantages. Although the impact on the incidence of major complications is unknown, it is clear that the severity of the injury is greater with powered instrumentation. Therefore, care is given to maintain excellent visualization of the cutting blade and avoid apposition directly againstcritical areas including the skull base and orbit. The microdebrider can safely remove tissue freely accessible within the sinus, such as tissue curreted from the underlying bone. The limited ability to provide anatomic localization from the specimen collected from a microdebrider trap becomes an important issue in patients with occult neoplasm



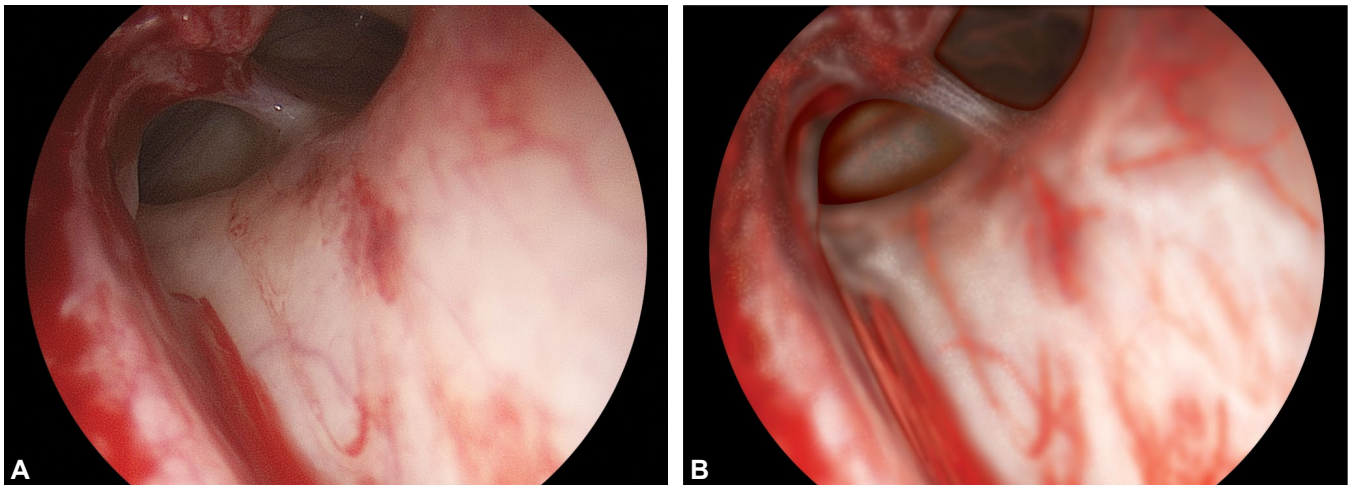
Figs. 49.7A and B: Completing anterior ethmoidectomy.



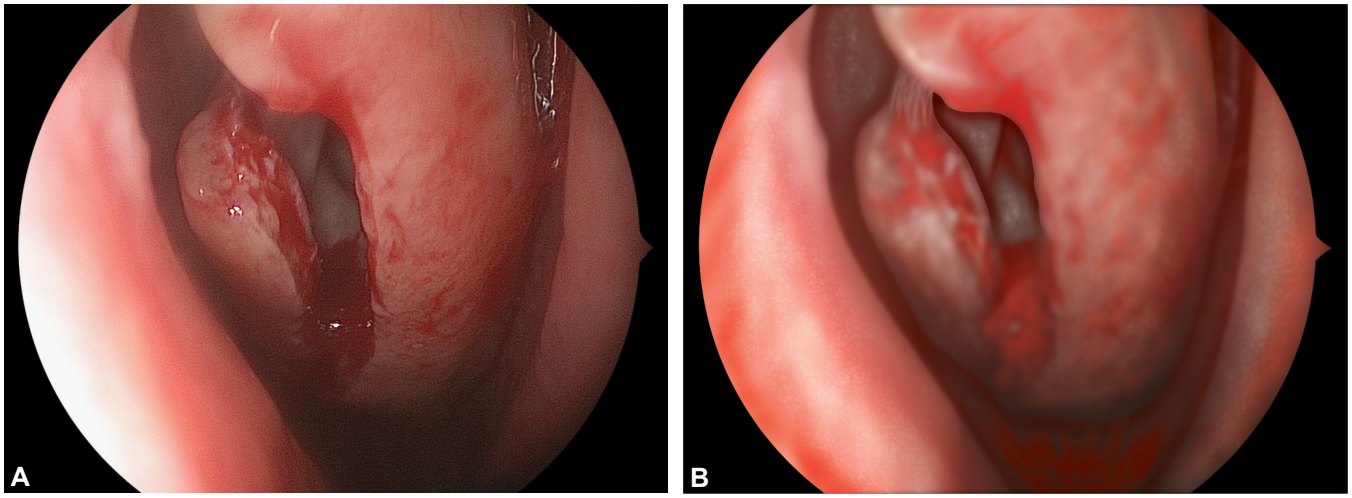
Figs. 49.8A and B: Frontal recess area.

in the setting of chronic inflammation. It is therefore important to separate the contents of the two sides in bilateral procedures that are captured in specimen containers from the powered devices. Routine analysis of specimens obtained with cold instrumentation and distinctly identified anatomic sites addresses this issue. Powered instruments are nearly essential for advanced endoscopic procedures including skull base surgery, frontal sinus drill-out procedures and endoscopic DCRs.

If the frontal sinus is normal on the preoperative CT scan, no dissection in the frontal recess area is necessary and might in fact prove harmful. On the other hand, if the sinus is diseased, the frontal recess area must be cleared of obstructing ethmoid air cells. If this is known and planned from the beginning, this maneuver may be done following the uncinectomy but prior to removing the bulla ethmoidalis. This is because the frontal sinus generally physiologically clears between these two structures and can be easily located by following the bulla ethmoidalis superiorly to the area posterior to the anterior-superior attachment of the middle turbinate. The area is best visualized with 45° and 70° endoscopes (Figs. 49.8A and B). The ethmoid cells in the frontal recess area should be removed with 45° and 70° instrumentation until the frontal sinus ostium can be easily visualized (Figs. 49.9A and B). A variety of instruments are available including front-back, side-side cutting forceps, angled mushroom forceps, and angled curettes. Bear in mind that the ostium is close to



Figs. 49.9A and B: Frontal sinus ostium.



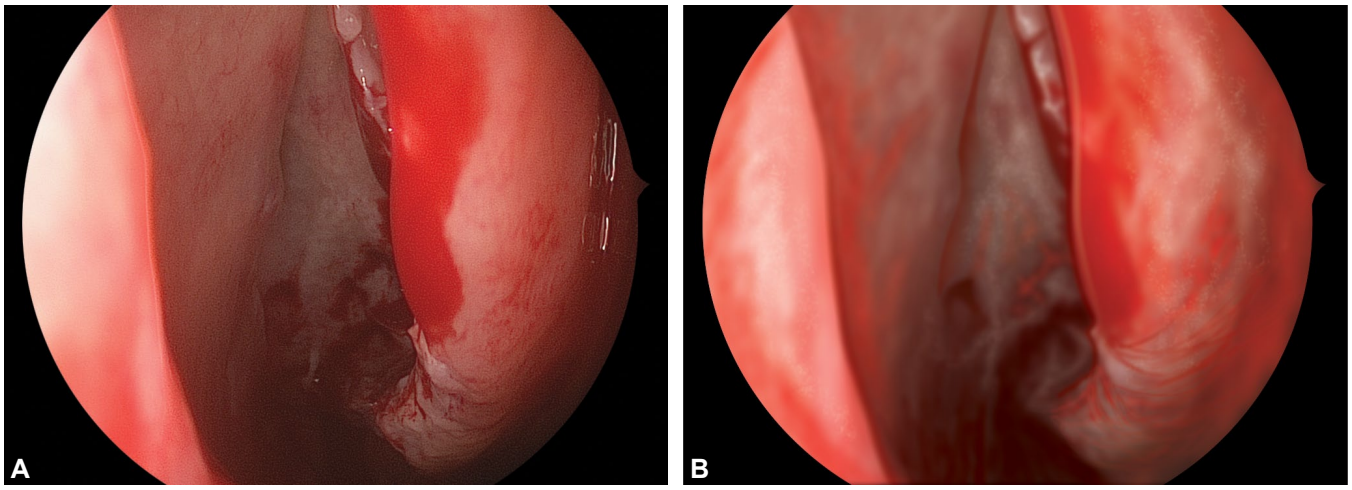
Figs. 49.10A and B: Incision in concha bullosa.

the back wall of the frontal sinus and just posterior to that is the anterior ethmoidal artery and the anterior cranial fossa. Therefore, the trajectory of movements should be mostly in a posterior to anterior trajectory.

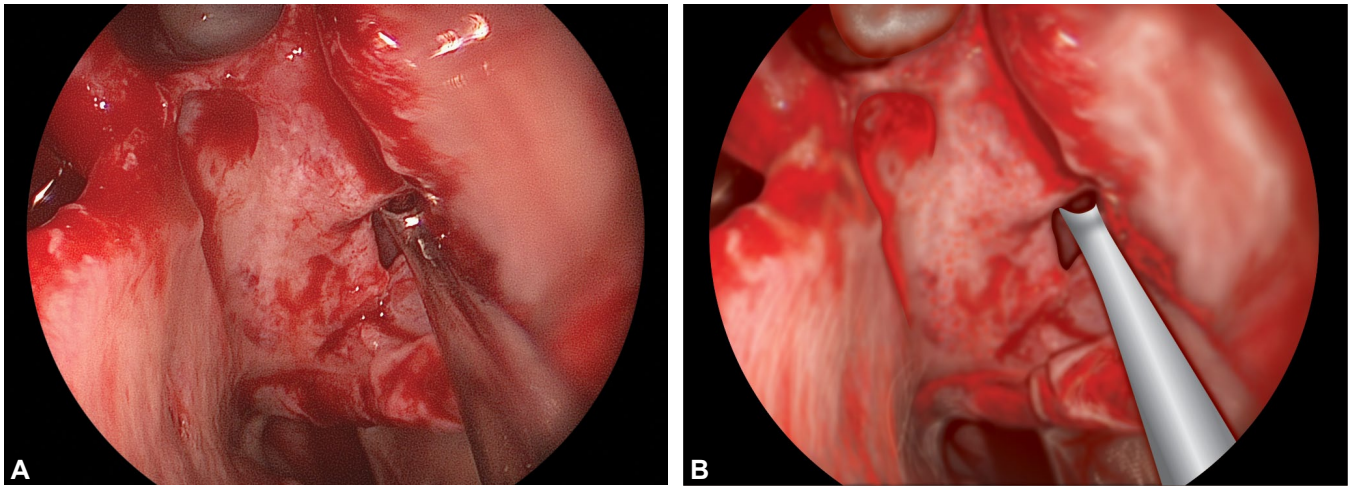
In standard uncomplicated ostiomeatal complex disease, the procedure would now be complete.

In general, the middle turbinate is left undisturbed if it is in a position and anatomic configuration to allow for outflow tract patency. However, if there is a paradoxically bent middle turbinate or a concha bullosa within the middle turbinate, additional procedures are probably warranted.[4,5] The paradoxically bent middle turbinate (convex laterally) is best managed by removing the bottom two thirds of the turbinate back to the basal lamella. This will completely uncover the ostiomeatal complex and allow for excellent space for sinus physiology and access for postoperative care. Some surgeons do this routinely, paradoxically bent or not.

A concha bullosa may be managed by making an incision into the anterior head of the middle turbinate with a sickle knife (Figs. 49.10A and B). One can then use straight cutting middle turbinate scissors to make an incision along the inferior edge of the middle turbinate and then an incision along the superior part of the lateral wall of the concha bullosa below the superior attachment. The lateral wall can then be grasped with cutting instrumentation and removed.[6] This will greatly widen the middle meatus (Figs. 49.11A and B). Care must be taken when doing this maneuver to not destabilize the middle turbinate, which will significantly increase the risk of



Figs. 49.11A and B: Widened middle meatus following resection of lateral wall of concha bullosa.



Figs. 49.12A and B: Perforating basal lamella.

adhesions to the lateral wall. A few technical points are in order. It is probably safest to remove the uncinate process and the anterior ethmoid air cells with straight biting forceps or a microdebrider. The bulla ethmoidalis should be first opened medially close to the middle turbinate. The straight biting forceps should be held vertically so that the articulating jaw does not point toward the lamina papyracea. The natural drainage pathways of the anterior ethmoid air cells are medial. The anterior tip of the middle turbinate may also be resected when there is polypoid degeneration of the mucosa, which can lead to difficult visualization postoperatively.

The extent of ethmoidectomy that should be performed in patients with limited ethmoid disease is not well defined. Potential advantages of performing a total ethmoidectomy in patients with disease limited to the anterior ethmoid sinuses include maximizing patency and the theoretical principle of extending the surgery one level beyond the disease. Disadvantages include potentially disrupting healthy sinonasal function, exposure of the patient to unnecessary risk from additional surgical dissection and propagating spread of the infection. However, if the patient has posterior ethmoid disease then a complete ethmoidectomy is clearly in order. One should remember that the sphenoid ostium and the maxillary ostium are on approximately the same axial plane. So the basal lamella should be perforated with a straight biting forceps on the same axial plane as the maxillary ostium and close to the middle turbinate attachment to the basal lamella (Figs. 49.12A and B). The posterior ethmoid air

cells can then be widely opened with a straight biting forceps or microdebrider with care being taken not to go superiorly until the sphenoid sinus is reached. The superior turbinate is a good landmark for identifying the sphenoid ostium.

Once the front face of the sphenoid sinus is reached, the posterior ethmoid air cells are opened laterally to the lamina papyracea. One should then change to the upbiting forceps in addition to the microdebrider for the more superior cells. There are now three landmarks clearly in view: (1) the maxillary ostium, (2) the sphenoid ostium, and (3) the anterior-superior attachment of the middle turbinate. Using these landmarks, one can then start to exenterate the superior ethmoid air cells under direct vision. Remember that the maxillary ostium is on the same parasagittal plane as the lamina papyracea in the overwhelming majority of patients and this is easily confirmed on preoperative CT scan. Initially, the advancement superiorly should be close to the lamina papyracea as the bone of the roof of the ethmoid is typically thicker laterally close to the orbit than it is medially as it approaches the cribriform plate. The lateral lamella of the cribriform plate is the most common site of iatrogenic CSF leak.[7] This is attributed to its thinness, variable and often low position, and proximity to the medial boundary of the dissection. Assessment of the depth of the cribriform plate on preoperative CT scan is an important step in preoperative planning and can be classified by the Keros classification. In performing clearance of the superior ethmoid cell partitions, the superior boundary is the fovea ethmoidalis. This is most easily identified in the posterior ethmoid cells given their larger size and fewer numbers. This anatomy is well visualized on the sagittal images of the preoperative CT scan. A posterior to anterior dissection of the superior ethmoid cells takes advantage of both the ease of identification of the fovea ethmoidalis in the posterior ethmoid cells and the natural downward slope of the skull base. In a posterior to anterior dissection, a straight horizontal vector of force will avoid the skull base since it is at its lowest point at the start of the movement. The final step in a posterior-anterior dissection involves clearance of anterior-superior ethmoid partitions and allows for a widely exteriorized ethmoidectomy cavity with the following boundaries: middle turbinate medially, lamina papyracea laterally, fovea ethmoidalis superiorly and anterior face of the sphenoid sinus posteriorly.

Once the ethmoidectomy is complete, the sphenoid sinus can be opened if that is necessary. Most commonly, the sphenoid antrostomy is designed to be in continuity with the ethmoidectomy cavity. This can be achieved either by identifying the natural sphenoid ostium in the sphenoethmoid recess and extending it laterally or by opening the anterior face of the sphenoid sinus in the posterior most ethmoid cell. The natural ostium is generally identifiable in the sphenoethmoid recess, medial to the superior turbinate, lateral to the nasal septum, and directly above the basisphenoid, approximately 10–12 mm above the choana (Figs. 49.3A and B). If not visible secondary to mucosal inflammation, gentle palpation in this area with a ball-tipped seeker or a curette will generally allow for its identification.

Of note, the ostium is typically positioned at the upper two thirds of the entire height of the sphenoid sinus. Therefore, once identified, the sphenoid sinus ostium is expanded initially in an inferior direction to minimize the risk of inadvertently injuring the planum sphenoidale. The initial down fracture can be performed with a curette forceps and then expanded with a sphenoid punch or downbiting Kerrison forceps. To bring the sphenoidotomy into continuity with the ethmoid cavity, the antrostomy is extended laterally and the lower edge of the superior turbinate may be removed.

Alternatively, the sphenoidotomy may be performed through a transethmoidal approach. This is performed by creating a controlled fracture of the anterior face of the sphenoid sinus in the posterior most ethmoid sinus. Maintenance of a downward and medial trajectory is necessary to minimize the risk of skull base or carotid injury. Once the sphenoid sinus cavity is identified, the ostium is circumferentially widened. Powered instrumentation should be used selectively and with great care and ideally only after the sphenoid sinus landmarks are visible. The risk of major neurovascular injury is especially heightened in patients with dehiscence of the optic nerve or internal carotid artery. Arterial bleeding from the posterior nasal septal branch of the sphenopalatine artery is often encountered and is marked by pulsatile bleeding at the inferior edge of the sphenoidotomy. This should be controlled with cauterization at the time of surgery. It is rarely necessary or worthwhile to do any work within the sphenoid sinus itself in patients with inflammatory CRS. Remember that the intersinus septum is rarely midline and is often attached posteriorly to the carotid canal.

PANSINUSITIS

Although the surgical principles, techniques and instrumentation are similar when applied to different phenotypic variants of CRS, important distinctions do exist. In patients

with pansinusitis, especially with severe polyposis, the operation should be approached somewhat differently. The primary goals of creating widely patent outflow tracts and clearance of obstructive polypoid tissue have the equally important goals of mitigating the ongoing inflammatory process and improving access for topical therapy. Therefore, it is often efficacious to consider a partial middle turbinectomy. This may involve clearance of grossly polypoid tissue and preservation of the normal architecture. Preservation of the middle turbinate whenever possible is appropriate, given the potential adverse events that may occur with resection: arterial bleeding, skull base injury, postoperative lateralization of the stump with obstruction of the middle meatus and frontal recess, loss of an important surgical landmark for future revision cases, permanent loss of olfactory function. In patients with severe, refractory, polypoid CRS, the ability to manage the postoperative cavity is paramount and it may be appropriate to consider a partial resection of the middle turbinate. This may target the inferior and lateral portions of the middle turbinate and maximizes the patency of the paranasal sinus outflow tracts. This is most easily accomplished by clamping the middle turbinate with straight tonsil forceps for 30–60 seconds. This will leave behind a crushed area that will not bleed. The straight cutting endoscopic scissors or thru-cut forceps can then be used to cut along this crushed area to the front face of the sphenoid sinus and the lower part of the middle turbinate removed. Hemostasis with a cautery may be required.

This maneuver alone will accomplish a significant part of the ethmoidectomy, particularly posteriorly. The complete ethmoidectomy is then performed as previously described. The maxillary ostium is identified and enlarged as needed. The frontal recess area is then cleared of obstructive polypoid tissue and ethmoid partitions. Although the techniques and instrumentation are similar to the previously described concepts, there are important distinctions. Powered instrumentation is particularly useful in these cases to clear polypoid tissue and maintain visualization, even with an increased amount of bleeding. Maximizing the dimensions of the outflow tracts is important in these patients to allow for increased delivery of topical therapy in the postoperative setting. Finally, obtaining hemostasis is especially challenging in these patients. A variety of things can be done to assist with hemostasis. Systematic use of topical decongestants, local anesthesia, and hypotensive anesthesia as described above is essential. A variety of absorbable and nonabsorbable packing materials are commercially available with the theoretical goals of hemostasis, splinting the middle meatus open, and preventing adhesions. The authors have tried a large number of materials over the years and most worked satisfactorily. The cheapest and most effective at this time seems to be a topical hemostatic powder made from potato starch.

POSTOPERATIVE MANAGEMENT

There are a variety of ways of doing the postoperative care-probably as many as there are surgeons doing this procedure. Many do aggressive saline irrigations followed by steroid sprays while others do essentially nothing. As a rule, regardless of the postoperative care, the results are generally excellent (Figs. 49.13 and 49.14).

Most surgeons see the patients frequently in the office in the postoperative period for debridement of the operative site to hopefully accelerate healing with the least amount of scar tissue formation. The debridement is done under local anesthesia using suction and forceps as necessary to remove crusts, thick mucus, adhesions, etc. Management of the ongoing inflammation and infection in the early postoperative is critical to overall success.

There are several occasions with specific diseases where slight alterations in the normal care of the patient are in order. One of these is Samter's triad (nasal polyposis, asthma, aspirin sensitivity). It has become quite clear in recent years that if patients are desensitized to aspirin in

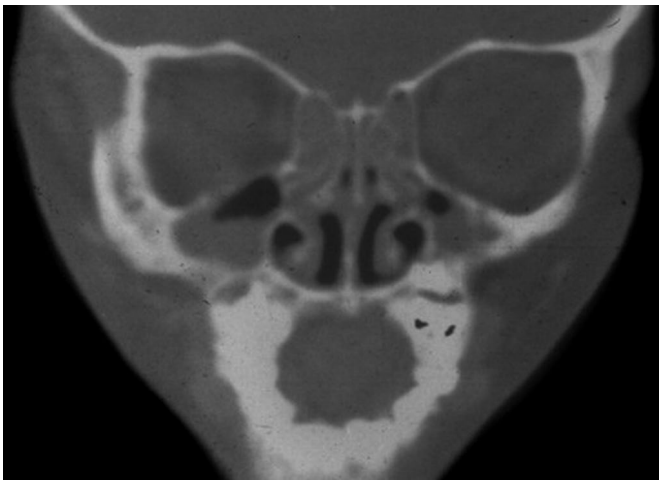


Fig. 49.13: CT scan of patient with classic ostiomeatal complex disease.

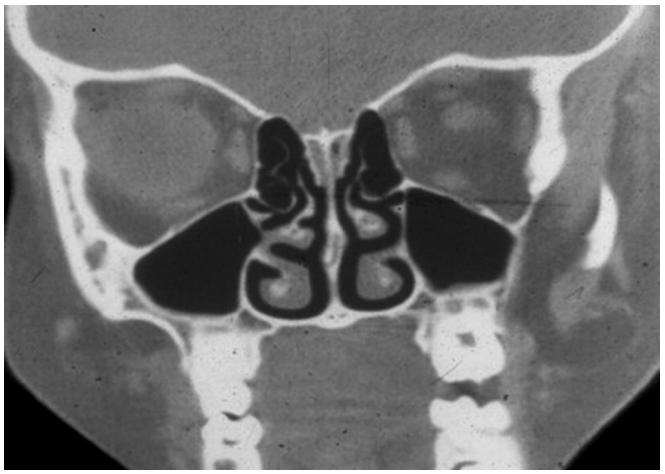


Fig. 49.14: Postoperative CT scan of patient in Figure 49.13.

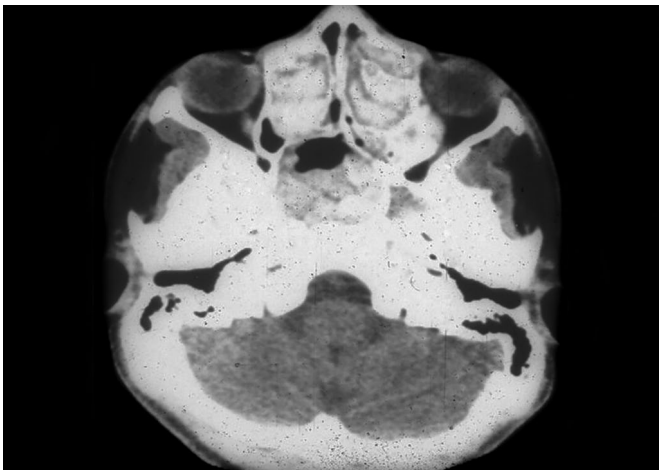


Fig. 49.15: Preoperative CT scan of patient with allergic fungal sinusitis.

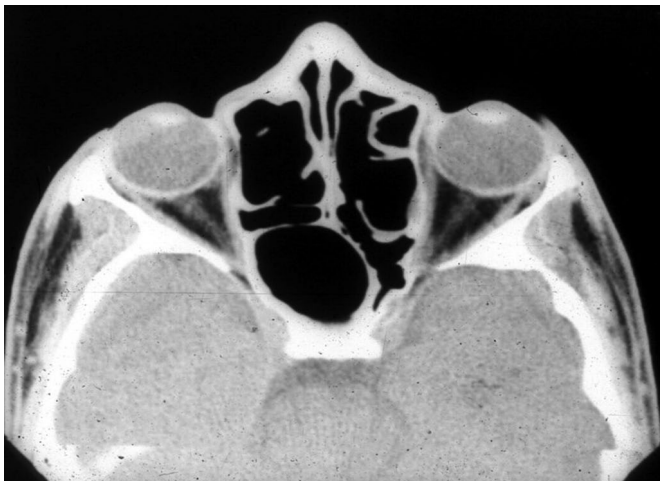


Fig. 49.16: Postoperative CT scan of the patient in Figure 49.15.

the early postoperative period, they will do much better over time. Desensitization needs to be done by an allergist skilled in this procedure. In the end, the patient generally may take aspirin for life. For that reason, the desensitization should be performed after the surgery, not before, in order to avoid a break in the aspirin regimen.

A second disease of note is allergic fungal sinusitis. This may be a unilateral or bilateral process. The patients generally present with complete nasal airway obstruction and polyps. Generally, one will be suspicious of the diagnosis on the preoperative CT scan, which frequently shows heterogeneous material within the involved sinus or sinuses and often bone expansion and virtually always polyps. During the course of the procedure in this disease one will encounter very thick tenacious mucus that is a dirty brown-gray color reminiscent of peanut butter. The key to success in this procedure is to remove all fungal elements from all involved sinuses and to create widely patent outflow tracts. The senior author routinely irrigates all involved sinuses with betadine solution at the end of the procedure since betadine is fungicidal. When this is done successfully, recurrence is unusual (Figs. 49.15 and 49.16).

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CHAPTER

50

Revision Sinus Surgery

Justine BF Millar, Dustin M Dalgorf, Richard J Harvey

Although endoscopic sinus surgery (ESS) is generally highly successful, failure has been reported to be in the vicinity of 10–25%.[1] This chapter examines some of the reasons due to which surgery can fail. Surgical failure usually arises from poor disease factors, suboptimal surgical technique, and insufficient postoperative maintenance therapy. Revision surgery is often more challenging, but the principles of surgery remain the same, i.e. to create a single functional sinus cavity preserving mucosa and allowing topical access so adjunctive medical therapy is permitted. Revision surgery will succeed through attention to both anatomical landmarks, ensuring a single functional cavity, and addressing the intrinsic mucosal factors driving chronic rhinosinusitis (CRS).

WHY IS THERE PERSISTENT MUCOSAL DISEASE?

Disease Pathogenesis

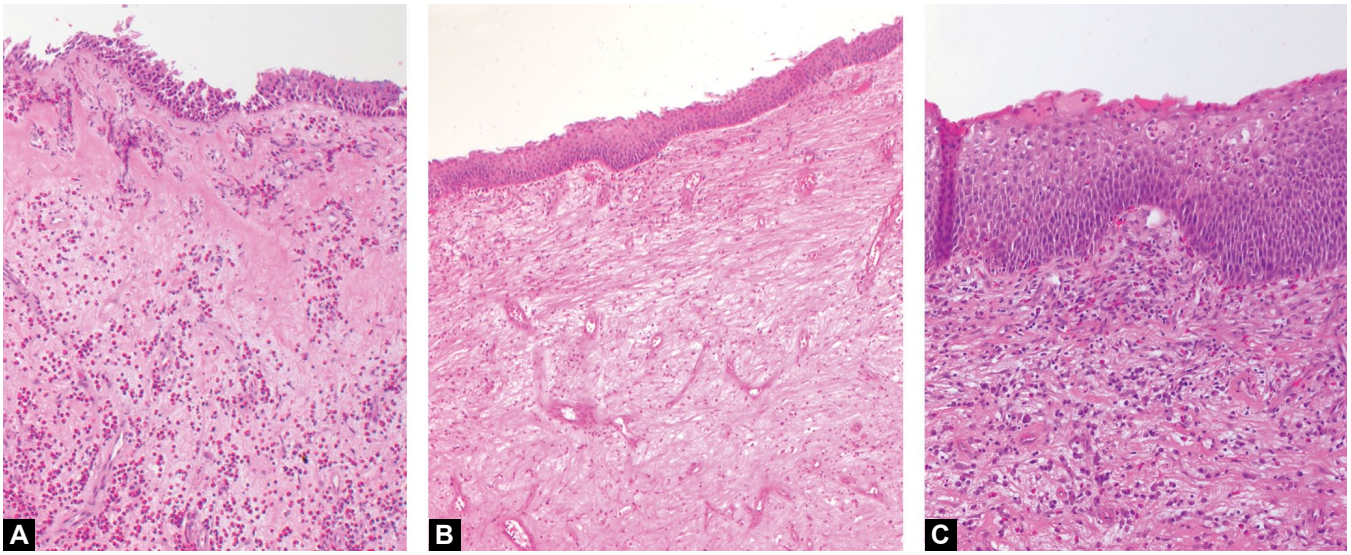
Chronic rhinosinusitis is considered similar to other chronic inflammatory epithelial diseases, where failure of normal mechanical and innate immunity results in a dysfunctional host response.[2] Mucosal disease in CRS is considered to be the result of three main driving forces, namely, that of intrinsic mucosal inflammation, local microbial colonization, and mucociliary dysfunction.[3] Individuals often exhibit a dominant contributing factor within this triad, with the other two factors being disease modifiers.

Mucosal Inflammation

Mucosal inflammation is the defining feature of CRS and other chronic airway conditions.[4] CRS evolves from a cascading progression of disease events. Patients with CRS can be classified either by phenotype or endotype. Endotype is confirmed on histopathology and is generally either eosinophilic or noneosinophilic. Eosinophilic disease is associated with asthma, aspirin sensitivity, and nasal polyposis. The propagating event in eosinophilic disease is usually intrinsic mucosal inflammation (Figs. 50.1A to C). The mucosal inflammation leads to mucosal ulceration that in turn promotes pathogenicity of local microbial community resulting in invasion of the epithelium. The subsequent epithelial damage, edema, and mucus changes lead to impaired mucociliary function. Impaired mucociliary transport consequently may also lead to local infection. The local microbial community contributes to the cascade by exposing mucosa to proinflammatory products, such as exotoxins. Mucosal damage can also occur directly from environmental factors such as cigarette smoke inhalation, or indirectly from inhalent allergens via immune responses.[3]

Local Microbial Community

Local microbial community forms the second contributing feature of the triad of CRS. The microbial community can exist as either as a planktonic form or in a biofilm and includes viruses, bacteria, and fungi. The planktonic microbial community interacts with the mucosa through proinflammatory mediators such as exotoxins and capsular polysaccharides. These trigger an acute inflammatory response and impair mucociliary motion. This response is propagated by microbial communities living in biofilms.



Figs. 50.1A to C: Significant sinus disease with histological appearance of eosinophilia and features of remodeling.

Superantigens such as Staphylococcus may induce eosinophilic inflammation in at least some cases of CRS. Bacterial infection can be facilitated by mucosal inflammation and impairment of ciliary function caused by viral infections.[5] Although the local microbial community can initiate an inflammatory response, they are considered to function more as disease modifiers than etiologic factors.

Mucociliary Dysfunction

Mucociliary function is impaired in CRS; however, it is rarely the primary cause of CRS. The mucociliary apparatus comprises a mucous blanket with beating cilia and is the major mechanism of innate immunity. Abnormalities in cilial function occur in conditions of altered cilial structure, function, and coordination. This may occur primarily or secondarily. Primary ciliary dysfunction includes primary ciliary dyskinesia associated with Kartagener syndrome. Most patients with CRS demonstrate secondary ciliary dysfunction, which is a result of inflammation and infection.[6] The mucous properties are affected by hydration and glycoprotein composition. Volume of mucous production is affected by the hypersecretory states as seen in CRS. Mucociliary clearance is impeded by ostial obstruction and recirculation. This delayed mucociliary flow prolongs contact time with microbes, antigens, and inflammatory substances, promoting further microbial colonization and inflammation, creating a perpetuating cycle (Fig. 50.2).[3]

IMPLICATION FOR TREATMENT

Chronic rhinosinusitis is by definition a chronic disease where treatment is focused on symptom control rather than on cure; however, normal mucosa is always the goal. The triad of mucosal inflammation, microbial community, and mucociliary dysfunction coexists with positive feedback between them (Fig. 50.2). This leads to the involvement of all three factors in the disease process. Defining the propagating factor of the triad, however, is critical in the treatment strategy.[3] Currently, patients with discrete mucociliary dysfunction or simple untreated infection appear to have the best prognosis. In contrast, those with intrinsic mucosal inflammation require greater care and are more resistant to shor-term treatment.

Treatment of Propagating Factors

Managing Mucosal Inflammation

Mucosal inflammation can be treated with macrolides and corticosteroids. Long-term macrolide therapy has been shown to be affective in the modulation of IL-8 production and thus works as a neutrophilic modulator. However, there is no evidence to show that macrolides work on eosinophilic disease.[7] Macrolides also function by interfering with biofilm formation, reduce mucosal inflammation, and as a result diminish mucous production.[7] Systemic steroids act as generalized immune suppressants. Topical steroids, in the form of irrigation, have a good effect on

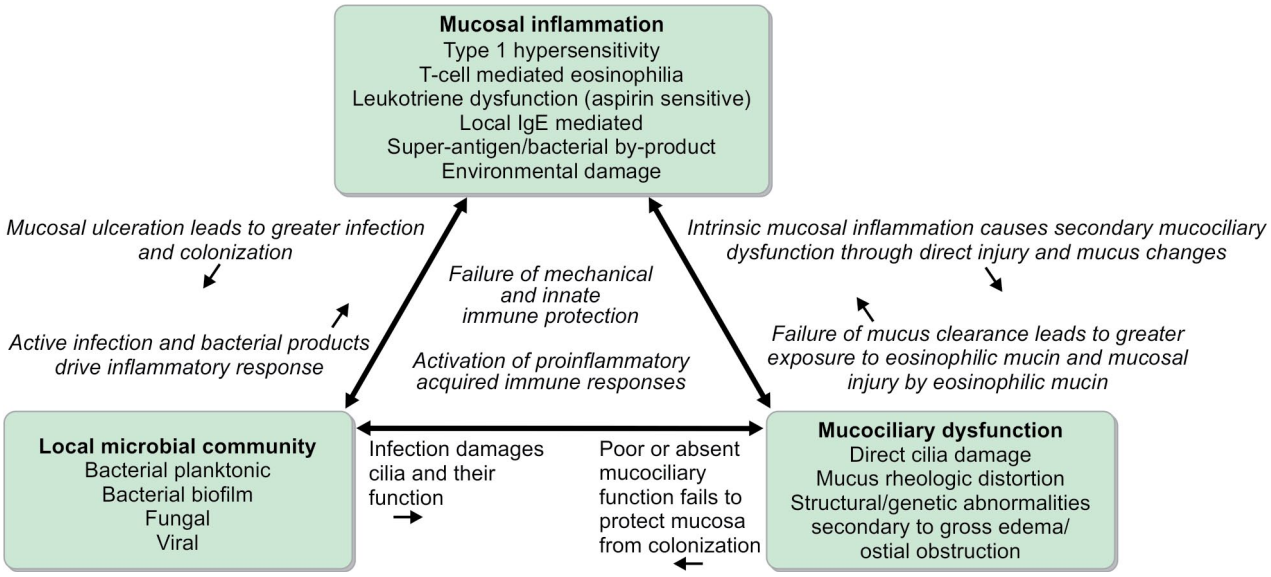


Fig. 50.2: Chronic rhinosinusitis (CRS) triangle.

Fig. 50.3: Patient using sinus rinse.

open sinus mucosa with minimal systemic absorption[8] (Fig. 50.3). If the steroid wash cannot penetrate into the sinuses, e.g. due to postoperative scarring, then they may influence turbinate reactivity and reduce some nasal symptoms without actually modifying the disease process. Adequate surgery allows effective maintenance therapy. Patients with a predominant inflammatory component to their disease, such as asthma and atopic disease, respond to corticosteroid therapy. Doxycycline has also been shown to reduce polyp size in patients with inflammatory disease when compared to placebo.[9]

Restoring Microbial Community

Microbial communities can be treated with antibiotics and surfactants. Planktonic bacteria can be effectively treated with targeted antibiotic therapy. Most antibiotics have little effect on bacterial biofilms, with the exception of macrolides. Topical antibiotics can be effective in high concentrations. Surfactants applied topically can physically disrupt biofilms and inhibit biofilm formation.[10] As with other topical therapies, surfactants and antibiotics are only effective if they have contact with sinus mucosa, and only in the postoperative state.[8] Current research indicates that restoring the normal sinus microbiome has protective mechanisms, although the exact mechanism by which these microbes protect sinuses is as yet unknown. Lactobacilli, e.g. have been shown to lower the surrounding pH through their production of lactic acid. This changes the local environment of the sinuses and is thought to influence the coexistence of other more pathogenic microbes.[11] More pathogenic microbes such as superantigen exotoxin producing *Staphylococcus aureus* have been shown to stimulate eosinophilic inflammation through production of Th2 cytokines and local IgE formation.[5] Consequently restoring the normal sinus microbiome is thought to reduce *Staphylococcus aureus* colonization, leading to a reduction in sinus mucosal inflammation.

Replacing Mucociliary Clearance

Mucociliary clearance is most commonly treated with saline irrigation. Saline irrigation can augment or replace mucociliary clearance by physically removing proinflammatory substances (eosinophilic mucin, infected crusts or antigens).[12] Patients with crusting, as a result of dehydrated secretions, are excellent candidates for this. Saline irrigation can also be mixed with antibiotic preparations or steroids to allow adequate delivery of these substances to open sinuses.

Treatment Philosophy

Endoscopic sinus surgery is widely employed to manage CRS refractory to medical treatment. Traditional concepts for surgery in CRS have centered on relieving ostial obstruction and enhancing ventilation. Historically, the postulated effects of ESS include improved mucociliary mass mucous blanket transport, overall reduction in inflammatory mucosal surface area, and brief shift in Th1 inflammatory response in the postoperative healing mucosa.[13] It is becoming increasingly evident that the most powerful effects of ESS may simply be topical access to sinus mucosa. Current postoperative care regimes may be the intervention factor that resolves continuing inflammation rather than the surgery itself.

WHY DID THE PRIMARY SURGERY FAIL?

Incorrect Diagnosis

Disease Process Not One of Ostial Occlusion

Chronic rhinosinusitis is generally a result of the interacting triad of intrinsic mucosal inflammation, local microbial community and mucociliary dysfunction. Ostial occlusion has been shown to induce sinus infection and deranged mucociliary clearance; however, it is rare in the absence of other pathology.[14] Relieving ostial occlusion in most patients with CRS without follow through with ongoing topical therapy has little effect.[15] This is especially so in patients with nasal polyps and concomminant airway conditions like asthma.[16]

Inflammatory Disease Process

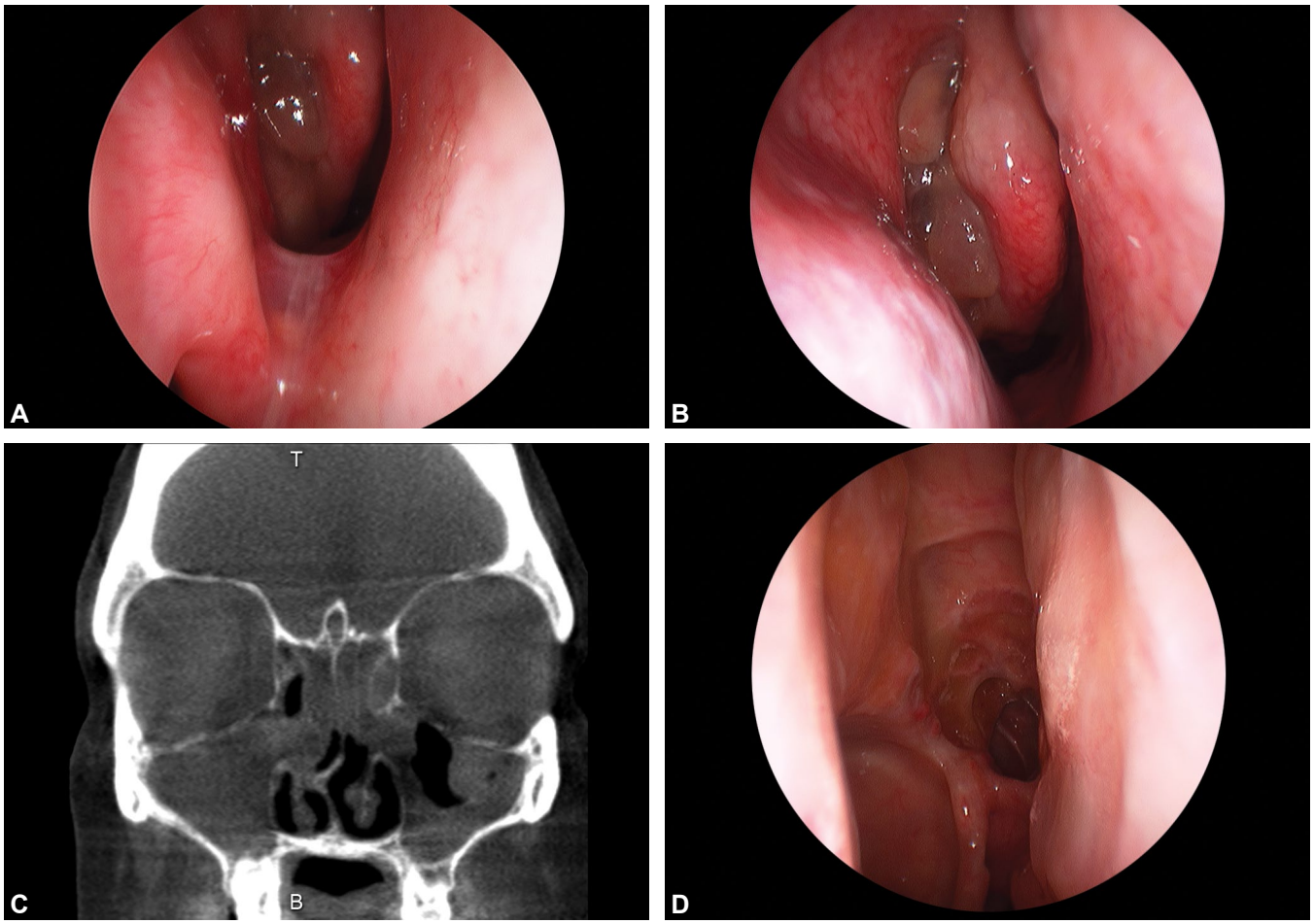
Patients with CRS can be subclassified according to either phenotype or endotype. Phenotype takes into account what is seen on nasendoscopic examination and divides patients into either CRS with or without polyps. Endotype is confirmed on histopathology and is classified as either eosinophilic (>10 eosinophils per high power field) or noneosinophilic.[17] Eosinophilic CRS is often associated with nasal polyps. However, the phenotype and endotype are different in many patients, as tissue eosinophilia is also present in up to 19% of patients with CRS without polyps.[17] Eosinophilic CRS is associated with clinical severity, poor outcome, and high recurrence rate after ESS[15]. This group of patients is likely to require long-term anti-inflammatory therapy. Single-modality therapy such as ESS alone is unlikely to produce satisfactory results. Failure to recognize these patients preoperatively and continue anti-inflammatory treatment in the postoperative setting can lead to treatment failure. (Figs. 50.4A to D).[15]

Persistent Rhinitis

It is important to separate the etiology of nasal symptoms. As many as 40 % patients with CRS will have a concomminant history of persistent rhinitis (usually allergic). Allergic rhinitis (AR) is common, as much as 25% of the population,[18] and can produce nasal congestion, mucus production, loss of smell, and other CRS-like symptoms. Patients with significant AR in need of concurrent turbinate procedures should also be offered appropriate immunotherapy.

Iatrogenic

Endoscopic sinus surgery has evolved from microsurgical techniques with mucosal stripping to minimal techniques to maximal open cavity techniques with mucosal preservation. This shift has resulted from an improved understanding of the pathogenesis of CRS. Simple surgical techniques to improve ventilation of the sinuses, while adequate in some situations, are now considered insufficient to treat CRS alone and have led to higher levels of treatment failure. Studies have shown that approximately 10% of patients require revision surgery within 3 years.[19] Other studies have reported up to 50–100% recurrence rates for patients with nasal polyposis.[20] The problem with limited ESS techniques is that it may induce scarring, iatrogenically affecting sinus outflow tract or creating mucus recirculation. This iatrogenic induced scarring of sinus outflow results in both ongoing CRS and exacerbation of symptoms. Poor cavity healing precludes effective application of topical therapies. Additionally, nasal mucous recirculates either if the true sinus ostium is not



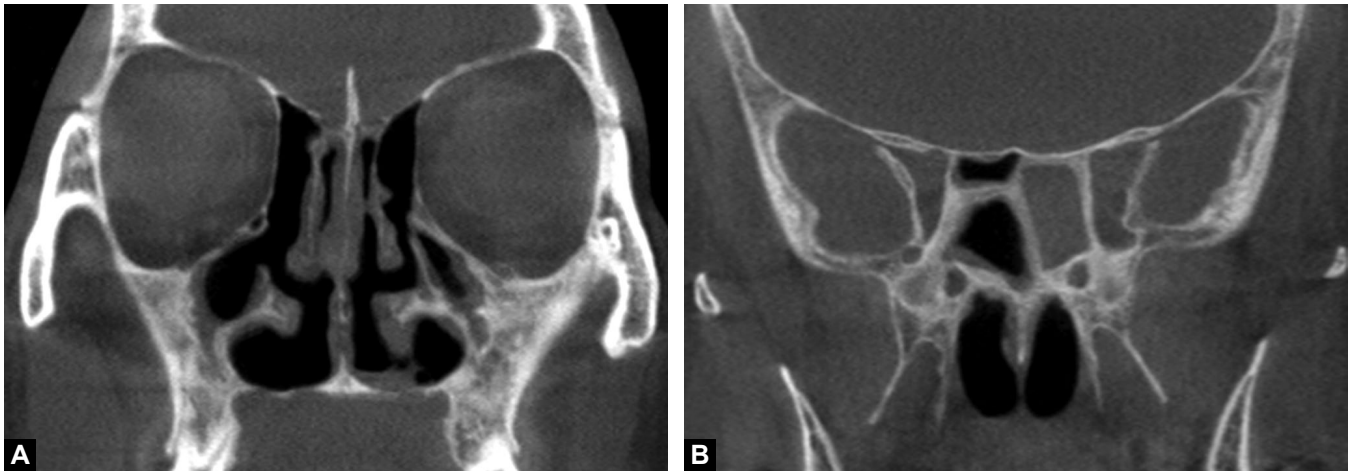
Figs. 50.4A to D: (A and B) Clinical photographs showing obstructed sinus due to polyps; (C) CT of same patient demonstrating nasal polyps and obstructed sinuses; (D) postoperative clinical photograph demonstrating healthy, wide-open sinus cavity.

opened or if accessory ostium is created iatrogenically. This recirculation increases the risk of persistent sinus infection.

Musy and Kountakis evaluated a prospective series of patients undergoing revision ESS and reported that the most common alterations include lateralization of the middle turbinate (78%), incomplete anterior ethmoidectomy (64%), scarred frontal recess (50%), retained agger nasi cell (49%), incomplete posterior ethmoidectomy (41%), middle meatal antrostomy stenosis (39%), and retained uncinate process (37%).[21] These findings have been confirmed in other case series.[22] Other reasons for incomplete surgery may be due to reports of approaches to safe posterior dissection recommending proceeding parallel to the maxillary ostium that may leave ethmoid cells behind.[23] All of these anatomic findings suggest incomplete surgery that has led suboptimal cavity design and ultimately surgical failure.

Systemic Disease

While local factors are the main cause of CRS, occasionally, when patients fail to respond to therapy, the cause may be an underlying systemic disease. There are a substantial number of systemic diseases that can cause CRS. These can be characterized as vasculitic and granulomatous diseases, neoplastic diseases, immunodeficiency diseases, and mucociliary diseases. Inflammatory disease includes Wegener granulomatosis, sarcoidosis, and Churg-Strauss Syndrome. Immunodeficiency diseases include acquired immunodeficiency disease syndrome (AIDS), or patients on chemotherapy for neoplastic and hematological diseases. Mucociliary disease is made up of primary ciliary dyskinesia associated with Kartagener syndrome and cystic fibrosis. Pathologic changes in systemic disease occur in three general ways. First, the general pathophysiology of the disease may affect the tissues of the sinonasal tract.



Figs. 50.5A and B: Computed tomography showing osteitis.

Second, the unique mucosal histology of the sinonasal tract may make an otherwise minor pathologic process more severe and apparent. Third, a systemic disease may affect the tissues of the sinonasal tract as part of a symptom complex. Patients with systemic disease are difficult to treat and tend to display worse CRS and are maybe refractory to treatment. Although patients with systemic disease need investigation of other involved organs and may require systemic therapy, their local treatment often remains unchanged to primary CRS patients.

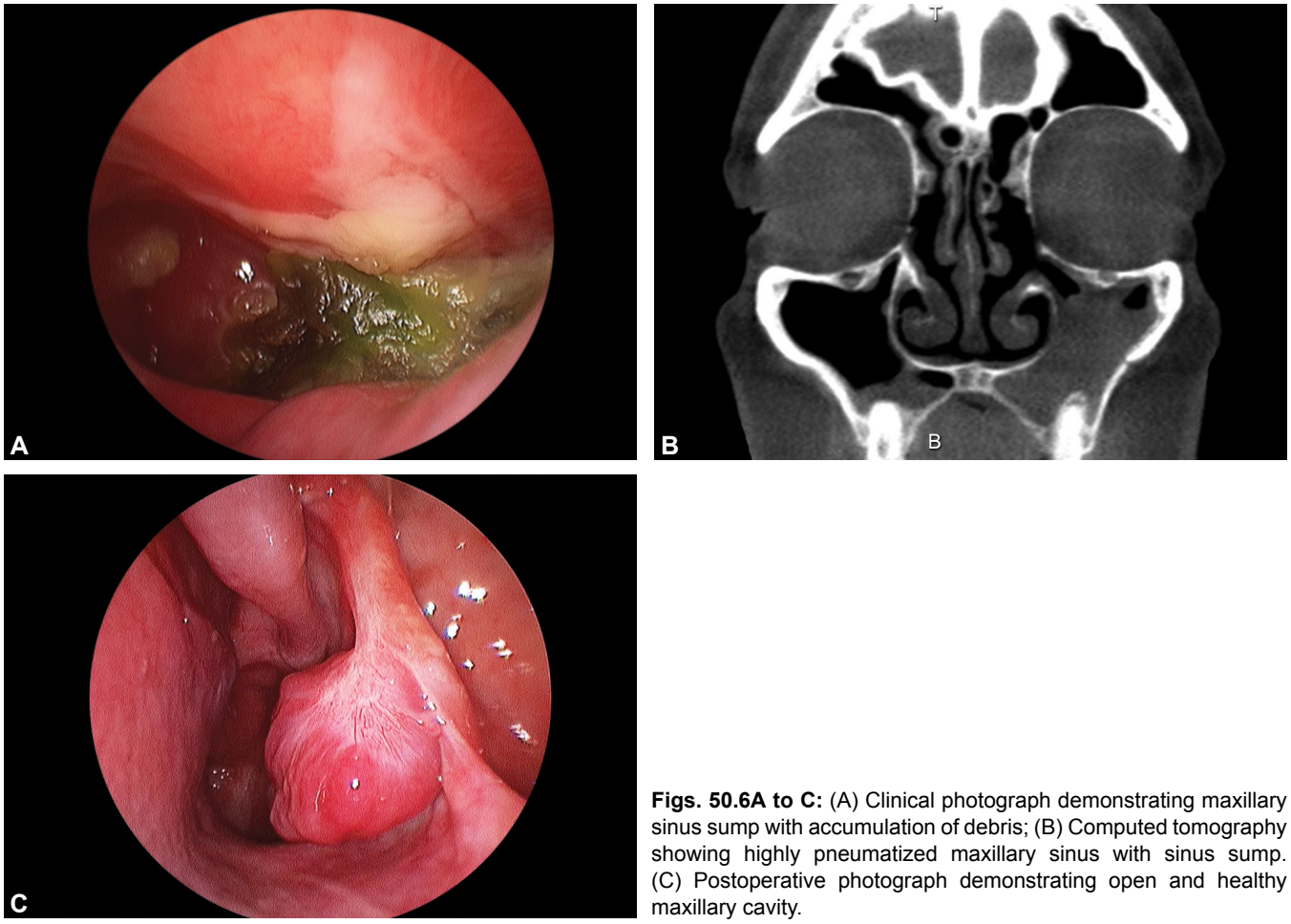
WHAT IS GOING TO BE ACHIEVED BY REVISION?

Which Corners of the CRS Treatment Model Will Be Improved by Revision?

All corners of the treatment model should be improved with revision surgery. Revision sinus surgery creates an open sinus cavity that permits the topical delivery of corticosteroids, surfactants, antibiotics, and saline irrigation. The first and dominant disease corner is mucosal inflammation. Bad mucosal disease-driven predominantly by intrinsic mucosal inflammation may result in large polyps obstructing the sinuses. Large polyps are unlikely to resolve simply with medical treatment without surgery.[24] This is because they obstruct the delivery of topical therapy and often contain remodeling changes not resolved by medical treatment alone. Even though large polyps should be removed during revision surgery, care must be taken not to strip the mucosa because there is good evidence to suggest that stripping mucosa induces osteitis[25] (Figs. 50.5A and B). Osteitis once established is difficult to treat. In addition, the other two disease corners, local microbial community and mucociliary dysfunction, also contribute to reasons for revision surgery. The role of surgery is not only to clear diseased tissue but also to create a cavity that patients can manage with topical treatment.

Sump Effects

A sinus sump is defined as an area of the sinuses that does not drain adequately. Sumps can be seen in either the maxillary or sphenoid sinuses. Maxillary sinus sumps are often seen in patients with highly pneumatized maxillary sinuses. This is where the sinus is pneumatized below the floor of the nose (Figs. 50.6A to C). These patients experience pooling of secretions within this sump and as a result local microbial communities become established and the cycle of mucosal inflammation starts up. Medical treatment of the sump is difficult because washes are retained in the sinus and may contribute to the disease process. Treatment of sump effects of the maxillary sinus involves medial maxillectomy to the nasal floor. In cases where the maxillary sinus is pneumatized beyond the floor of the nose, treatment becomes very challenging. Sphenoid sinus sumps are also seen in patients with well-pneumatized sphenoid sinuses. The sump can occur due to inadequate surgery where the floor of the sinus is not visualized and as a result secretions and topical therapies are retained in the sinus. To treat the sphenoid sinus adequately, it is necessary to lower the front face of the sphenoid sinus until the posterior septal branch of the sphenopalatine artery is reached. Treatment of the sphenoid sinus sump involves a sphenoid sinus Lothrop with adequate visualization of the sphenoid floor.



Figs. 50.6A to C: (A) Clinical photograph demonstrating maxillary sinus sump with accumulation of debris; (B) Computed tomography showing highly pneumatized maxillary sinus with sinus sump. (C) Postoperative photograph demonstrating open and healthy maxillary cavity.

Not Topical Access

Topical therapy delivery for CRS is shaped by a variety of factors. Factors include delivery techniques, surgical site of the sinus cavity, delivery device, and fluid dynamics.[26] The ability of the therapy to reach the appropriate region of the paranasal system is vital. Studies have demonstrated that there is very little distribution of topical solution to the nonoperated sinuses. Distribution in nonoperated sinuses is probably partial and only in the order of less than 2% of the total irrigation volume[27] and only 3% with nebulization.[28] The frontal and sphenoid sinuses are essentially inaccessible before surgery.[26] An ostial size of greater than 4–5 mm is required to even begin seeing penetration to the maxillary sinus.[26] The access afforded by a large fronto-maxillary-sphenoid-ethmoidectomy cavity facilitates adequate topical therapy. However, once the therapy has reached the target site, its success is heavily dependent on the local microenvironment. The local microenvironment includes the presence and composition of the mucus blanket, the mucociliary clearance, direct mucin-drug binding, and the permeability of the mucosa. The efficiency of the therapy is mediated by two potentially competing actions these are mechanical lavage and drug delivery.

The role of saline irrigation has historically been to mechanically clear mucous. However, there is an increasing perception that saline also has a contributory role in the resolution of inflammation and potentially works by enhancing ciliary beat activity, removing antigen, biofilm, inflammatory mediators, and playing a part in sinonasal mucosa protection. Topical saline preparations vary from commercial single use and multiuse products to homemade solutions. Regardless of the solution used, it appears that large volume delivery such as with a squeeze bottle is best at managing CRS[29] (Fig. 50.3). In addition to clearing the mucous blanket, saline preparation allows other drugs, such as corticosteroids to be delivered to the sinus mucosa.

Revision surgery is required when there is inadequate access for topical treatment. This may either be due to obstruction by large polyps or iatrogenic scarring, or from insufficient previous surgery. Adequate topical treatment is the cornerstone to successful outcomes post-revision ESS.

SURGICAL TECHNIQUE

Understanding Sinus Anatomy as Fixed Landmarks and the Boundaries of the "Box"

Orbital Line

Revision surgery is challenging because, in contrast to operating on virgin sinuses, the usual landmarks have been removed or altered by previous surgery. Nasal landmarks can be divided into anterior and posterior land marks.[30] There are seven recognized anterior landmarks. They include the nasal floor and inferior turbinate, posterior choana and eustachian tube opening, maxillary sinus roof (orbital floor), posterior wall, and the medial orbital wall. There are three posterior landmarks. They include the posterior skull base, lateral sphenoid wall (defining the orbital apex and optic canal), and skull base (sphenoid roof to posterior frontal table and clear view of orbital axis). The uncinate process, turbinates, and ethmoids may all be unrecognizable or absent from previous surgery; therefore, orientation depends on fixed anatomic landmarks. The most reliable fixed landmark is the nasal floor. The orbit is also an essential fixed landmark. The orbital floor forms the roof of the maxillary sinus.[30] Harvey et al. reviewed 300 CT of sinuses and found that orbitalfloor or maxillary sinus roof was never higher than the sphenoid roof or lowest cribriform height[30] (Fig. 50.7). Patients who had a very high and well-pneumatized maxillary sinus had a reduced distance between the orbital floor and critical anatomy, but the orbital line was still always below the skull base. Patients with a well-pneumatized maxillary sinus were also more likely to have a tighter and narrower corridor to the sphenoid and cribriform. The average distance from the orbital floor to the sphenoid roof was 11 mm and to the cribriform was 10.1 mm; this is within one or two instrument depths. Casiano looked at direct distances from the medial orbital wall to the carotid, optic nerve, ethmoid roof, and anterior ethmoid artery.[31] He found that there was approximately 14 mm between these landmarks and none of them were less than 10 mm. These

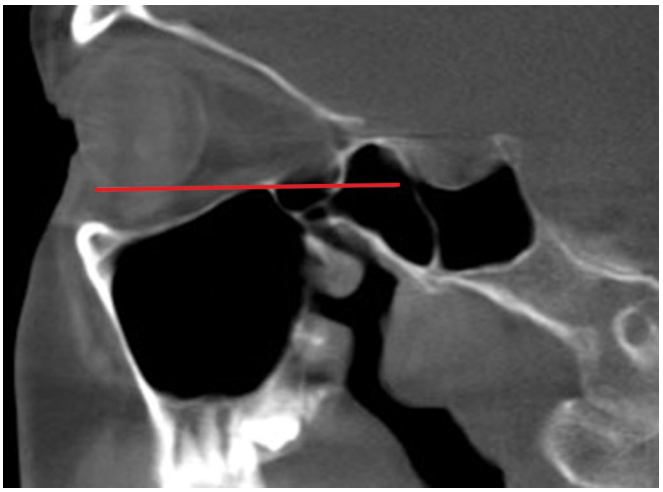


Fig. 50.7: Computed tomography of orbital floor never being higher than sphenoid roof.

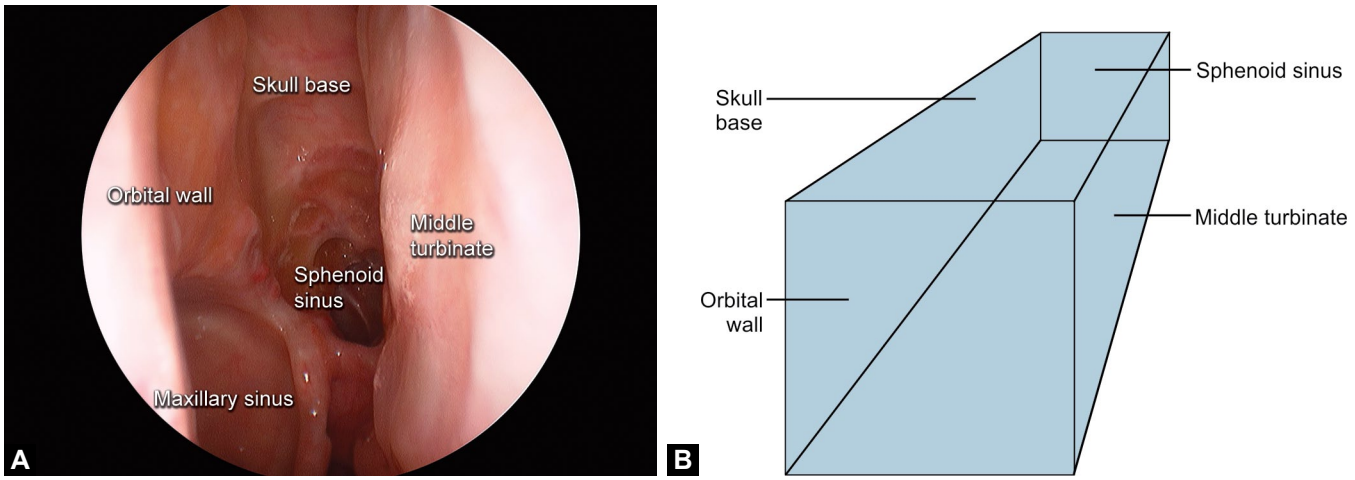
fixed anatomical landmarks are reassuring for the surgeon planning revision surgery where the normal landmarks may be lost, and as long as the orbital floor and medial wall are identified the surgery can proceed safely.

Boundaries of the Frontal as "Box"

Conceptually the anatomy of the sinuses can be divided into two basic boxes.[32] These can be defined as the main surgical box and a vertical frontal box. During revision surgery, understanding the boundaries of the surgical boxes is crucial for surgical planning as well as for intraoperative orientation when the normal anatomy is distorted. Failure to recognize the boundaries of these boxes can result in incomplete surgery or complications.

The paranasal sinus box boundaries include the olfactory recess (middle and superior turbinates) medially, orbital wall laterally (lamina papyracea), and the skull base superiorly (Figs. 50.8A and B). Within the confines of this box, a series of pneumatized air cells and variants of this normal anatomy must be dissected. The clinical significance of an Onodi cell is that it can pneumatize over the optic nerve exposing it to injury during surgery. These cells can also be mistaken for the true sphenoid sinus, leading to incomplete surgery if not recognized.

The vertical or frontal box sits directly above and within the confines of the anterior box. The boundaries of the vertical box define the frontal sinus recess and include the middle turbinate and intersinus septum medially, orbital wall laterally, nasofrontal beak anteriorly, and skull base and posterior table of the frontal sinus laterally.



Figs. 50.8A and B: (A) Clinical photograph showing sinus box (B).

To define the limits of the frontal recess (vertical box), various cells that may encroach on this space from the anterior, posterior, medial and lateral directions must be considered during surgery. Anterior structures intruding into this space include the agger nasi cell, the lateral uncinate process, and frontal cells. Supraorbital ethmoid cells, suprabulla cells, and the ethmoid bulla make up the posterior structures intruding on the frontal recess. These cells can become quite large and can be mistaken for the skull base or frontal sinus. Failure to recognize this preoperatively on CT imaging will also result in incomplete surgical dissection of the frontal recess. Medial structures intruding on the frontal box include intersinus septal cells and medially inserting uncinate process. Lateral impinging structures include frontal cells, the agger nasi, and a lateral uncinate process attachment.

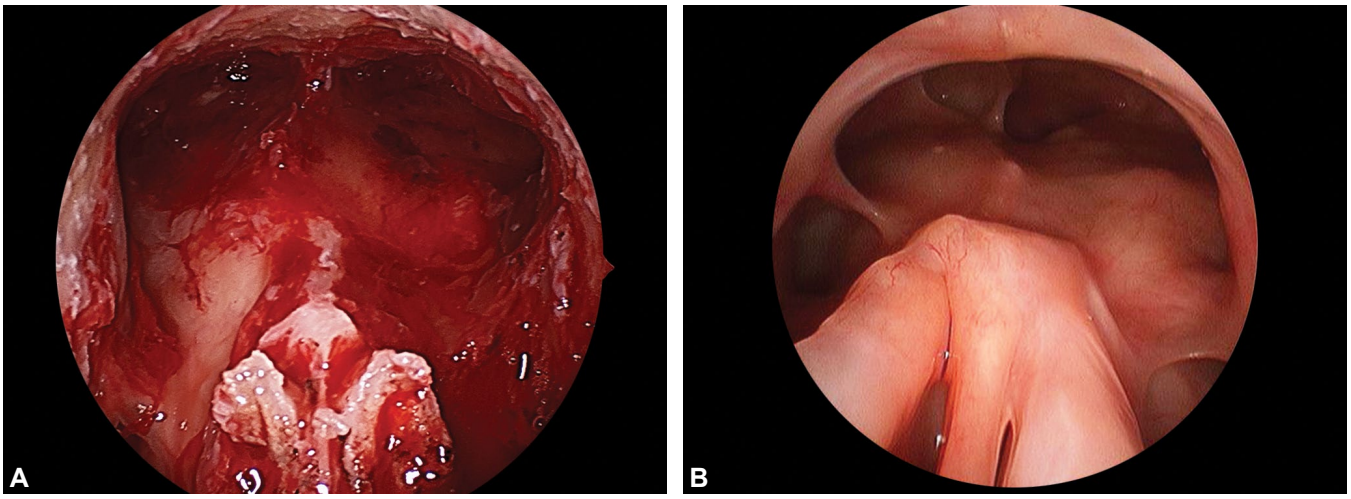
The Salvage Operation

Fontal Sinus Salvage (aka Lothrop/Draf3)

The outside-in modified endoscopic Lothrop procedure (MELP) is based on the traditional MELP. MELP has become recognized as an option in managing a wide range of different pathologies, including refractory frontal sinus inflammatory disease,[33] mucoceles,[34,35] frontal sinus cerebrospinal fluid (CSF) leaks,[36] and in the management of frontal sinus tumors.[37] Access provided by the Lothrop cavity also facilities postoperative tumor surveillance and topical therapy.[38,39] The Lothrop cavity is bounded laterally by the orbital plates of the frontal bone and periosteum of the skin over the frontal process of the maxilla on both sides.[40] The posterior limit is the first olfactory fascicle. This demarcates the forward projection of the olfactory bulb. The anterior limit of the dissection is the plane of the anterior table of the frontal sinus[41] (*see* Figs. 50.11A to H). Open approaches to the frontal sinus include the osteoplastic flap approach.[42] The problems associated with an external approach include cutaneous scarring, scalp hematoma,[43] embossment, and cosmetic deformity. MELP avoids these problems. The traditional inside-out MELP requires the identification of anatomical landmarks that may be lost in revision surgery. This is because in traditional MELP bony removal follows the identification of one frontal recess at the first step. This often involves the use of angled endoscopes and identification of the frontal sinus recess may be difficult in revision surgery. The outside-in approach identifies the limits of the endoscopic Lothrop cavity early and allows wide-open access making it technically feasible and a safe procedure for revision surgery (Figs. 50.9A and B and 50.1).

Surgical Technique[41]

The surgical steps required for this procedure involve, firstly, removing the mucosa over the frontal process of the maxilla. This is medial to the plane in line with the medial orbital wall. The anterior septal window is created anterior to the insertion of the middle turbinates at the level of the upper half to the upper one-third of the middle turbinate to allow bilateral access. This dissection is anterior to the first olfactory fascicle on each side, which is discovered posteriorly. The superior bony septum is drilled down to give a smooth working surface. Dissection starts at the demucosalized area on the frontal process of the



Figs. 50.9A and B: Photographs showing outside in Lothrop cavity (MELP): (A) operative photograph; (B) 12-month postoperative clinical photograph.

maxilla. This is continued laterally until the periosteum of the overlying skin is identified on one side and then the contralateral side. A wide operative field is quickly developed as the bone is removed between these lateral margins. The mucosa of the floor of the frontal sinus is rapidly identified. Bone removal is continued on a broad front, avoiding entry into the frontal sinus mucosa until there is wide access to the floor of the frontal sinus on both sides. The dissection is continued anteriorly and superiorly to the frontal recesses laterally and the first olfactory fascicle medially. This ensures that the frontal recess and inferior part of the frontal sinus always lies between the drill head and the skull base. The floor of the frontal sinus is removed. A thin shelf of bone that remains anteriorly at the frontal recess is removed using a 2 mm Kerrison rongeur bilaterally. At this stage, an angled endoscope may be used, if required for better visualization of the anterior wall that defines the anterior limit of the cavity. Any remaining bony overhang in the frontal beak area is removed. The interfrontal sinus septum is lowered toward the first olfactory fascicle to achieve the final cavity.

Maxillary Sinus Salvage (Also Known as Modified Medial Maxillectomy)

Surgical management of chronic maxillary sinusitis via standard middle meatal antrostomy is highly effective with success rates approaching 90%.[44] Despite surgery and aggressive medical therapy, a subset of patients will continue to have mucosal inflammatory disease and recalcitrant maxillary sinusitis. Traditional techniques used to treat maxillary sinusitis such as Caldwell–Luc procedures and inferior meatal windows may in fact contribute to the inflammatory mucosal disease. Odontogenic disease may also provide a persistent inflammatory stimulus.[45,46] The maxillary sinus also contrasts to other gravity dependent drainage pathway sinuses in that the mucociliary clearance must work against gravity. The dependent portion of the maxillary sinus may serve as a reservoir for tenacious secretions and persistent inflammation. After Caldwell-Luc surgery, the inferior portion of the maxillary sinus may be left with scaring. The modified medial maxillectomy (MEMM) developed from the need to address these issues, but its application is broad. The MEMM has been demonstrated to improve inflammatory maxillary disease[47] in two ways. The first one by allowing increased delivery of nasal wash to the maxillary sinus and the second by improving access to the inferior and dependent portion of the maxillary sinus. The canine puncture technique described by Sathananthar et al.[48] is also an effective method for removal of inflammatory disease polyps in the inferior aspect of the maxillary sinus. The MEMM has the added advantage of improving access to the maxillary sinus in the postoperative setting, improving gravity-dependent drainage, and reducing the sump effect. Wang et al.[49] in a retrospective review of 46 patients who underwent MEMM found that 37 patients had complete resolution of their disease at 3 months. Woodworth et al reported successful treatment in 18 of 19 patients who underwent MEMM.[47] Revision surgery on recalcitrant maxillary sinus disease is well served by the wide-open exposure gained from the MEMM technique.

Surgical Technique

After topical decongestion and infiltration of the lateral nasal wall and inferior turbinate, endoscopic evaluation of the maxillary sinus is performed to ensure communication of the antrostomy with the natural ostium of the maxillary sinus.[49] The anterior third of the inferior turbinate is preserved to prevent atrophic rhinitis and damage to the nasolacrimal duct. A posterior stump of the inferior turbinate is also maintained to allow for effective cauterization of the sphenopalatine artery branches that enter the inferior turbinate. A mucosal flap based on the floor of the nose is then created by elevating the mucosa of the lateral nasal wall of the inferior meatus in the subperiosteal plane. The medial maxillary wall is then resected. At the completion of the resection, the inferior extent of the resection should approximate the floor of the nose. The posterior resection should approximate the posterior wall of the maxillary sinus, although branches of the sphenopalatine artery may be encountered with extensive dissection. Care should be taken to avoid injury to the descending palatine nerve posteriorly and the lacrimal system anteriorly. When indicated, the maxillectomy can be extended anteriorly underneath the lacrimal duct. After achieving wide access to the maxillary sinus, polyps and nonfunctional hyperplastic mucosa are removed but the mucosa is not stripped. After thorough irrigation of the sinus, the mucosal flap is laid across the nasal floor into the maxillary sinus to cover the area of exposed bone along the inferior maxillary bony cut (Figs. 50.10A to F).

Sphenoid Sinus Salvage (aka Sphenoidotomies and Septectomy, Sphenoid Lothrop)

Common causes of sphenoid sinus dysfunction include severe osteitic bone and contracted lumens, which can be caused by iatrogenic mucosal stripping, a fungus ball, or chronic sphenoid sinusitis. Radical mucosal stripping procedures have been previously used in obliteration techniques with fat or other materials. These are not routinely performed for inflammatory disease, but have been used for repair of CSF leaks such as is seen after pituitary surgery. The sphenoid is difficult to truly obliterate as there is a risk of injury to surrounding structures. Therefore, the obliteration techniques often exacerbate sinus disease. Modern surgical approaches to the sphenoid are typically endoscopic. Unlike the frontal and maxillary sinuses due to its deep-seated location, no real option for open surgery exists. Establishing a patent outflow tract and creating access for topical medical therapy are critical for surgical success. Options for access are either unilateral or bilateral.[50] Unilateral sphenoid sinusotomies can be performed using the transethmoid or direct parasagittal approach. The principle of surgery for sphenoid disease is mucosal preservation and maximal sphenoidotomy dimensions. Revision surgery cases typically have osteitic bone, which has a tendency to scar and contract more than nonosteitic sinuses. The sphenoid sinus "Lothrop" is to establish a wide-open sphenoid sinus cavity (Figs. 50.11 and 50.12, and 50.2).

Surgical Technique

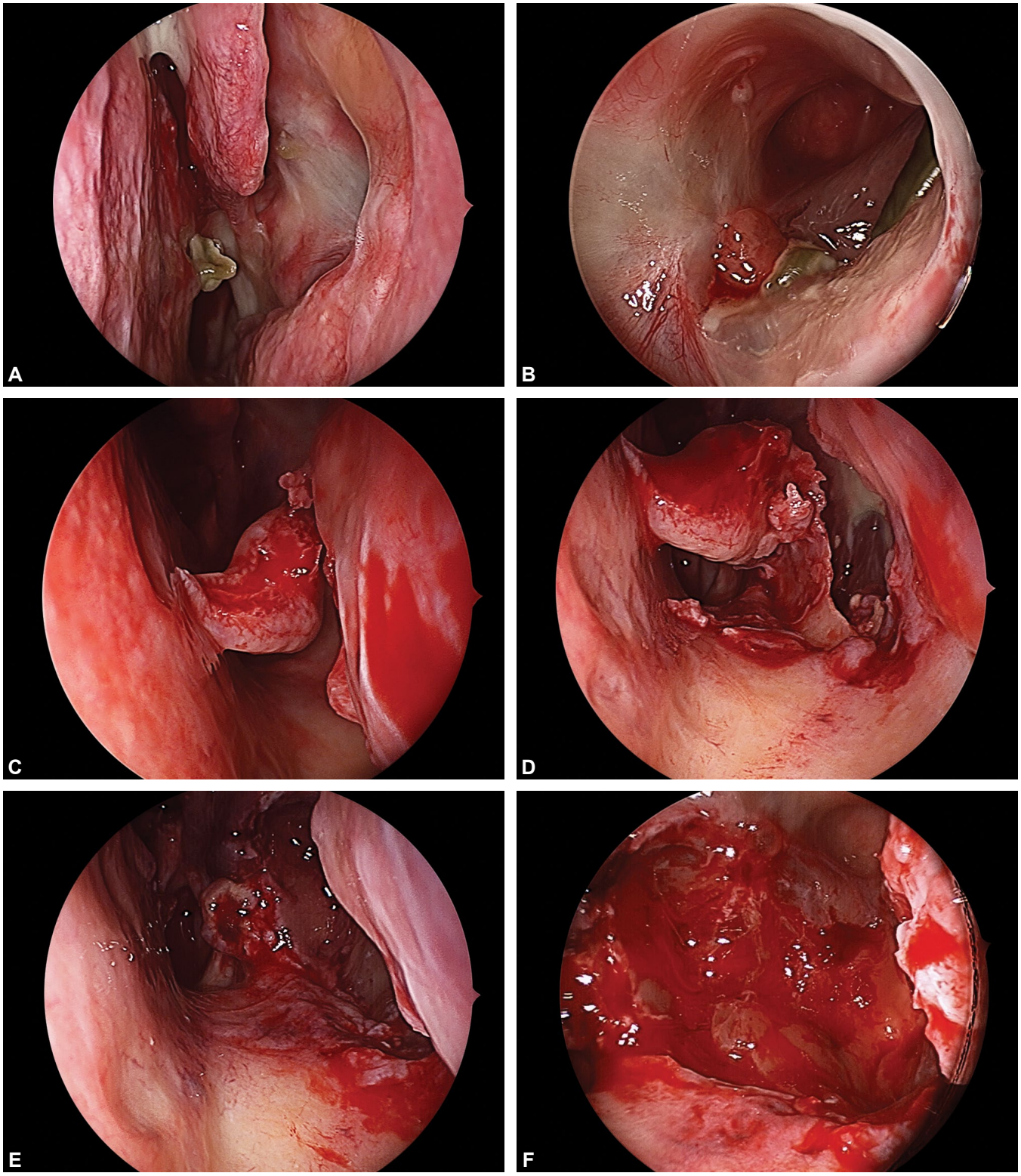
Submucosal elevation over the face of the sphenoid will help avoid the posterior septal branch of the sphenopalatine artery. After elevation of this mucosal flap, a wide open sphenoidotomy is created using a Kerrison punch. Taking down much of the floor of the sphenoid can often be advantageous in creating a large neo-ostia. Every effort should be made to preserve the mucosa while resecting the osteitic bone. Once the bony opening is enlarged to skull base, orbit, inner sinus septum, and inferiorly as much as possible, the sphenoid sinus mucosa can be incised and any pus, fungal concretions, or other inflammatory mucous within the sinus can be removed.

If the natural outflow tract of the sphenoid scars postoperatively but the inner sinus septectomy remains patent, then the sinus will remain ventilated and safe, even though the outflow tract is nonanatomic through the contralateral sinus. The approach to surgery is typically similar to that for trans-septal pituitary surgery. A large posterior nasal septectomy is performed for access. Bilateral sphenoidotomies are then performed so that both sphenoid sinuses, the rostrum, and the planum can be visualized with one view of the endoscope. The inner septum is then removed back to the face of the sella. As with the inner sinus septectomy of the frontal sinuses, this site is often untraumatized by prior surgery and less likely to scar and contract than revision surgery through the previously operated area of the native sphenoid os. Care must be taken to perform this inner sinus septectomy with cutting instruments or drills. Twisting and pulling of the inner sinus septum can result in an indirect injury to the internal carotid artery, because the inner sinus septum often inserts into the carotid.

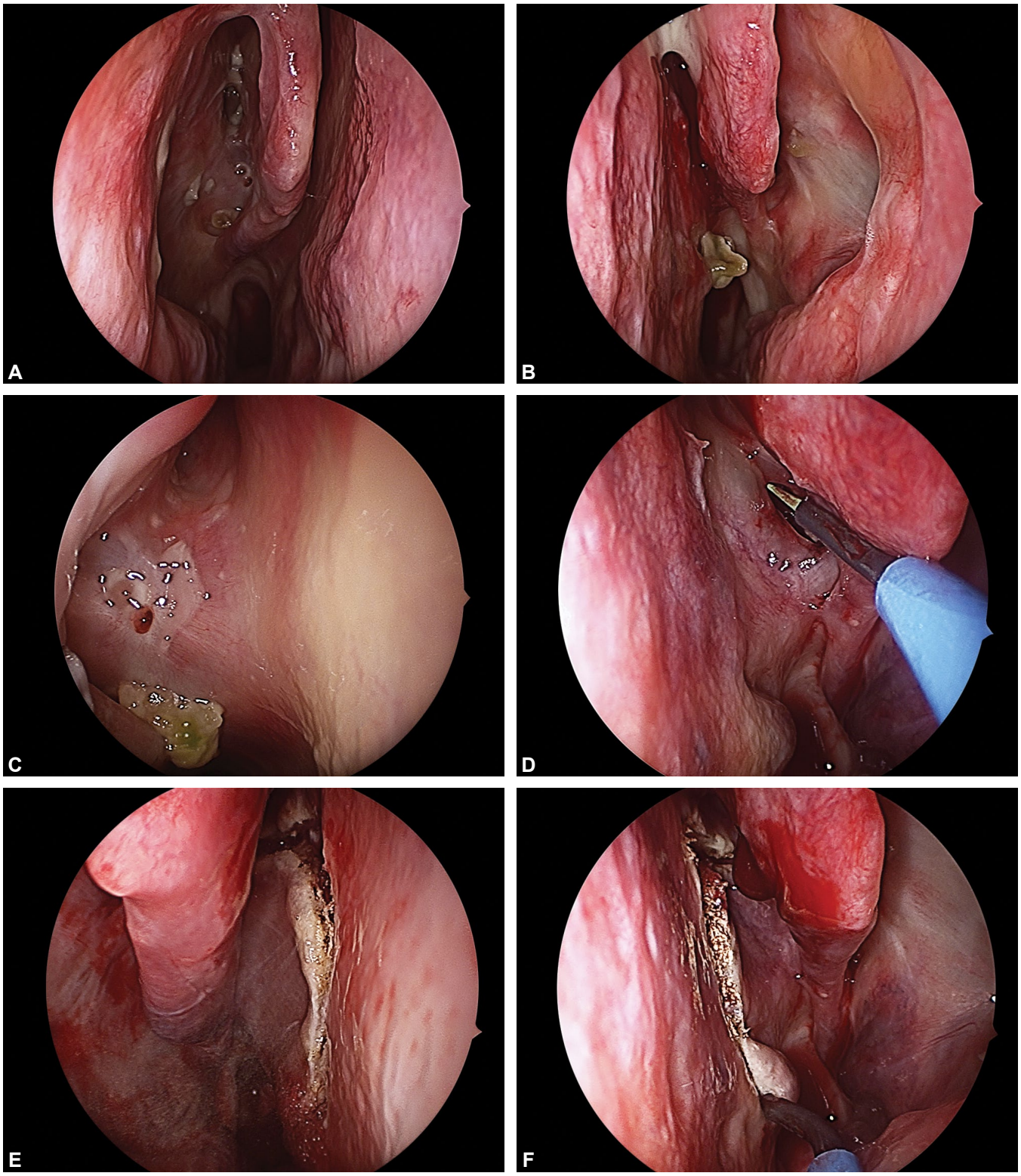
Osteitis

What Does It Mean?

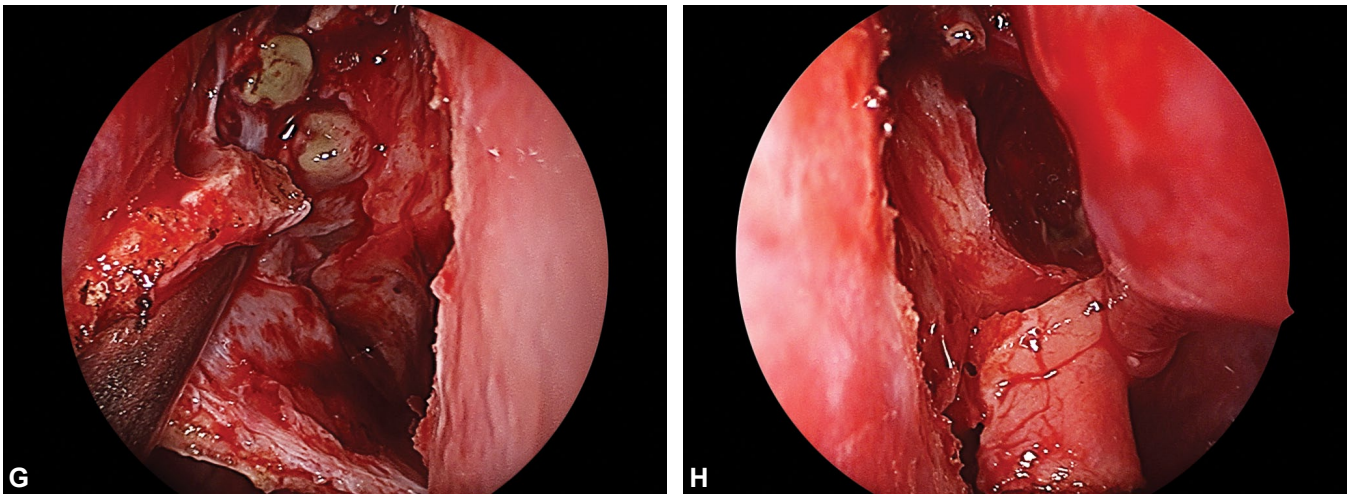
The mechanism of osteitis in CRS is poorly understood and is yet to be fully defined. Osteitis is generally found to



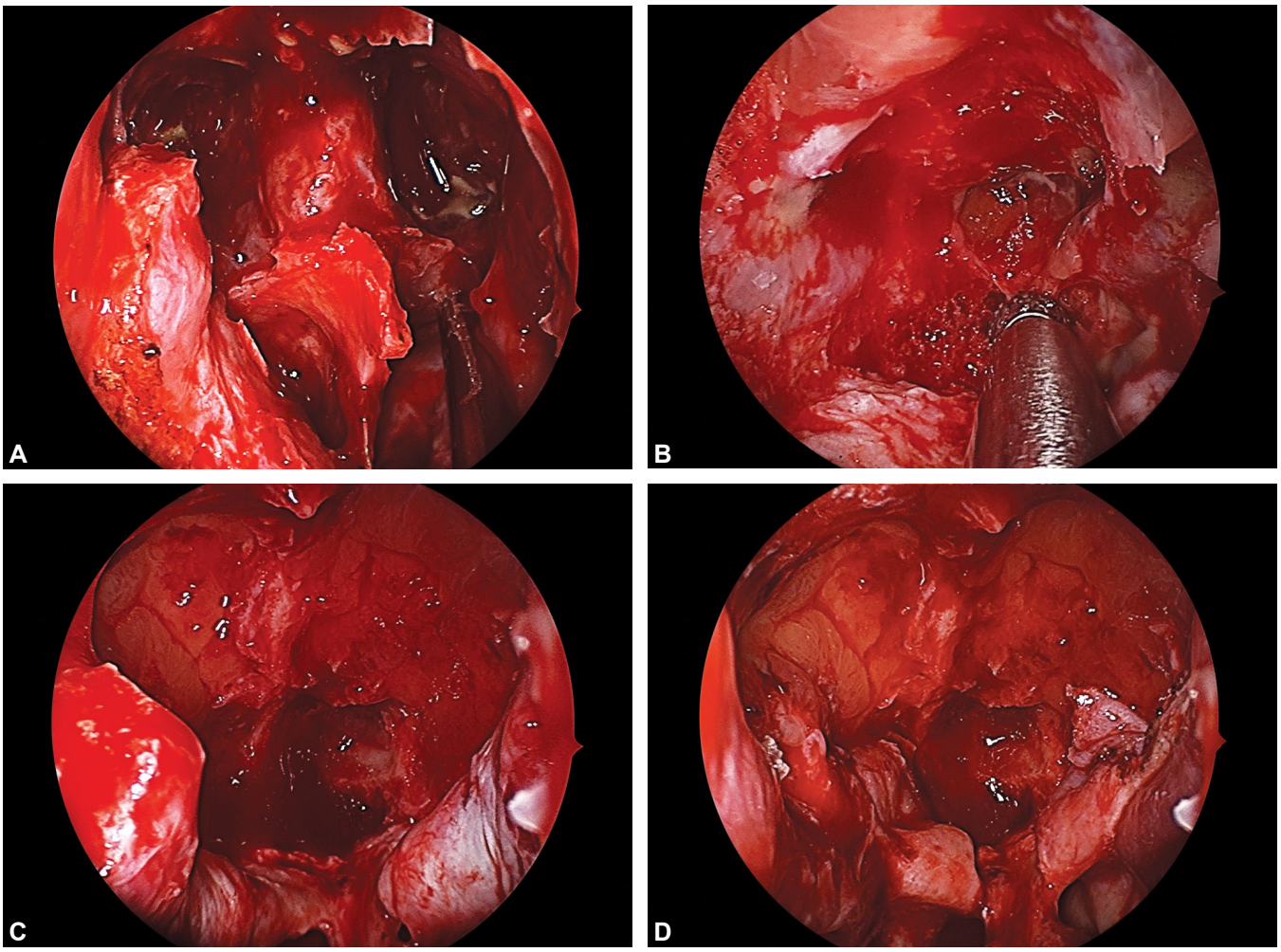
Figs. 50.10A to F: Operative photographs showing medial maxillectomy steps. (A and B) Left maxillary sinus obstructed with scar and inflammatory tissue; (C) Inferior turbinate resected with anterior third being preserved to prevent atrophic rhinitis and damage to the nasolacrimal duct; (D) Medial wall taken down to nasal floor; (E) A posterior stump of the inferior turbinate is also maintained to allow for effective cauterization of the sphenopalatine artery branches that enter the inferior turbinate; (F) Final maxillary sinus cavity.



Figs. 50.11A to F: Operative photographs showing sphenoid sinus Lothrop steps. (A) Right nasal cavity after decongestion; (B) Left nasal cavity after decongestion; (C) Photograph showing sphenoid sinus obstruction with scar tissue; (D) Diathermy used to make incision; (E) Incision on septum right; (F) Incision on septum left with submucosal elevation over the face of the sphenoid to help avoid the posterior septal branch of the sphenopalatine artery.



Figs. 50.11G and H: (G) Large posterior nasal septectomy is performed for access; (H) Bilateral sphenoidotomies are then performed so that both sphenoid sinuses, the rostrum, and the planum can be visualized with one view of the endoscope.



Figs. 50.12A to D: Operative photographs showing sphenoid sinus Lothrop steps. (A) Removal of sphenoid sinus floor; (B) Drill used to remove sphenoid floor and inner septum, which is then removed back to the face of the sella; (C and D) Final sphenoid cavity.

be associated with previous surgery (Fig. 50.5). Its occurrence appears to rise with the rising number of previous operations.[51] However, mucosal loss from surgery is not a simple answer to the origins and implication of osteitis. Osteitis is also experienced in nonoperated patients with an incidence of 5[52]–33%.[51] Bacteria may play a role in the pathogenesis of osteitis by infecting the sinus walls either in planktonic or biofilm form. However, bacteria have not been found to be present in bone of the paranasal sinuses.[53] Osteitis is thought to be due to an inflammatory process rather than a chronic bone infection of osteomyelitis. The osteitic bones potentially serve as a nidus for inflammation. This may explain medical and surgical treatment failures. Osteitis is a feature of CRS that is associated with both systemic and local tissue eosinophilia. Severe inflammation may contribute to circulating cytokines that promote neo-osteogenesis and these patient may need to be considered for longer courses of postoperative systemic corticosteroid.[25]

POSTOPERATIVE CARE

Meticulous postoperative care is important to realize a successful result following ESS surgery. Failure of adequate postoperative care can lead to potentially avoidable complications. Such factors as exposed bone, the mix of old blood, retained secretions and unresorbed packing predispose the patient to infection and inflammation. Inflammation provides a potential framework for scarring and early disease recurrence. Avoidable complications include ostial stenosis, synechiae, middle turbinate lateralization, and rapid polyp recurrence. The return of normal mucosal histology and ciliary function often takes longer than 12 weeks following surgery.[54] Diligent postoperative follow-up is recommended to ensure that the sinus cavity healing is on track.

Currently various postoperative care regimes are employed. Rudmik et al. recommended in a recent multi-institutional review the use of nasal saline irrigations, in-office sinus cavity debridement, and topical nasal steroid sprays.[55] The only counter recommendation was use of routine topical decongestants because of the risk of increasing pain and rhinitis medicamentosa. To standardize postoperative care protocols, more research is required.

Nasal Irrigations

The role of saline irrigations in early postoperative period remains controversial. However, despite the controversy in the literature, most experts agree that the benefits of early postoperative saline irrigation use outweigh the harm. Saline solution douching has been well established as a treatment adjunct in CRS.[29] The timing of use in postoperative care for patients with CRS is still under debate. There is significant variation in the volume, delivery mode, and frequency of saline irrigations. Nasal douching should aid with debris removal and soften crusting in the nose potentially making in-office debridement easier.

A number of randomized trials have been conducted to evaluate the impact of saline irrigation on outcomes following ESS.[56,57] It is difficult to draw conclusions from these trials because all study methodologies were heterogeneous and used different postoperative care protocols with different saline irrigation volumes and frequencies. No study was able to demonstrate consistent improvement with saline irrigation. Although saline irrigation has been demonstrated to be useful in the management of CRS when used in high volumes, the effects of saline volume in the early postoperative setting have not yet been properly evaluated. There was no real consensus as to the best time to start irrigation. However, most saline irrigation regimes were implemented within 24–48 hours after ESS.

Corticosteroids

Local

Topical corticosteroid therapy, delivered as either a spray or irrigation, is a central component of anti-inflammatory CRS medical therapy.[39] The effectiveness of using topical corticosteroids in the early postoperative state is still the subject of debate with the optimal delivery method, timing and dose of topical corticosteroids the key points of discussion. The success of local drug delivery to the paranasal sinuses depends on both the surgical state of the sinuses and the method of topical delivery. A wide-open surgical corridor allows topical access to the sinus mucosa. The high volume irrigation containing 'off label' steroid formulations seem to have a better sinus penetration in comparison with nasal sprays. Steroid nasal spray tends to provide a better nasal coverage. Topical steroid nasal irrigation may be safer because there is less systemic absorption compared to steroid sprays. Unlike systemic steroids, topical steroids have minimal systemic effects and therefore can be used in the long term. High volume steroid irrigation regimes commonly consist of 1 mg budesonide in 240 mL of saline. A four-spray dose delivers a 256 μg dose to the nasal cavity. Common topical nasal

steroid sprays include fluticasone, mometasone, and budesonide. There have been several randomized, double-blind, placebo-controlled trials evaluating topical nasal sprays in the early postoperative period. In these trials patients with nasal polyps seem to respond best from postoperative topical steroids with reported success rates of up to 94%.These patients also experienced a reduction in nasal polyp recurrence and an increased length of time to polyp recurrence. Failure to respond to topical steroid treatment may be predicted by poor response to oral prednisone in the preoperative period. The timing for starting topical nasal steroid is poorly defined but most studies start between 2 and 6 weeks after surgery.

SYSTEMIC DELIVERY

Although systemic steroids provide excellent improvement in CRS clinical status, balancing the benefits with the potential for harm remains a challenge. To minimize the risk of adverse events, most experts use short-course protocols such as durations between 7 and 14 days with moderate doses of 30–40 mg.[58] The use of a tapering dose schedule is controversial. Patients with eosinophilic nasal polyposis seem to have a greater response to oral prednisone than patients with noneosinophilic nasal polyposis.

POSTOPERATIVE ANTIBIOTICS

Post ESS infections can develop as a result of several factors including temporary ciliary dysfunction, retained secretions, old blood, and incomplete remucosalization and colonization with bacteria and biofilm. Infections can lead to increased nasal crusting, discharge, and scarring. Traditionally, post operative antibiotics have been recommended for 7–10 days. Recent randomized controlled trials comparing postoperative antibiotics to placebo have demonstrated small improvements in postoperative endoscopic appearance at the 5 and 12 day mark. The antibiotics of choice should be either culture directed or penicillin based or macrolide that target common sinonasal pathogens.

CONCLUSION

The patient failing ESS, especially one performed "elsewhere," is rarely a simple case of poor surgery. Revision ESS patients should be considered for both local anatomical and disease factors that may contribute to the poor outcome. When surgery is contemplated, a clear goal of what is to be achieved from revision surgery is important. Completion surgery and salvage procedures have fixed anatomical landmarks for surgical orientation. Relying on image guidance will not replace the skills required in revision surgery. Greater focus on the inflammatory nature of CRS via both systemic and local therapies is usually associated with improved outcomes.

VIDEO LEGENDS

Video 50.1: Modified medial maxillectomy.
Video 50.2: Salvage bilateral sphenoidotomy.

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CHAPTER

51

Endoscopic Surgery of the Frontal Sinus

Calvin C Wei, Joseph B Jacobs

CHALLENGES TO ACCESSING THE FRONTAL RECESS

The frontal sinus is the most difficult sinus to address surgically due to the relatively inaccessible location of the frontal recess above and behind the anterior insertion of the middle turbinate. The close proximity of the medial orbital wall, cribriform plate, anterior ethmoid artery, and anterior cranial fossa impairs visualization and access to the frontal recess. In addition, the high degree of variability in frontal cell configuration can make identification of the frontal recess difficult. The presence of frontal recess cells results in mucosal surfaces being in close proximity, increasing the potential for mucosal scarring and frontal sinus stenosis after surgical manipulation. These factors make the maneuvering of instruments in this limited space difficult and increase the risk of surgical failure.[1]

BOUNDARIES OF THE FRONTAL RECESS

The boundaries of the frontal recess are the superior attachment of the middle turbinate medially, the lamina papyracea laterally, the skull base superiorly, the nasofrontal beak anteriorly, the ethmoid bulla posteriorly and the inferior wall of the agger nasi cell inferiorly. The frontal recess is a potential space that is funnel-shaped with the most narrow superior portion being the internal frontal sinus ostium. The frontal recess is a space which is subject to narrowing by frontal recess cells, which include the agger nasi cell, supraorbital ethmoid cells, frontal cells (type I–IV), frontal bullar cells, suprabullar cells, and interfrontal sinus septal cells. There are four types of frontal cells as classified by Bent and Kuhn (Figs. 51.1 to 51.4). These include a type I cell, which is a single cell just above the agger nasi cell; type II cells, which are a tier of air cells above the agger nasi cell; a type III, cell which is a single cell extending into frontal sinus; and a type IV, which is a single cell contained completely within frontal sinus.[2] Type I and II frontal cells are located below the level of the frontal sinus floor, while type III and IV frontal extend into the frontal sinus itself. A thorough understanding of the configuration of these cells is important

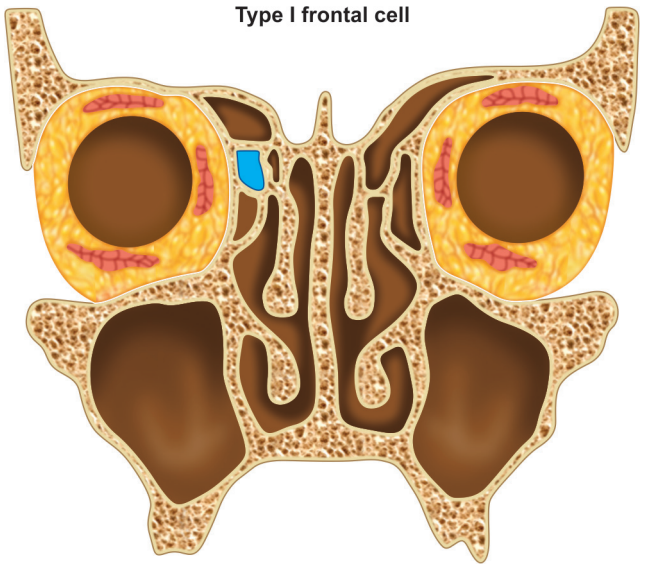

Fig. 51.1: The type I frontal cell is a single cell above the agger nasi cell.

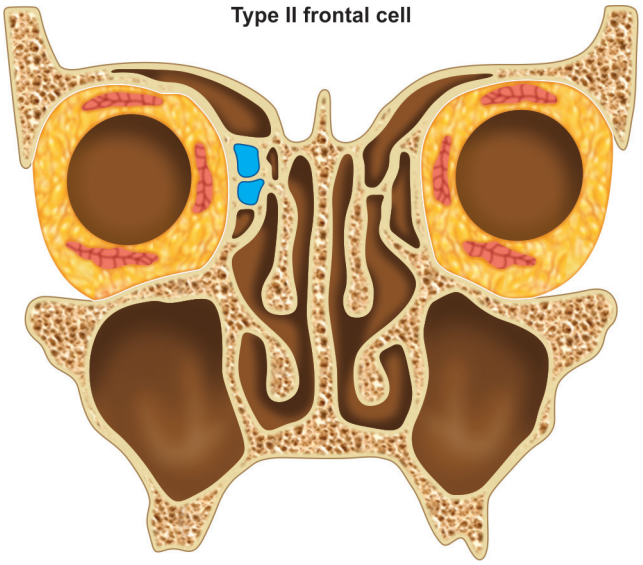

Fig. 51.2: Type II frontal cells are a tier of air cells above the agger nasi cell.

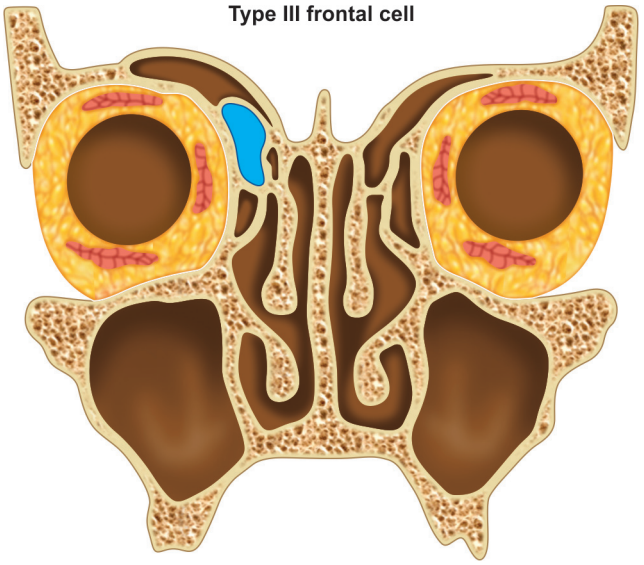

Fig. 51.3: The type III frontal cell is a single cell extending into the frontal recess.

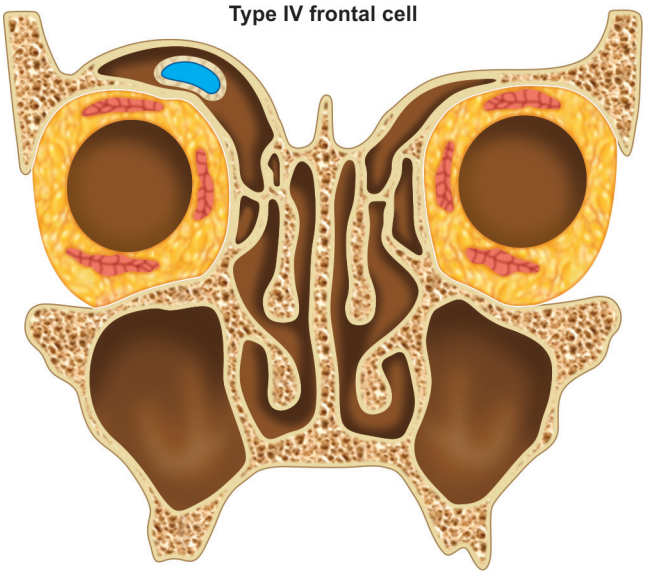

Fig. 51.4: The type IV frontal cell is single cell contained completely within the frontal sinus.

in identifying the frontal sinus outflow tract when performing a frontal recess dissection.

HISTORICAL PERSPECTIVE

The osteoplastic flap with frontal sinus obliteration has been accepted as the surgical gold standard for the treatment of chronic frontal sinus until the endoscopic era. The osteoplastic flap with frontal sinus obliteration, however, had a long-term failure rate of 25% and was associated with frontal bossing, supraorbital neuralgia, donor site complications, and difficulty with postoperative surveillance of mucocele development.[1] In 1991, Draf described a series of endoscopic techniques for addressing the frontal sinus ostium with increasing levels of invasiveness (Draf I–III). The goal of these frontal sinusotomy techniques is to create a durable communication between the nasal cavity and frontal sinus specifically tailored to the pathology that is being addressed, whether inflammatory or neoplastic. The most invasive of these techniques, the Draf III procedure, also known as the endoscopic modified Lothrop procedure (EMLP), was based on the external technique invented by Lothrop in the 1800s in which the medial frontal sinus floor, superior nasal septum, and intersinus septum were resected.[3]

DRAF I DRAINAGE

The Draf I frontal sinusotomy is the least invasive of the frontal sinus approaches. The Draf I sinusotomy consists of a thorough removal of the anterosuperior ethmoidal cells obstructing the frontal sinus outflow tract and does not manipulate the frontal recess itself.

Indications

Draf recommends that the Draf I drainage procedure be utilized when chronic frontal sinusitis is the result of

obstruction of the frontal sinus outflow tract at the level of the frontal recess, either from inflammatory or iatrogenic causes.[4] The Draf I sinusotomy clears ethmoidal disease inferior to the level of the frontal ostium and restores ventilation of the frontal sinus by relieving obstruction of the frontal sinus outflow tract. The Draf I sinusotomy can also be utilized in revision endoscopic sinus surgery when residual ethmoid partitions obstruct the frontal sinus outflow tract.

Perioperative Considerations

Examination of the CT before starting the Draf I drainage should focus on identification of high risk anatomy, including the presence of the anterior ethmoid artery below the skull base, dehiscence of the lamina papyracea (especially in revision surgery), the depth of the lateral cribriform lamella and the height and slope of the ethmoid skull base. The CT should also be studied to determine the location of the frontal sinus outflow tract in relation to frontal cells, including the agger nasi, frontal, and suprabullar cells. For example, an agger nasi cell will displace the frontal sinus outflow tract posteriorly and a suprabullar cell will displace the frontal sinus outflow tract anteriorly. While the agger nasi cell itself is not removed during a Draf I frontal sinusotomy, the precise localization of the frontal sinus outflow tract will allow successful clearance of the anterosuperior ethmoid cells obstructing the frontal sinus outflow tract.

Technique

After middle turbinate medialization, uncinectomy, and ethmoidectomy are performed, a 45° mushroom punch, Bachert and Hosemann forceps are used to remove anterosuperior ethmoid cells that are obstructing the frontal sinus outflow tract. The mucosa of the frontal sinus outflow tract is carefully preserved without manipulating cells within the frontal recess itself. A 30, 45, and/or 70° endoscope may be helpful in visualization of the anterosuperior ethmoid cells.

DRAF IIA DRAINAGE

The Draf IIA frontal sinusotomy involves removal of the frontal cells that extend into the frontal recess (Fig. 51.5). By removing these cells that impinge on the frontal sinus outflow tract, the frontal recess is cleared to its maximal extent. The frontal recess cells which may impinge on

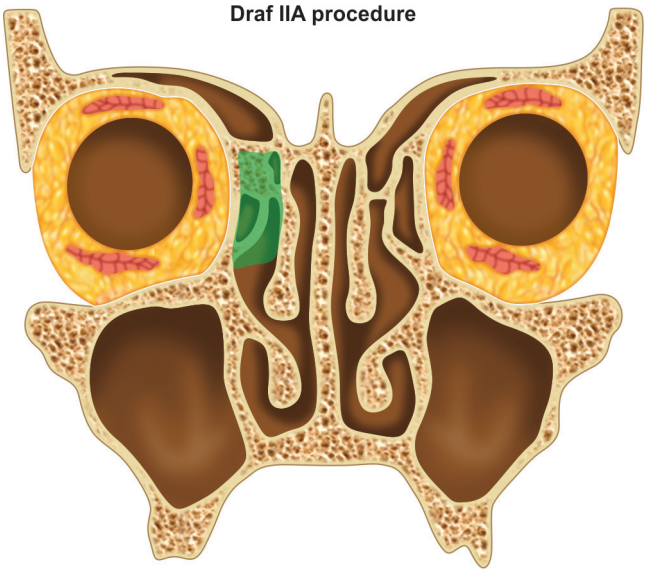

Fig. 51.5: The Draf IIA procedure removes the frontal cells that protrude into the frontal recess.

the frontal sinus outflow tract include the agger nasi cell, supraorbital ethmoid cells, type I–IV frontal cells, frontal bullar cells, suprabullar cells, and interfrontal sinus septal cells. Removal of the agger nasi cell ("uncapping the egg") and the anterior wall of the ethmoid bulla will most commonly reveal the frontal recess and allow clearance of the frontal recess by removal of adjacent frontal recess cells.

Indications

Indications for Draf IIA drainage include chronic rhinosinusitis that involves the frontal recess or sinus, nasal polyps obstructing the frontal sinus outflow tract or involving the frontal sinus, complicated acute frontal sinusitis necessitating immediate drainage, medially based frontal sinus mucoceles, and removal of benign tumors including osteomas and inverted papillomas involving the medial aspect of the frontal sinus. Draf suggests that the presence of healthy mucosa is a prerequisite for performing the Draf IIA sinusotomy in order to ensure that the widened frontal ostium heals open.[4] Anatomic considerations should also be weighed before performing the Draf IIA sinusotomy. The Draf IIA sinusotomy is more likely to be successful when the removal of frontal recess cells yields a wide natural frontonasal outflow tract.[5] A type IIA drainage procedure is recommended in frontal sinuses with a large anterior-posterior diameter with

an anticipated minimum diameter of the frontal neo-ostium of 5 mm or more.[6] It is also indicated in those patients with a hypoplastic internal nasal spine and a broad ethmoid.[4] As the majority of revision frontal sinus surgery is performed to address remnant uncinate processes, agger nasi cell partitions and/or frontal recess cells, the Draf IIA sinusotomy is sufficient for the majority of revision cases if the anterior-posterior dimension of the frontal sinus is sufficient for the frontal recess to remain patent after surgery.

Perioperative Considerations

Thorough evaluation of a CT scan is essential before performing a Draf IIA drainage procedure. The sagittal view of the frontal recess provides critical information about the anterior-posterior dimension of the frontal recess. A larger anterior-posterior frontal recess dimension allows greater room for manipulation of instrumentation and less chance for injury to the skull base. A greater working dimension also prevents stripping and trauma to the nasal mucosa which may lead to frontal ostium stenosis and osteoneogenesis. The sagittal view provides the best overview of the cell configurations that may impinge on the frontal recess. As discussed earlier, these include the agger nasi cell, supraorbital ethmoid cells, type I–IV frontal cells, frontal bullar cells, suprabullar cells, and interfrontal sinus septal cells. Preoperative understanding of the configuration of these cells facilitates their complete removal.

Technique

After performing a standard uncinectomy, maxillary antrostomy, anterior and posterior ethmoidectomy and sphenoidectomy as warranted, the anterior ethmoid artery is defined at the insertion of the basal lamella of the middle turbinate at the skull base. This area marks the transition between the axial and coronal planes of the skull base. Accurate identification of the medial orbital wall and skull base are essential. The frontal sinus outflow tract is identified by using direct visualization and by probing with frontal sinus seekers or angled curettes. The most common configuration of the frontal recess is the agger nasi cell anteriorly and the supraorbital ethmoid and ethmoid bulla posteriorly; thus, the frontal sinus outflow tract will be located between these bony partitions. The cell walls are fractured anteriorly and inferiorly and the resulting bony fragments are removed with 55° and/or 90° Kuhn through-cutting frontal sinus punches. Angled giraffe forceps can also be used to remove free bony partitions. A common pitfall of the Draf IIA frontal sinusotomy is failure to remove the superior cap of the agger nasi cell when mistaking the endoscopic appearance of the agger nasi cell body for the frontal sinus itself. Additional frontal cells that impinge upon the frontal sinus outflow tract are resected. Frontal cells (types I–IV) can be down-fractured and removed with a combination of through-cutting forceps and giraffe forceps. Type III and type IV cells, due to their superior-based location within the frontal sinus, may necessitate trephination if located beyond the reaches of standard frontal sinus instrumentation. Resection of the bony partition between the supraorbital ethmoid cell and frontal ostium may widen the frontal recess further. The supraorbital ethmoid cell results from pneumatization of orbital plate of the frontal bone by air cells from the frontal recess or suprabullar recess. It is usually located posterior to the frontal ostium and anterior to the anterior ethmoid artery and may narrow the frontal recess posteriorly. If the supraorbital ethmoid cell is present, the partition between it and the frontal ostium can be resected using a through-cutting forceps. It is important not to mistake the supraorbital recess for the frontal sinus itself. The supraorbital ethmoid cell is removed in a similar fashion with through-cutting forceps with particular attention paid to identifying and protecting the skull base.

DRAF IIB DRAINAGE

A Draf IIB drainage involves unilateral resection of the frontal sinus floor between the lamina papyracea and the nasal septum (Fig. 51.6). The head of the middle turbinate is resected to gain access the medial frontal sinus floor. A combination of punches or drills may be used depending on the thickness of the frontal sinus floor. The Draf IIB sinusotomy creates the maximal opening of the frontal sinus on one side.[4]

Indications

Indications for Draf IIB drainage include revision frontal sinus surgery for persistent frontal sinus disease or significant osteoneogenesis of the frontal recess, and pathology that involves the lateral aspect of the frontal sinus. Draf writes that the recommended indications for type IIB drainage include all indications for a type IIA drainage; however, if the resulting frontal sinus ostium is less than 5 × 7 mm from the type IIA approach, a type IIB

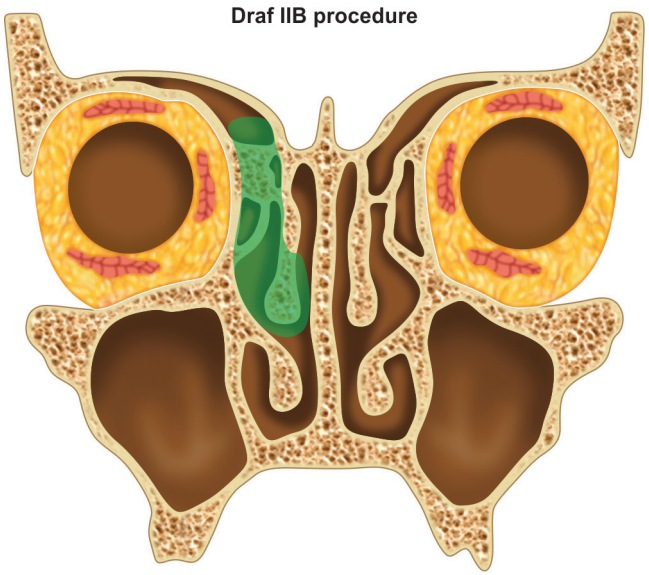

Fig. 51.6: The Draf IIB procedure removes the frontal sinus floor from the lamina papyracea to the nasal septum.

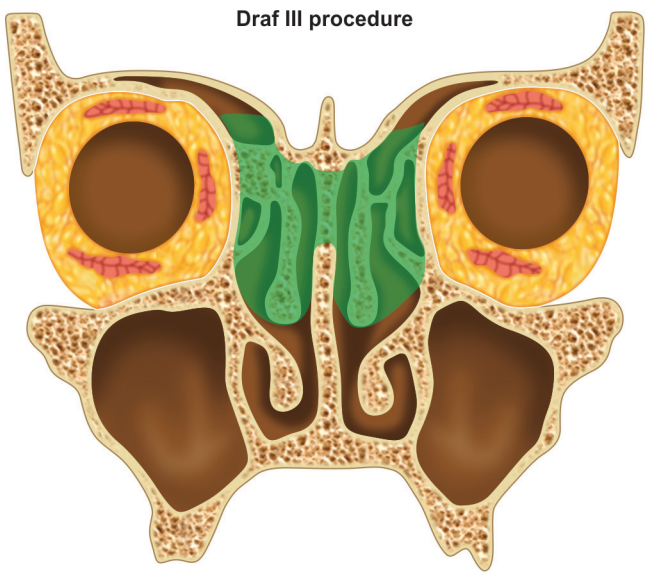

Fig. 51.7: The Draf III procedure removes the frontal sinus floor from the lamina papyracea to the contralateral lamina papyracea.

drainage should be performed. While the Draf IIB drainage is not usually performed as an initial procedure, the presence of a narrow anterior-posterior or medial-lateral dimension, osteitic middle turbinate and/or the presence of an interfrontal septal cell may necessitate a Draf IIB sinusotomy to create a durably patent frontal ostium.[7]

Perioperative Considerations

Perioperative considerations for the Draf IIB frontal sinusotomy are similar to those of the Draf IIA procedure. The axial view on CT is helpful for assessing the anterior-posterior dimension of the frontal sinus floor that will be removed during the procedure. The depth of the lateral cribriform plate should be examined to prevent violation of the skull base medially.

Technique

A type IIB frontal sinusotomy is performed by resecting the frontal sinus floor medially from the lamina papyracea to the nasal septum. After the frontal ostium is clearly identified, an upturned mushroom punch or Hosemann punch are used to remove the frontal sinus floor. After the anterior-posterior dimension of the frontal recess is identified, the medial-lateral dimension of the sinusotomy is widened. Extending the frontal sinusotomy into an interfrontal septal cell is another technique to widen the frontal recess.

DRAF III DRAINAGE

The Draf III procedure, otherwise known as the endoscopic modified Lothrop procedure (EMLP), creates the maximal communication of the frontal sinus into the nasal cavity by removal of the superior nasal septum and frontal sinus floor from lamina papyracea to the contralateral lamina (Fig. 51.7). Draf first described the endoscopic modification of the Lothrop procedure in 1991.

Indications

The Draf III sinusotomy is indicated when endoscopic frontal sinusotomy has failed. The presence of neo-osteogenesis or poor-quality mucosa would also necessitate a Draf III sinusotomy to create a durable frontal sinusotomy. While not usually performed as an initial procedure, Draf suggests this procedure as the primary surgery in patients with poor prognostic factors, which include severe polyposis, Samter's triad, mucoviscidosis, Kartagener's syndrome, and ciliary immotile syndrome. He also recommends a Draf III approach for the removal of benign tumors, including inverted papilloma and osteomas that are located medial to a vertical line through the lamina papyracea, in addition to certain malignant tumors that just reach the frontal recess.[8] Certain anatomic factors, such as frontal sinuses with a narrow anterior-posterior diameter, a hyperplastic internal nasal spine or a highly narrow ethmoid cavity would favor utilizing the Draf III approach.[4]

Contraindications to the EMLP include small, underdeveloped frontal sinuses and a narrow anteroposterior diameter between the anterior skull base and nasal bones.[9]

Perioperative Considerations

Of critical importance when determining the feasibility of the Draf III approach is the total anteroposterior dimension at the floor of the frontal sinus. While the exact cutoff varies between studies, a good working distance would be at least 1.5 cm.[10] This measurement includes the thickness of the nasal beak. Narrower anteroposterior dimensions make manipulation of instrumentation difficult and increase the risk of injury to the skull base. Another measurement to take into account is the so-called "accessible dimension" that represents the space available to maneuver instruments within the frontal ostium and to remove the frontal sinus floor. This dimension is defined as the distance between the tangential line to the skull base into the frontal sinus and the tangential line to the posterior aspect of the nasal beak. This distance should be more than 5 mm to ensure adequate space for frontal sinus instrumentation.[11]

Technique

After a frontoethmoidectomy is performed and the skull base and lamina papyracea are clearly visualized, the head of the middle turbinate is removed using angled frontal through-cutting forceps. The frontal ostium is widened and removal of frontal cells impinging upon the frontal recess is performed with a combination of Bachert, upbiting mushroom, and angled frontal through-cutting instruments. Removal of the frontal sinus floor proceeds from the ipsilateral lamina papyracea to the septum using frontal sinus punches. This series of maneuvers is also performed on the contralateral side. The superior nasal septum is removed. The diameter of this opening should be approximately 1.5 cm.[4] The removal of the superior nasal septum at the junction of the superior nasal septum at the junction of the quadrangular cartilage and perpendicular plate of the ethmoid is important to facilitate the removal of the medial frontal sinus floor and assists in widening the surgical field.[8] The triangle of bone formed by the anterior frontal sinus floor known as the nasofrontal beak is removed with a burr. Identification of the first olfactory fiber forms the posterior boundary of the sinusotomy to prevent violation of the cribriform plate. Special care should be made to avoid circumferential mucosal injury, particularly at the lateral and posterior mucosal margins of the frontal sinus. Messerklinger found that frontal sinus cilia transport mucus up the interfrontal sinus septum, across the frontal sinus roof in a lateral direction, and medially along the frontal sinus floor to the ostium.[12] Forty to sixty percent of mucus is cleared out of the frontal sinus along the lateral aspect of the frontal recess; thus, it is critical that injury to the lateral frontal sinus mucosa be minimized.

Complications

The possible complications for the Draf I–III frontal sinusotomies are similar and include injury to the skull base with dural laceration and CSF leak, injury to the periorbita, and postoperative disturbance of sense of smell. As the anatomy encountered during Draf procedures, especially in revision cases, can be distorted with absent anatomic landmarks, the accurate identification of the medial orbital wall and the skull base is essential to avoiding complications.

Postoperative Care

For the entire spectrum of Draf frontal sinusotomies, postoperative care is essential to maintaining patency of the frontal recess or frontal neo-ostium. After performing Draf IIA, IIB, and III drainage procedures, it is essential to debride the frontal recess or frontal neo-ostium of blood clot and mucous to prevent superinfection, restenosis, or mucosal scar formation. The timing of postoperative debridement varies between surgeons, but typically occurs from postoperative day 3–7. Medical management during the postoperative period is crucial. Some authors use soft, flexible silastic stents, or finger stalls to facilitate hemostasis and re-epithelialization of denuded bone.

OUTCOMES OF DRAF PROCEDURES

The vast majority of outcome studies for endoscopic frontal sinus surgery centers on the Draf III procedure, otherwise known as the endoscopic modified Lothrop procedure (EMLP). Several evidenced-based reviews have been performed evaluating the efficacy of EMLP versus osteoplastic flap for the management of frontal sinus disease. The osteoplastic flap with frontal sinus obliteration is the gold standard against which the EMLP is compared.[13] However, assessing outcomes of the EMLP is difficult secondary to the lack of studies with long-term follow-up.

Determining the results of endoscopic frontal sinus surgery requires a long postoperative follow-up, as frontal sinus stenosis can occur years after frontal sinus surgery.[14] While the osteoplastic flap with frontal sinus obliteration has success rates of 93% with an 8-year follow-up as quoted in the literature, it is not without significant morbidity, including forehead numbness, frontal bossing, osteomyelitis of the frontal bone flap and mucocele formation.[15] In addition, the procedure has possible complications that are secondary to misdirected osteotomies beyond the confines of the frontal sinuses, including dural exposure, dural laceration with cerebrospinal fluid leak, and orbital injury.[16] Anderson et al. performed a literature search and meta-analysis of studies examining the safety and efficacy of the EMLP. They found 18 studies that fulfilled their inclusion criteria, nine of which were level II-2 evidence and nine of which were level III-3 evidence. The indications, preoperative evaluation, surgical details, and outcomes for EMLP were evaluated for this aggregate population of 612 patients. They found that the most common indications for EMLP formation were chronic frontal sinusitis (75.2%) and mucocele (21.3%). Almost all EMLP patients (>99%) were discharged home within 24 h of surgery. The rate of major complications, which included CSF leak, tension pneumocephalus and posterior table dehiscence, occurred in less than 1% of patients; and minor complications, including increased crust formation, epistaxis, anosmia or hyposmia, nasal bone dehiscence, philtral pressure ulcer and transient blurry vision, occurred in 4% of this population. Objective, direct endoscopic evaluation of the frontal sinus cavity following surgery was performed in 12 of these studies. In these patients, serial examination of the frontal cavity revealed patency or partial stenosis in 95.9% at last follow-up. Most studies noted that stenosis of the neo-ostium occurred within the first year following surgery.[13] Subjective symptom data were also examined following EMLP. A total of 82% of patients reported significant improvement or total resolution of their frontal symptoms, 16% reported no significant change, and 1.2% reported worsening of their symptoms. They found that the failure rate of EMLP, defined as the need for any revision surgery in the frontal sinus, was 13.9% (85 out of 612 patients).

Frontal Sinus Rescue

The frontal sinus rescue procedure is formally known as the revision endoscopic frontal sinusotomy with mucoperiosteal flap advancement. This procedure is an alternative technique to the Draf IIA, IIB, III drainage procedures and is specifically utilized when frontal sinus stenosis occurs after endoscopic sinus surgery when a destabilized, partially resected middle turbinate moves laterally and compromises the patency of the frontal recess.

Technique

Under endoscopic visualization with a 45° or 70° endoscope, the lateral attachment or adhesion of the middle turbinate remnant is released. Mucosa from the medial and lateral aspect of the middle turbinate is elevated. The medial based mucoperiosteal flap is developed. The bony middle turbinate remnant is removed using a giraffe forceps. The lateral based mucoperiosteal flap is preserved and advanced over the former middle turbinate attachment point. The mucosa of the lateral frontal recess is not disturbed as natural mucociliary flow of the frontal sinus is directed along the lateral frontal recess. An extended frontal sinus rescue procedure has also been described when the frontal recess is too narrow for adequate mucus clearance. A channel is cut into the middle turbinate from its attachment at the agger nasi to its skull base attachment; the lateral based mucoperiosteal flap is then preserved and advanced as with the frontal sinus rescue procedure.[17]

COMBINED ABOVE AND BELOW APPROACH

The first description of the combined endoscopic trephination and frontal sinusotomy was made by Wigand in 1978.[18] The Above and Below approach consists of the standard endoscopic view combined with an additional trephination through which angled endoscopes can be inserted to further visualize the frontal sinus from above. In certain situations in which a purely endoscopic approach is inadequate, the combined Above and Below approach may be indicated. Indications for the Above and Below approach include laterally based frontal sinus lesions; obstructive type III or IV frontal cells; large tumors or inflammatory lesions involving the lateral frontal sinus including osteomas, inverted papillomas or fibrous dysplasia; frontal sinus trauma with involvement of the frontal recess or posterior table; revision frontal sinus cases with extensive scarring or neo-osteogenesis; and emergent decompression of Pott's puffy tumor.

Technique

Once the endoscopic frontal recess dissection is performed to its full extent, the external approach is initiated. A 1–2 cm incision is made through the medial eyebrow. A self-retaining retractor is placed. A 4 mm drill bit is used to perform the external trephination and a Kerrison rongeur is used to enlarge the trephination. An angled endoscope is inserted through the trephine and the remaining pathology is visualized through the trephine. The location of the trephination can be altered to target the pathology being addressed. While the standard incision for trephination is located in the brow line medial to the supraorbital neurovascular bundle, the incision can be placed lateral to the supraorbital notch for management of lateral frontal sinus mucoceles or osteomas.[19] Image-guided trephination has also been utilized to localize the trephination location to the precise pathology within the frontal sinus.[20] The supraorbital and supratrochlear neurovascular bundles must be protected during trephination. The trephine can be enlarged to 6–8 mm to allow both the endoscope and instrumentation to be passed through it. Additional pathology, whether it be a residual superior aspect of a type III or IV frontal cell, inverted papilloma, or osteoma, can be resected using appropriate instrumentation.

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CHAPTER

Minimally Invasive Sinus Surgery and Balloon Sinuplasty

52

Peter J Catalano

The field of rhinology has undergone significant change and has seen substantial innovation over the past 15 years, with much more to come in the near term. However, before we can move forward, we must have a solid understanding of the past, so we can participate in the innovation and help create the future. In this chapter, the topics of minimally invasive sinus surgery and balloon sinuplasty (BSP) will be addressed, as both have had a significant hand in moving the specialty forward.

Minimally invasive sinus surgery must not be confused with minimal access surgery. The latter simply means we use an "abdominal port" instead of an incision, or a single burr hole instead of a craniotomy. In the case of rhinology, we use the nostrils instead of facial incisions. What defines minimally invasive surgery is what happens after minimal access is achieved, and it is here that consensus is often lost. At present, functional endoscopic sinus surgery (FESS) has no definition, other than that it is performed using an endoscope with minimal access to the nose and sinuses via the nostrils. Beyond this, there is no consensus on what FESS means, how it should be performed, its goals, and how to measure its outcomes. Are we treating a patient or an X-ray? Why do we require a different burden of proof for different procedures, and different authors? Despite the progress in rhinology, there are many unsettled and confusing issues for many of us. In this chapter, I will define MIST, and answer these troubling questions.

MIST, or minimally invasive sinus techniques, is the embodiment of minimally invasive sinus surgery and was the first truly minimally invasive sinus procedure described. MIST is unique for the following reasons:

- It is the only intranasal sinus procedure with a defined beginning and end; thus the surgeon knows when to stop operating (a novel concept!).
- It is based on a step-wise anatomic progression, which allows the surgeon to perform the operation in a structured manner, akin to all other surgical procedures (i.e. parotidectomy).
- It is consistent and reproducible from patient to patient, so that if someone were to say "I had a MIST procedure," everyone would know what operation was performed. This is in contrast to FESS, which transfers little information to the patient or treating physicians.
- It leaves all ostia intact, and instead targets the sinus transition spaces (ethmoidal infundibulum, frontal recess, and hiatus semilunaris superioris).
- It leaves no bone exposed at the end of the procedure, thus preserving all mucosa, even if edematous and seemingly diseased (mucosal reversibility).
- It minimizes the use of forceps or "grab and tear" metal instruments in favor of dissection with a microdebrider which permits real time suction and true tissue cutting at the tip of the instrument.
- It does not use nasal packing, septal splints or sutures.
- It preserves the middle turbinates.
- It does not require postoperative debridement (Figs. 52.1 to 52.5).

If one compares this definition to what is currently done under the guise of "functional" sinus surgery, the differences should be readily apparent. Thus, MIST is a targeted tissue sparing procedure that is consistent from one patient to the next, and whose goal is to perform the

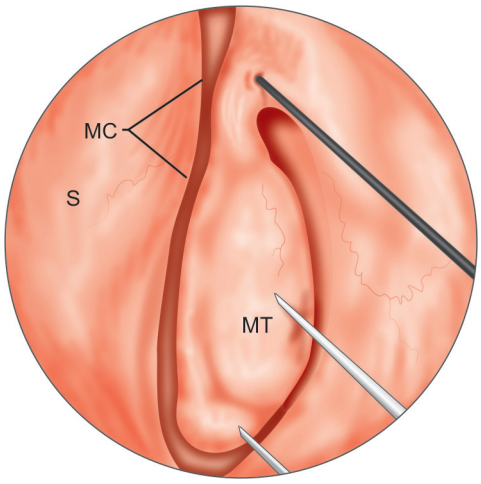


Fig. 52.1: Injection sites into the left middle turbinate (MT) prior to MIST. (S: Nasal septum).

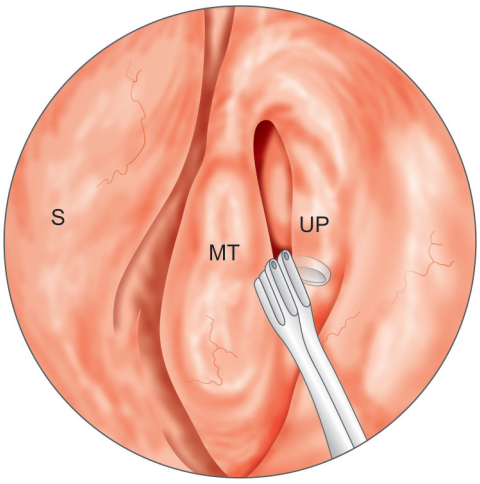


Fig. 52.2: Pediatric backbiter is placed into the middle meatus, then opened so that the cutting blade can be placed into the ethmoidal infundibulum via the hiatus semilunaris. (UP: Uncinate process; MT: Middle turbinate).

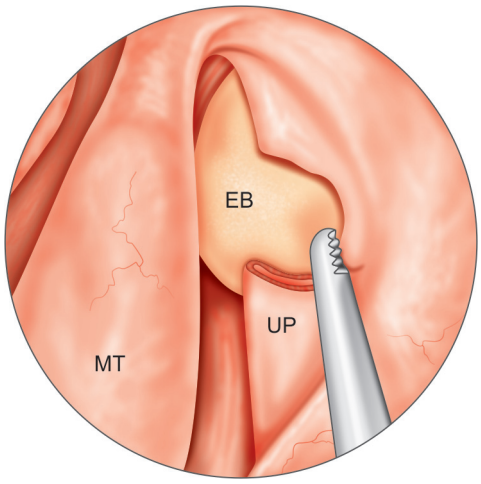


Fig. 52.3: After uncinotomy with the backbiter, a microdebrider is used to remove the remainder of the uncinate process (UP). (EB: Ethmoid bulla).

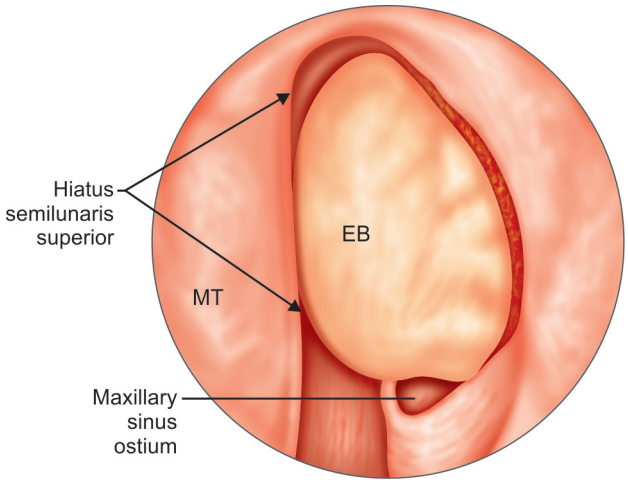


Fig. 52.4: A complete uncinectomy is performed, exposing the maxillary sinus ostium inferiorly, the ethmoid bulla (EB), and the hiatus semilunaris superioris (arrows).

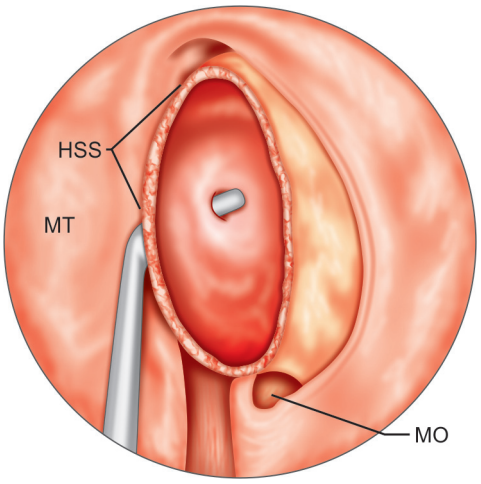


Fig. 52.5: Ethmoid bulla removed with a microdebider, showing the maxillary sinus osmium (MO), anterior ethmoid sinus ostium at tip of seeker, and anterior ethmoid sinus drainage pathway via the hiatus semilunaris superioris (HSS).

minimal amount of surgery required to restore normal function to the nose and sinuses. It is a patient-centric procedure, meaning it is designed to address patient symptoms, not the extent of disease on a CT image. It is important to obtain CT imaging in all patients seen with a chronic sinus history; however, one must remember that CT imaging is only one piece of data, one test result, and should be used to aid the physician in his/her decision making and management. It is not the ultimate or definitive piece of information upon which management should be based.

One of the main tenants of MIST is that sinus disease, mucosal disease, is reversible and that aggressive surgery is not required to make patients better. There are several peer-reviewed manuscripts on outcomes from MIST,[1–5] and all are very favorable, thus proving that a maxillary sinus antrostomy (MSA) is not required as a routine part of ESS. In fact, there are now compelling data to show that an MSA can actually promote more virulent sinus bacteria and lead to biofilm formation.[6] The take home message here is that while an MSA can work, it is not necessary in the majority of sinus procedures. Furthermore, there is not a single medical article that proves the need for, or efficacy of, an MSA! There is NO DATA to support a procedure that has been performed as a matter of routine, since 1987, and yet there is convincing data to show that an MSA is not needed and that there is no functionally critical size for maxillary sinus ostia. I have visited many sinus surgeons in their operating rooms over the years and just as they were about to make an MSA I would ask, "Why are you going to do that?" The answers I received in almost all cases were either "Because that is what I always do?," or "Isn't that what you were taught?," or "Because we have to open the sinus and look inside." These replies prove nothing more than a simple truth—that surgeons are often victims of their training and experience. While we all rely on the teachings of our mentors, I would hope there is no mentor who believes that a student's learning ended when they graduated from residency or fellowship, or that management of patients in 1987 should be the same as in 2013. Learning is a continuous process that extends throughout one's career and it is impossible for any one person to know all, or to anticipate new information that might alter patient management in the future. For if changes were not inevitable and necessary, we would still be using candles, riding horses, and walking barefoot.

The irony is that the concepts of MIST are not new, and actually precede those of contemporary ESS where an MSA is commonplace. Messerklinger's "functional" concepts did not include an MSA, and its origin remains elusive to this day. Messerklinger[7] believed in the reversibility of diseased mucosa, in transition space surgery instead of surgery on the sinus itself, in sparing mucosa and middle turbinates, and restoring mucociliary function by eliminating mucosal contact. It is the departure from these principles that has allowed for MIST to emerge and for new technology to transform rhinology.

The history of MIST begins with Messerklinger; however, he did not describe a technique as much as he provided a philosophy of management. This is likely why the MSA "crept" into the FESS procedure and became routine. After Messerklinger, there was a hiatus until the mid-1990s when Reuben Setliff, frustrated by his results with FESS, searched for a better alternative. In 1994, he introduced what was then called "small-hole surgery" and first presented his technique in a chapter in *Otolaryngology Clinics of North America*.[8,9] Reuben realized that the MSA was more of a problem than a solution and thought by avoiding the MSA, surgical morbidity would be reduced, revision rates would be lowered, and outcomes might even improve. In about 1994, he first introduced the microdebrider,[10] thereby eliminating the need for the typical "grab and tear" forceps of the day, and provided true cutting capability and real-time suction at the working end of the device. We are all aware of how this technology has revolutionized rhinologic surgery worldwide, but few realize that it was also this technology that allowed "small-hole surgery" to be done with even less morbidity than had been predicted or appreciated.

At this same time, Dave Parson introduced the retrograde approach[10] to the uncinate process and ethmoid infundibulum. This technique eliminated the risks and inaccuracies of using a sickle knife to incise the anterior attachment of the uncinate to the lateral nasal wall. Retrograde approach allowed the surgeon to open the infundibulum from a posterior-medial position, which is furthest from the lamina papyracea and therefore a much safer technique. The risk of orbital injury has been significantly reduced by use of this retrograde approach. Figures 52.1 to 52.7 demonstrate the step-wise anatomical progression that is the hallmark of the MIST procedure.

In the late 1990s—early 2000 time period, all the elements were in place for consolidation into what was to be called MIST—the minimally invasive sinus technique. Thus, MIST combined Setliff's philosophy of small-hole surgery, with the true cutting accuracy of the microdebrider, and the retrograde uncinotomy described by Parson. Outcomes from MIST were reported in 2003[2] and

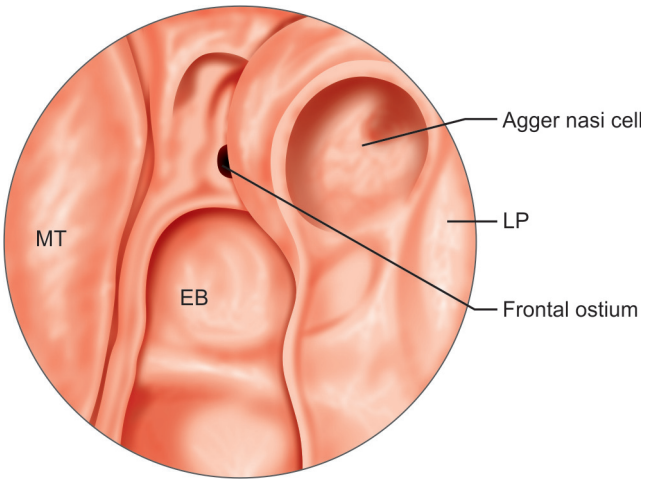


Fig. 52.6: At completion of MIST dissection, the ethmoid bulla (EB) is opened. The middle turbinate (MT) is preserved, and the frontal recess leading to the frontal sinus can often be visualized (arrow). (LP: Lamina papyracea).

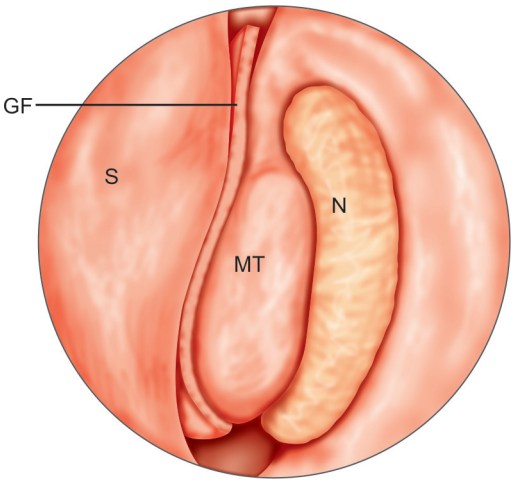


Fig. 52.7: At the completion of the procedure, a thin piece of gel-film (GF) may be placed between the septum and the MT, and an absorbable dressing (N) is placed in the middle meatus.

showed for the first time that less invasive, targeted sinus surgery (without an MSA) could reliably produce *durable results that were even better than those from FESS*. The authors compared 100 patients who had MIST with 100 patients previously reported by Glichlich et al. who had FESS. The FESS group results were reported after a follow-up of 1 year while the MIST outcomes were reported after a follow-up of 2 years. Both groups were closely matched with respect to demographics and extent of disease, and both studies used the chronic sinusitis survey that was the only validated outcome metric for rhinology at the time.

Morbidity in the MIST group was extremely low and the revision rate over the 2-year period was only 6%. Interpretation of this last bit of data means that 94% of patients were treated appropriately with a less invasive procedure, while 6% needed more surgery than originally appreciated. It also means that had FESS been performed initially, 94% of patients would have been "overoperated upon," or subjected to a larger, more morbid operation than necessary. It is this latter point that is the crucial and validating point in minimally invasive rhinology—namely that the vast majority of patients need a targeted and limited intranasal intervention to eliminate symptoms, and therefore procedures such as MIST should be the initial surgical procedure, or procedure of choice, for treating inflammatory sinus disease.

To further prove the reduced morbidity of MIST, a subsequent study was performed and published on MIST in the geriatric population, aged 65–93 years.[1] The purpose of this study was to evaluate if MIST produced an increase in surgical or medical comorbidities in the elderly. The results again showed that surgical morbidity was extremely low and exacerbation of medical comorbidities was similarly very low. The later included minor complications such as urinary retention (1), transiently elevated blood pressure (2), transient atrial fibrillation (1), and self-limiting dizziness (2). The main outcome point was that MIST could be safely performed in the oldest, most frail members of society with very low surgical and medical morbidity, thus availing these patients of a surgical option for their chronic sinusitis that might not have been considered with FESS.

In 2004, Albu and Tomescu[5] from Romania published their report on 133 patients who underwent ESS and either had an uncinectomy or MSA (follow-up was 19 months). They concluded that "the size of the maxillary sinus opening had no influence on the outcome of ESS for chronic maxillary sinusitis." Their work further supports the concept that an MSA is unnecessary in most patients and should not be performed as a routine part of ESS.

Currently, my indications for an MSA are limited and include surgery in the pterygopalatine space, removal of inverted papilloma from the maxillary sinus, creation of a mega-antrostomy in cases of recalcitrant maxillary sinusitis, and patients with Sampter's triad or fungal sinusitis. In the latter two cases, the MSA is no larger than 10 mm. It is important to remember that the surgeon can always revise his/her surgery and perform an MSA if

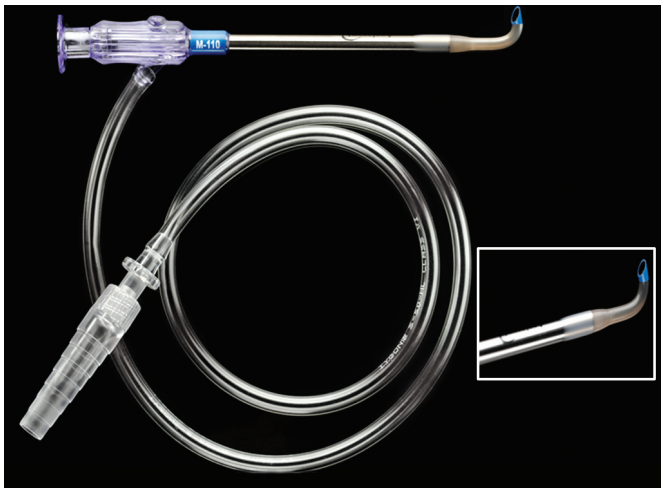


Fig. 52.8: Suction-capable guide catheter.

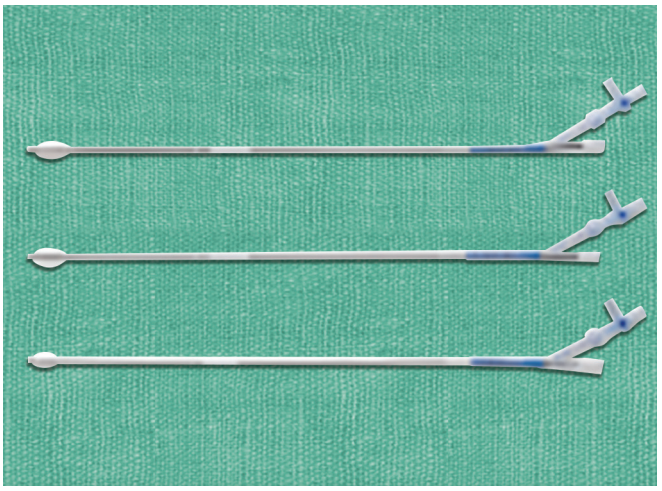


Fig. 52.9: Various balloon catheters.

clinically indicated; hence, the 6% revision rate reported for MIST. In my experience, most patients want the least amount of surgery possible. When performing MIST, the surgeon should counsel the patient that a limited procedure is appropriate for their condition and that a <10% chance exists that more or revision surgery may be required. It is also important to realize that surgical revision rates for sinus surgery have been lowered across the board by the adjunctive use of topical medications and nasal/sinus irrigations such as budesonide and antibiotics. Thus, advances in topical medication protocols provide even more reason to consider a minimally invasive surgical option today than ever before.

By the mid-2000s, MIST had gained in popularity worldwide and many surgeons were seeing the same results reported in the literature. With the concepts of MIST respected and appreciated by the rhinology world (even though many still believed in the need for an MSA), the stage was set for the next innovation.

Enter balloon dilation technology (BDT) or BSP, which was introduced to the market in September 2005 at the American Academy of Otolaryngology Annual Meeting in Los Angeles, CA. This technology is considered "disruptive," not because it interfered with conventional treatment or patient care, but because it introduced a paradigm shift to the treatment of patients with chronic rhinosinusitis (CRS), required new surgical skills not previously taught to otolaryngologists, and introduced a new surgical tool. Over the past 25 years, there have been four major technological advances in rhinology: the endoscope, the powered microdebrider, image guidance systems, and BSP. The minimally invasive concepts of Messerklinger, as described and discussed in the previous section on MIST, have been validated by BSP; hence, BSP is considered a "transition space tool." The functional elegance of BSP, coupled with its relative conceptual simplicity, earned BSP descriptors such as "innovative," "revolutionary," and "ingenious."

We will first discuss the theory of BSP and its application in the treatment of patients with CRS, including exciting new data on "functional preservation," the role of the uncinate process, and physiologic gas exchange principles within the sinus. A thorough review of the current literature as it relates to BSP is then followed by a discussion of clinical indications.

The Tools

The tools of BSP have evolved from two- to three-handed/two-operator systems to single-handed/single-operator devices. A basic BSP system is comprised of several disposable components including suction capable guide catheters (Fig. 52.8), flexible kink-resistant guidewires, balloon dilation catheters of various diameters (3.5, 5, 6, and 7 mm) (Fig. 52.9), and a manual pump mechanism to inflate and deflate the balloon catheters (Fig. 52.10). Fiberoptic guidewires and irrigation catheters are additional options for the surgeon (Fig. 52.11A). Fluoroscopy, initially a requirement of the technology to help guide and confirm proper wire and balloon placement (Fig. 52.11B), is now optional due to the introduction of the light wire. The latter uses the principle of transillumination of the sinus to confirm guidewire placement within the sinus

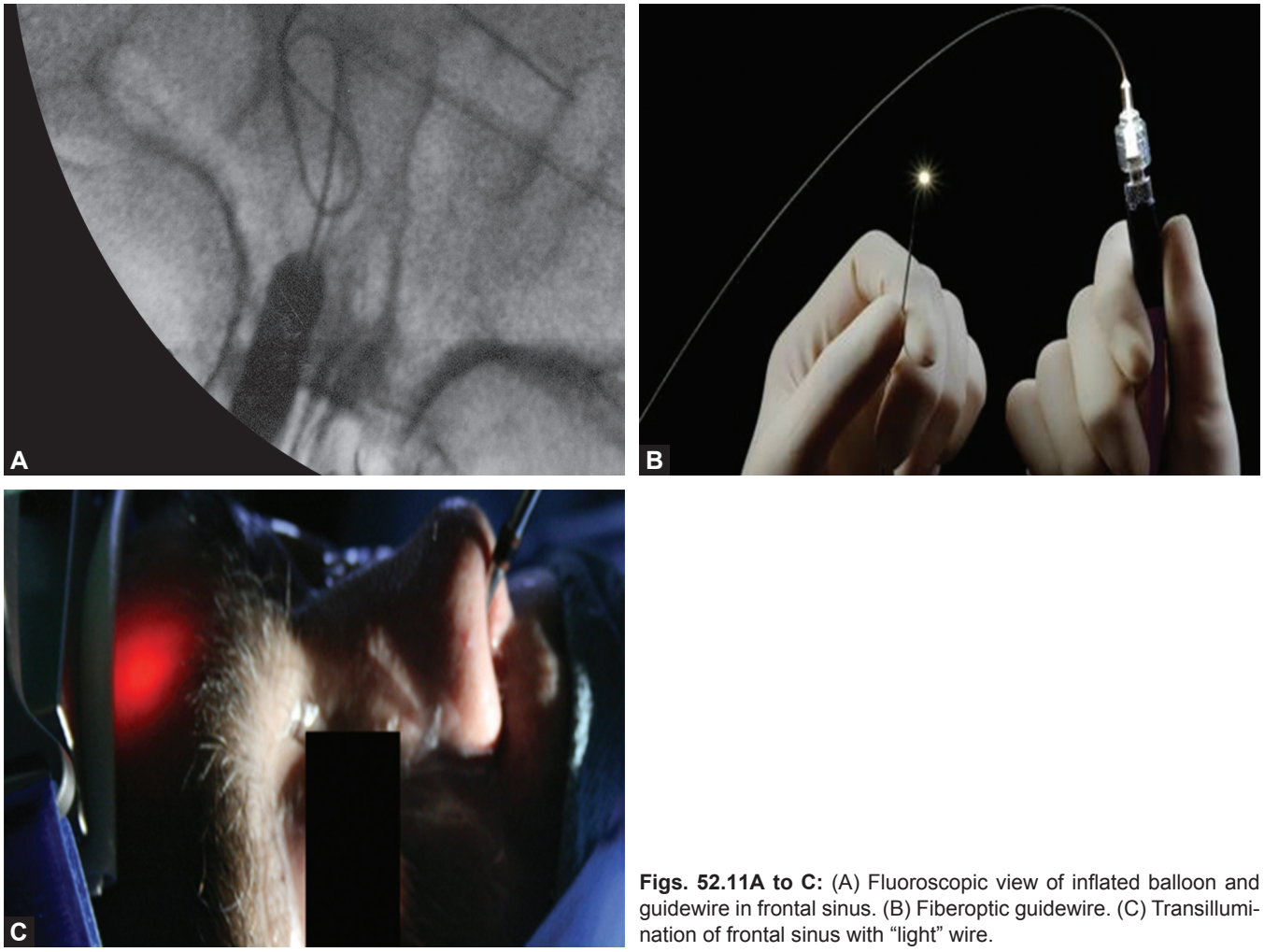
Fig. 52.10: Manual balloon pump.

lumen. The balloon catheter is then placed, inflated, and removed under endoscopic control. The balloons themselves are nonconforming and therefore can displace bone and tissue within the sinus transition space and/or ostia. Balloons are inflated to between 8 and 12 atm to achieve a clinical effect (note that a car tire's maximum inflation is 2 atm!). Issues related to balloon placement, choice of balloon size, and inflation time and pressure are discussed later in this chapter. While the central guidewire port of the balloon catheter can be used to irrigate a sinus once the guidewire has been removed, more effective sinus irrigation, especially in cases where thick tenacious material is trapped within the sinus, can be achieved with the use of multiport irrigation catheters (Fig. 52.12) designed to produce a whirlpool effect within the sinus and flush retained debris out through the newly dilated natural sinus os.

In 2008, new sinus balloons were introduced to provide an important benefit of shape retention between dilations. These balloons deflate in one fourth the time of the original balloons and resume their original compressed, wrapped configuration to permit easier passage through the sinus guides and transition spaces on subsequent applications in the same patient. In 2009, soft bevel-tipped, flexible suction-ready sinus guides were introduced to permit easier atraumatic access to the targeted transition space with the option for suction at the tip of the guide. This newer guide is especially useful in the small, narrow nose and in cases where there is bleeding at the target, such as after nasal polypectomy in the ethmoid sinus and/or frontal recess. In 2009, Entellus introduced the Express system that allows one-handed control of the entire BSP device (Fig. 52.13). The Entelus system does not use a guidewire but instead uses a metal probe to enter the transition space. The balloon catheter is then delivered over the probe and inflated. Acclarent's next generation device, SPIN (Fig. 52.14), also emphasizes functional independence by permitting the surgeon to hold the endoscope in one hand while placing the guide, introducing the guidewire and advancing the balloon catheter with the other. Both systems currently need an assistant to inflate and deflate the balloon. A new low pressure dilation system, SinuSys (Figs. 52.15 and 52.16), has recently been developed that uses an osmotically dilated membrane that can be placed and deployed into the sinus transition space using a simple introducer. The device absorbs water from surrounding nasal mucous to inflate the membrane and open the transition space. This process takes 45 minutes, after which the device is removed (Fig. 52.15). It is believed that "slow" dilation produces less recoil and therefore a larger dilation than prior systems. At present, there are three additional BSP technologies in development that will soon make their way to market.

As previously mentioned, BDT is essentially a transition space tool, targeting primarily the ethmoidal infundibulum and frontal recess. The sphenoid sinus does not have a transition space and is rarely involved with inflammatory disease. These transition spaces, or "prechambers" to Messerklinger, are slit-like in nature, having a maximum diameter of 1.5–2 mm, and even less in the symptomatic patients. Placement of a submillimeter guidewire and plus-millimeter balloon catheter into the transition space can be challenging at times, yet still represents the least traumatic means to access this anatomic area. Once in place, the balloon catheter is slowly inflated to between 8 and 12 atm, and during this process the opposing walls of the transition space are separated an amount equal to the diameter of the chosen balloon. This prying open of the transition space occurs via microfractures of the immediate peripheral bone (i.e. uncinate process), which once displaced, retains approximately 80% of its new diameter as the substructure heals. The retention of the new diameter may be closer to 95% with the SinuSys osmotic device mentioned earlier.

Prolonged high pressure dilations should be avoided as they are associated with ischemic injury to the local



Figs. 52.11A to C: (A) Fluoroscopic view of inflated balloon and guidewire in frontal sinus. (B) Fiberoptic guidewire. (C) Transillumination of frontal sinus with "light" wire.

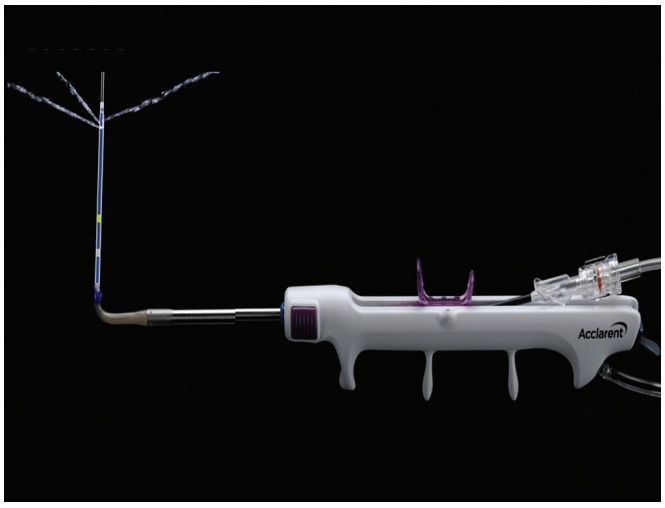


Fig. 52.12: Multi-port irrigation tip.

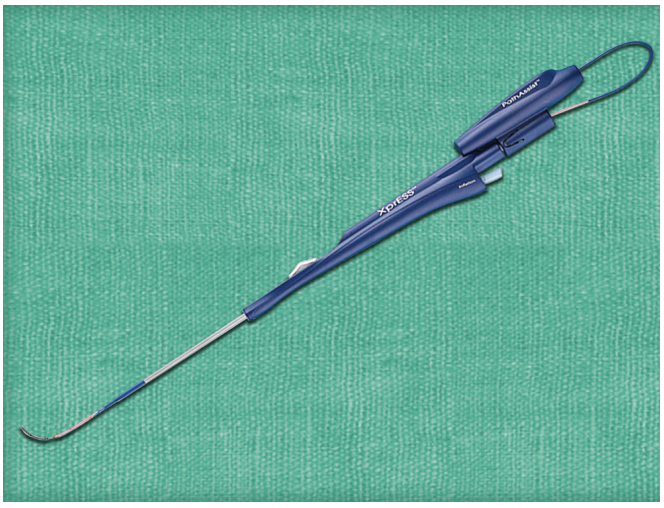


Fig. 52.13: Entellus XprESS system.

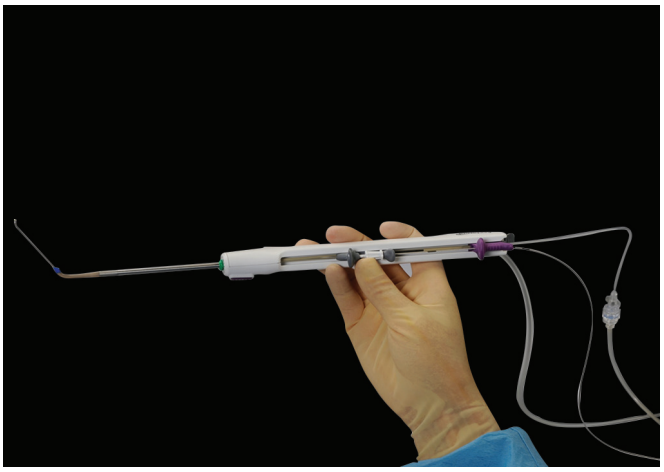


Fig. 52.14: "Spin" device with "light" wire, balloon and irrigation catheter combined for one-hand operation.

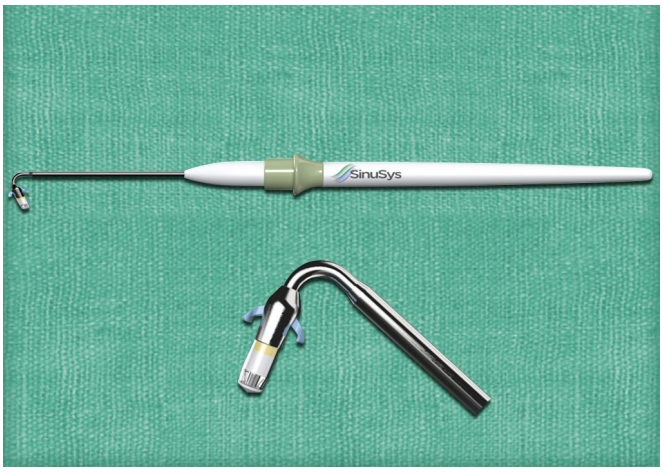


Fig. 52.15: SinuSys Vent-Os system.

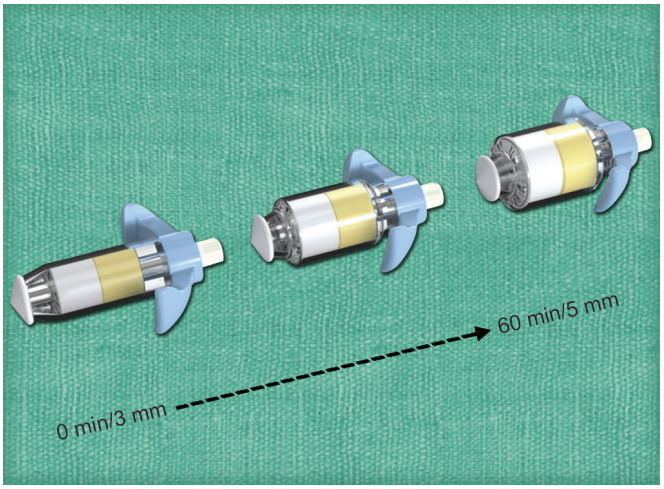


Fig. 52.16: Osmotic dilation device.

mucosa and can result is subsequent prolonged edema and injury. Once the BSP system is removed, the transition space has been transformed from a slit-like pathway exiting a given sinus into a circular/oval shaped tunnel of a given balloon diameter. Bleeding from the transition space mucosa may occur during or after dilation if the mucosa is torn due to either traumatic technique of balloon placement, or use of a balloon >5 mm. In the case of the latter, mucosal tears are linear in nature and heal quickly without clinical consequence. Circumferential tears are more likely to cause secondary contracture and are rarely, if ever, seen with proper BSP technique.

BSP tools can be used alone as a sole intervention for one or more sinuses, or in combination with more conventional endoscopic sinus surgical techniques, the so-called hybrid procedure. The most common scenario for the latter is when conventional ESS is performed on the maxillary and ethmoid sinuses and BSP is used on the frontal and/or sphenoid sinuses.

One of the most important aspects of BSP is preservation of the uncinate process, and it is the only surgical technique on the sinuses to do so. The role of the uncinate process remains in question. However, research to evaluate sinus airflow may provide some important clues. Several years ago, Dipak Nayak, an otolaryngologist in India, performed a few studies to determine the role of the uncinate process.[11] Nayak first used simple inhalational dye studies with methylene blue comparing dye deposition within the nose and sinuses in two groups of postoperative patients; with and without preservation of the uncinate process. He found dye within the maxillary and ethmoid cavities when an MSA was performed; however, dye remained only on the anterior middle turbinate and uncinate process when the latter were preserved. In a separate study, Nayak again produced two separate postoperative cohorts, either with or without an uncinate process, and followed them for 12 months. If the uncinate was preserved, the incidence of recurrent sinusitis and facial symptoms was significantly reduced. Nayak then proposed that the design of the uncinate process (i.e. open posteriorly) directs air into the sinus cavity and thus allows them to ventilate on exhalation.

However, recent work from Xiong in China[12,13] suggests an opposing viewpoint. Xiong's group designed mechanical airflow simulation models using actual human anatomic CT scan data. In their model, there is minimal to no air entering any sinus cavity in the human head during either phase of respiration! Airflow arched through the

nose with highest flow rates between the middle turbinate and lateral nasal wall. Xiong et al. then repeated their experiments using CT images from post-ESS patients who had a surgical ethmoidectomy and MSA. In these patients, there is a striking increase in maxillary and ethmoid sinus airflow. Khirene et al. recently measured intrasinus airflow before and after various sized MSAs and found that measurable airflow occurred within the maxillary sinus once the size of the middle meatal opening exceeded 20 mm^2.[14] Coincidentally, the cross-sectional area of a 5 mm diameter sinus balloon is exactly 20 mm^2.

This natural mechanical defense mechanism of the sinuses suggests that the uncinate process and anterior middle turbinate help filter inspired air and prevent exposure of the sinus mucosa to inhaled debris in the form of pollutants, allergens, carcinogens, etc.

There is a second natural defense mechanism that exists within the paranasal sinuses, herein termed the chemical defense mechanism. The latter consists of an interesting molecule called "NO," or nitric oxide.[15] The molecule is not the same as nitrous oxide (N_2O), the general anesthetic. NO is made within the maxillary sinus by the enzyme nitric oxide synthase. Research has shown that the natural concentration of NO within the normal maxillary sinus reaches toxic concentrations if inhaled. However, at these concentrations, NO has local antiviral, antibiotic, and antifungal properties, and will increase ciliary beat frequency.

In fact, the Nobel Prize was awarded in the mid-1990s to researchers who discovered the vasodilatory effects of NO and labeled it a signaling molecule within the body.[16] We have come to learn that NO comes in many forms. The free radical form is present within the vascular system and has a very short half-life, whereas the form active within the sinuses and airway is not a free radical and can persist for up to 11 minutes. It has also been shown that small amounts of NO (approximately 3 parts per billion) are inhaled into the lungs with each breath. Inhaled NO at this concentration has a vasodilatory effect on the lung increasing oxygen absorption. Inhalation of NO is now used as a therapy for hypoxic infants with immature pulmonary systems.[17]

Diffusion of gas from within the normal maxillary sinus has been shown by several researchers to be very slow, taking up to minutes to completely replace its volume by simple diffusion. NO is also heavier than air, thus the highest concentrations of NO occur at the floor of the maxillary pyramid depending upon the patient's position. Note that the maxillary os is always at the apex of the pyramid when we are in either the upright, supine, or lateral position. Thus, with the uncinate process in place, a small amount of NO leaks out of the maxillary sinus and into the lung with each inspiration. Subsequently, NO has a positive physiologic effect on oxygen uptake and sinus health. Furthermore, NO levels in inspired or exhaled air are undetectable after ESS in which an MSA has been performed. Thus, the washout of maxillary sinus NO, as predicted by Xiong, is a consequence of the MSA and may have untoward physiologic consequences as discussed next.

Can all of these findings relative to sinus airflow and NO production and function be purely coincidental? Is the bacteriology of recurrent CRS after ESS (virulent atypical organisms like *Pseudomonus, Escherichia coli,* and *Klebsiella*) in any way related to the loss of NO from the sinus after an MSA? Is uncinate preservation more important to the delicate balance of the gaseous physiology of the sinuses than some are willing to acknowledge? How else do we explain the high concentrations of NO within the normal maxillary sinus, its absence in CRS, and its vasodilatory effects on the pulmonary vasculature when inhaled in minute concentrations? One could argue that not all patients who have an MMA are disadvantaged, or are colonized by virulent pathogens, or show any measurable adverse pulmonary effects. While this may be true, the converse is as well, and thus knowingly creating an MSA when a primary, clinically valid alternative exists, seems irresponsible. I submit that a majority of patients given these facts would opt for conservatism, tissue preservation, and a more functional surgery. Note that the MIST procedure does not disturb the size of the natural maxillary sinus os and therefore there is no washout of NO, nor any of the unwanted consequences of an MSA noted previously.

There have been over 50 articles published on the use of BSP and it is impossible to review them all. The most important data are derived from the CLEAR studies, published in 2008 and 2009.[18–20] The studies were sponsored by Acclarent and involved some of the most notable rhinologists of our time, including Michael Sillers, William Bolger, Fred Kuhn, Winston Vaughn, and others. The three manuscripts report on the outcomes of BSP at 6, 12, and 24 month timepoints. All patients were followed using the SNOT-20 outcome metric, Lund-MacKay sinus CT grading scale, and endoscopic examination of the targeted sinus when possible.

Approximately 80% of sinus ostia were able to be seen postoperatively to determine patency, but one can

understand with a preserved uncinate process how this can be a challenging and difficult process.

The results at each timepoint show a statistically significant and durable improvement in reduced SNOT-20 scores, reduced Lund-MacKay scores, and ostial patency. One major problem with the study was the lack of rigorous criteria to determine which patients received a hybrid versus BSP procedure. Instead, this was left up to the discretion of the surgeon. These data are also unfairly critiqued as being "influenced by conflict of interest"; however, the surgeons involved are of the highest moral character and have never been accused of this type of behavior in prior work.

To better determine the benefit of BSP in some of the worst clinical conditions affecting the frontal sinus, Payne et al.[21] reviewed the radiographic changes in the frontal sinus after BSP. Study patients had either a completely opacified frontal sinus secondary to CRSwNP, or a clinical history of Sampter's triad, fungal sinusitis, or hyperplastic sinusitis. All patients underwent ESS, but had their frontal sinus(es) treated with a 5-mm balloon. Minimum follow-up was 6 months. Overall, 48% of patients had radiographic improvement in their frontal sinus for a minimum of 6 months after BSP, with over 60% showing durable improvement in the CRSwNP group. All patients had statistically significant improvements in SNOT-20, but these data were not reported because other sinuses were also treated simultaneously and there was no way to isolate SNOT-20 changes to frontal BSP alone. Using radiographic changes as the sole metric for improvement will only underestimate the number of patients who were clinically improved because radiographic changes are unlikely to normalize in patients with Sampter's or hyperplastic sinusitis despite a significant reduction in symptom scores. Many interpreted these outcomes as proof that BSP is not effective in relieving frontal sinus disease in clinically advanced cases. However, another interpretation, and the one intended by the authors, was to show that at least 50% of patients with clinically advanced frontal sinus disease can achieve significant improvement without aggressive frontal sinus surgery, thus sparing 50% of patients from unnecessary morbidity.

This was followed by a prospective study of 34 patients who failed medical therapy and required surgery of their frontal sinus. Patients were randomized into 2 groups; half of the patients received conventional Draf I or Draf IIa frontal sinus surgery and the other half underwent frontal BSP.[22] In this study, Plaza et al. demonstrated similar resolution of frontal sinus disease between the two groups on CT imaging. Overall Lund-MacKay scores were reduced from 19.2 to 3.6 after BSP and from 18.6 to 4.2 after FESS. Frontal sinus-specific LM scores were reduced from 1.9 to 0.5 after BSP and from 2.0 to 0.4 after FESS. Endoscopic frontal sinus patency was better after BSP (73% vs. 62%), but this difference was not statistically significant. Four patients required revisions surgery during the 12-month follow-up: one in the BSP group and three in the FESS group. Other than some minor postoperative bleeding, there were no complications in either group.

These results support the general experience that balloon dilation of the frontal sinus is a safe and equally effective treatment for patients with CRS involving the frontal sinus.

Ramadan published his work on BSP for pediatric sinusitis by first reporting a feasibility study in early 2010,[23] followed by a prospective nonrandomized study comparing outcomes after BSP to that for adenoidectomy alone.[24] The latter had been the "gold standard" treatment for recurrent sinusitis in children at the time.[25] His data clearly showed that BSP was a safe procedure in children with recurrent sinus symptoms and that BSP alone was far more successful than adenoidectomy in improving the symptoms of chronic sinusitis (82% vs. 52.6%, respectively). Several other authors have since shown similar outcomes using BSP alone to treat chronic sinusitis in children.

Most recently, Cutler et al.[26] reported their results of a prospective, randomized study comparing patients undergoing FESS with those undergoing BSP alone in a clinic setting. Patients were matched for extent of disease and other demographics. Follow-up was 6 months, and outcome metrics included SNOT-20 scores, time out of work, number of postoperative debridements, and postoperative discomfort. Their results showed patients undergoing BSP with or without ethmoidectomy required much fewer debridements, returned to work sooner, had less postoperative discomfort, and better SNOT-20 scores than those in the FESS arm. This is the first head-to-head comparison between ESS and BSP populations to be reported, and clearly supports the roles for BSP in treating surgical candidates with CRS.

Perhaps the issues that remain regarding the use of BSP relate to patient selection and cost. The latter will likely be addressed by simple market forces as more balloon devices are developed and more choice is available for surgeons. Market competition should drive prices down, as will less expensive technologies (i.e. SinuSys). To date, there are five different US medical device companies that manufacture and sell balloon dilation systems for chronic sinusitis. Patient selection is also becoming more

clear, with BSP being well accepted for patients with RARS, CRSw/oNP, and some patients with CRSwNP. However, many surgeons are pushing this envelope as well, especially with the advent of improvements in topical and targeted adjuvant medical therapy and are now using BSP when treating most of their patients with nasal polyps, and even some with Sampter's and fungal sinusitis. As stated earlier, BSP is a very forgiving technology, and in cases where outcomes were less than desired, leaves the surgeon and patient with the same treatment options after BSP as before.

In conclusion, minimally invasive sinus surgery is fast becoming the primary option for the surgical treatment of inflammatory nasal and sinus disease. It is based on sound principles, proven science, and excellent clinical outcomes. BSP, as an outgrowth or extension of minimally invasive surgery, has been placed under undue scrutiny and held to exceptional standards by those who hold fast to, and have a preference for, FESS. However, the data strongly support BSP and an equally effective treatment option for many patients with CRS and boast an unprecedented safety profile. Innovation causes change, and change requires an open mind and a vision for the future. BSP has been a "disruptive" technology for otolaryngology in many ways, and we and our patients are all the better for it. To this point, the majority of rhinologists worldwide envision the future of this specialty to be dependent upon catheter-based surgery coupled with drug delivery/elution technologies and that future begins now.

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CHAPTER

Open Approaches to the Paranasal Sinuses for Inflammatory Disorders

53

Esther Kim, James Duncavage

INTRODUCTION

Endoscopic surgery fundamentally altered surgical approaches to the paranasal sinuses when first popularized in the mid-1980s. This minimally invasive approach to the sinuses saved patients from external incisions and allowed surgeons improved visualization of the sinus cavities themselves. And so the open approach techniques began to wane significantly as the endoscopic techniques were perfected. In the modern era, external approaches are rarely used, and graduates of otolaryngology residencies seldom see these techniques. However, the "old" open approach techniques retain their relevance despite the advances in endoscopic approaches. In the following sections, we will describe the techniques themselves and discuss the current indications for these procedures in the endoscopic era. We hope that this chapter will serve as a guide to students and surgeons regarding the utility of open sinus procedures.

MAXILLARY SINUS

The endoscopic approach to the maxillary sinus has become the gold standard for treatment of maxillary sinus disease. In the majority of cases, the diseased maxillary sinus can be adequately treated with endoscopic maxillary antrostomy and appropriate postoperative medication regimen. However, two issues make the endoscopic approach alone insufficient in some cases. First, views of the most anterior, inferior, and lateral portions of the maxillary sinus can be difficult with standard endoscopes, even with 70° or 120° endoscopes. Inferior turbinate anatomy and the anterior-posterior distance from nares to posterior border of the nasolacrimal duct may be sufficiently large to prevent the surgeon from positioning the endoscope to visualize the inferior, anterior and lateral mucosa of the sinus. In patients with recalcitrant maxillary disease despite aggressive medical and endoscopic surgical therapy, mucosal abnormalities in these difficult-to-view areas may be the cause.

Second, the severity of the disease process may not be sufficiently addressed with even advanced endoscopic techniques. Recent literature challenges the idea that endoscopic maxillary antrostomy, either standard or mega-antrostomy, is sufficient to treat severe disease.[1,2] The mucosa in severe cases of chronic rhinosinusitis with or without nasal polyps may be overwhelmingly edematous and covered with thick mucin, and thus may be resistant to medical treatments even in the presence of a sufficient middle meatus antrostomy. Anecdotal experience exists that complete removal of severely diseased mucosa, or at least a significant debulking, results in significantly improved postoperative course and lower revision surgery rates.[3] This remains a controversial concept with limited supportive evidence. Additionally, the ability to distinguish between condemned and potentially salvageable mucosa remains challenging. Regardless, the ability to remove that mucosa is limited in endoscopic techniques because of visualization and instrument rigidity. Access to that mucosa requires a more radical approach through the anterior wall of the maxillary sinus. To address these issues, the sinus surgeon must look back to more traditional sinus surgery techniques including maxillary sinoscopy via canine fossa puncture and the Caldwell-Luc, canine fossa trephine approach.

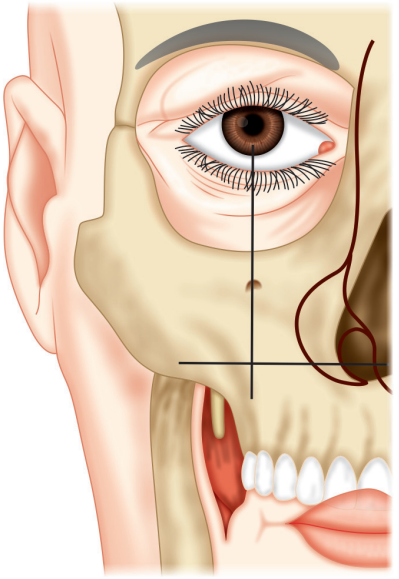

Fig. 53.1: Intersection of the midpupillary line and the horizontal line through the floor of the nasal vestibule. Redrawn from Kim and Duncavage.[5]

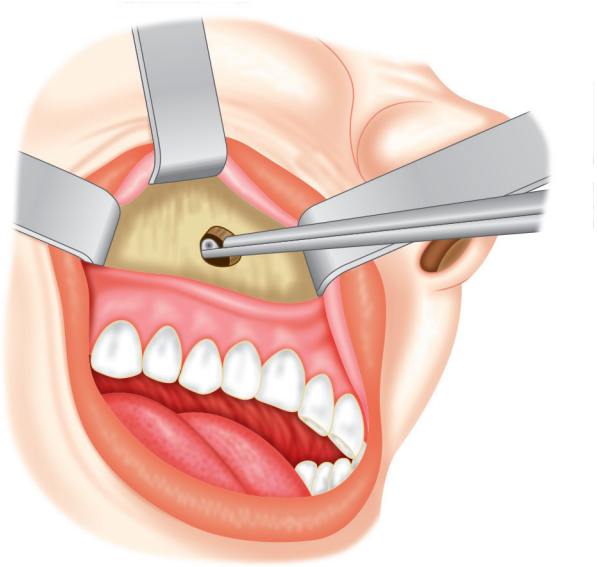

Fig. 53.2: Maxillary sinoscopy being widened using Kerrison rongeur after trocar entry. Redrawn from Kim and Duncavage.[5]

One option for investigation of the mucosa is maxillary sinuscopy through a sublabial, canine fossa puncture. For the sinuscopy, the surgeon uses an endoscopic trocar to traverse the canine fossa into the maxillary sinus. This trocar should be short, between 5 and 7 cm, so that the endoscope and instruments can be passed and all aspects of the maxillary sinus can be addressed, including the most anterior-inferior region. Robinson and Wormald described an ideal point of anterior entry into the sinus at the intersection of the midpupillary line and the horizontal line through the floor of the nasal vestibule.[4,5] Figure 53.1 depicts this point. Once this landmark is identified, a trocar is twisted to puncture the bone of the anterior wall of the maxillary sinus (Fig. 53.2). When the disease process is severe enough, endoscopic instruments may not be sufficient to remove the disease mucosa. To extend the sinoscopy approach into a Caldwell-Luc, the puncture siteis expanded using biting instruments such as Kerrison rongeurs and powered drills. The periosteum overlying the bone is carefully elevated to not injure the nerves. Primary closure of the puncture site is rarely indicated if the mucosal incision is no larger than the trocar itself. For the Caldwell-Luc, interrupted sutures with vicryl or chromic are sufficient to close the mucosal incision.

In both procedures, the trocar should not be hammered into the sinus because of the possibility of fracture of the anterior wall through the branches of the infraorbital nerve and anterior superior alveolar nerve with resultant facial numbness. Also, injury to the posterior wall of the sinus is a possibility. One must be mindful of the tooth roots, and stay above them with the puncture. With concomitant use of surgical navigation, the placement and trajectory of the puncture can be precisely planned. Careful attention to these guidelines will diminish the risk for dental numbness, facial hypoesthesia, and dentition injury. In general, published rates of complications from this procedure are 1–3%.[6,7]

The opposition to these procedure stems in large part from the concern for morbidity.[8] However, the data have shown that complications are minimal in experienced hands.[6,7,9–11] Additionally, evidence is building that this approach is successful in addressing severe disease. Cutler and Duncavage[10] reviewed 133 Caldwell-Luc procedures with a follow-up of 1–6 years. They found a 92% success rate with an average follow-up of 23.5 months. The most common risk for the Caldwell-Luc procedure is the failure of the surgery to cure the infection. Eight percent ($n = 53$) of subjects in this review did not respond to the surgery. In two of these three cases, failure was caused by trapped mucosa and these cases were successfully salvaged with a repeat Caldwell-Luc procedure. Other evidence demonstrates the utility of canine fossa trephine in recalcitrant disease.[1,2,12] Sieberling et al.[12] demonstrated that in 67 patients with an average of 2.83 previous endoscopic

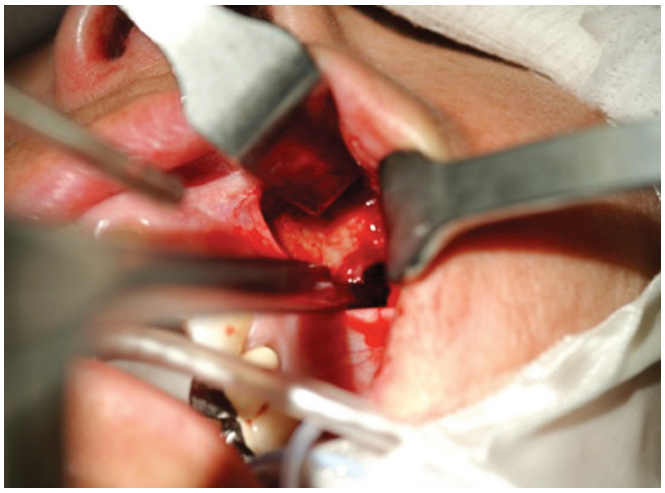

Fig. 53.3: Widening the maxillary window using a Kerrison rongeur.

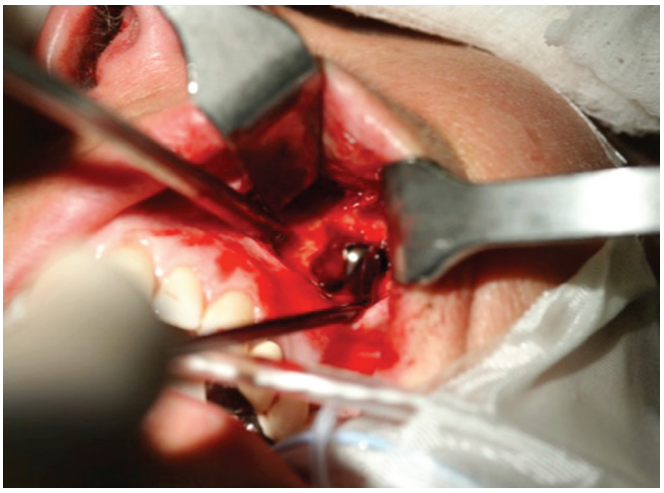

Fig. 53.4: Removing the lining of the maxillary sinus using a curette.

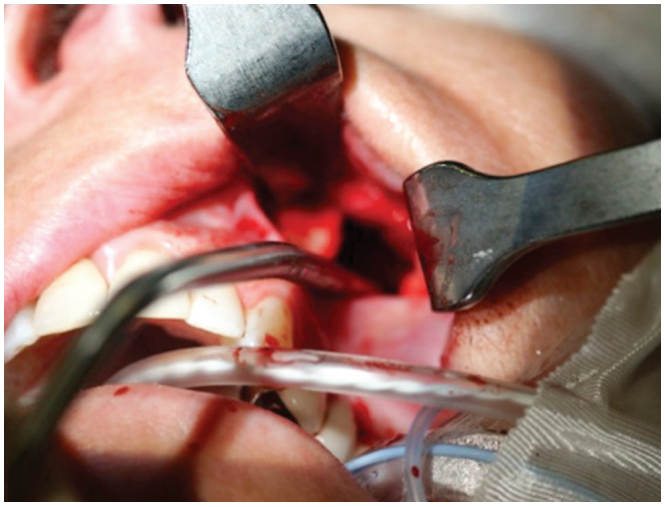

Fig. 53.5: Suctioning the contents of the maxillary sinus.

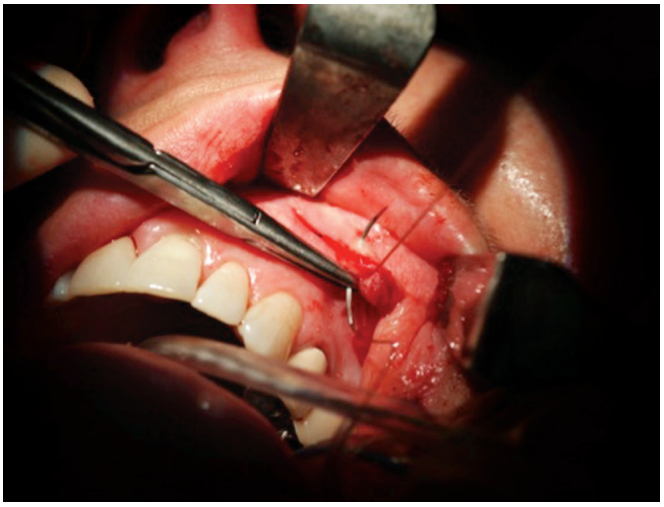

Fig. 53.6: Closing the gingival labial incision using a chromic gut suture.

sinus surgeries, the Caldwell-Luc trephine procedure resulted in clearance of disease. This is contrary to evidence by Lee et al.[11] that showed no difference in outcomes in a randomized control trial comparing Caldwell-Luc procedure and endoscopic maxillary antrostomy. But as Sieblerling et al.[12] point out, the variability in severity of disease across these studies makes definitive conclusions difficult.

Maxillary sinuscopy and the Caldwell-Luc procedure are important tools rhinologists should consider in the most difficult-to-treat patients, as it allows the surgeon to access and address potentially disease altering tissue. While the evidence is not definitive, these procedures should not be forgotten nor condemned.

Illustrative case: This patient had chronic maxillary sinusitis and after endonasal endoscopic maxillary antrostomy, it was determined that endoscopic instruments could not adequately address the most anterior-inferior portion of the diseased tissue. A Caldwell-Luc approach was used to remove the diseased mucosa (Figs. 53.3 to 53.6).

FRONTAL SINUS

Endoscopic approaches to the frontal sinus have been widely described,[13–15] and advances in treating the frontal sinus with the endoscopic modified Lothrop[13] have significantly decreased the use of external approaches. However, the frontal recess contains complex anatomy that requires great understanding in order to manage chronic

frontal sinusitis and other pathology. Despite extensive training on the anatomy, physiology, and management, the frontal sinus remains one of the most challenging areas to treat.[16] Scarring of the frontal recess after surgery, air cells within the sinus, disease at the far lateral aspect of the sinus, and the presence of tumors may present obstacles to a successful endoscopic approach. Below we describe two open frontal sinus approaches that can assist with challenging disease processes; the frontal sinus trephination and the osteoplastic flap.

Frontal Sinus Trephination

A frontal sinus trephine allows the manipulation of hard-to-reach areas in the frontal sinus by allowing endoscopes and instruments to be passed into areas that otherwise could not be reached via standard endoscopic approaches. It is also useful as an adjunct to standard endoscopic frontal sinus surgery to find the recess when the anatomy is severely distorted from previous surgery, scarring, ossification, or infection.[17–19]

The authors perform a frontal sinus trephine as an adjunct to endonasal techniques only if the target region is not accessible via standard endoscopic approaches. The forehead is prepped and the medial brow is injected with 1% lidocaine with epinephrine 1:100,000. A 0.5–1 cm incision is made approximately 1–1.5 cm from the midline at the inferomedial margin of the brow or within the brow. If the incision is placed within the brow, the blade should be beveled parallel to the hair follicles to avoid eyebrow alopecia and a better cosmetic result. The soft tissues are gently dissected, sparing the supratrochlear and supraorbital neurovascular bundles, until the frontal bone is exposed. The periosteum is dissected off the bone and the location for the trephine marked.

The location of the frontal sinus trephine has not been formally established. Traditional teaching recommends performing it close to the floor of the sinus, about 1–1.5 cm from the midline where the depth of the frontal sinus is the greatest thus minimizing the risk of posterior table penetration. Lee et al. recently measured the depth of the frontal sinus at 0.5, 1.0, and 1.5 cm from the midline and found no statistically significant difference in measurements. Lee did find an increased risk of cross trephination when performed 0.5 cm from midline because of the variable location of the intersinus septum.[20] Image guided surgery can be used to locate the safest area for the trephine. Image guidance trephination offers several advantages over "blind entry" in that it can specifically localize the target lesion, minimizes the size of the skin incision and trephination, and lowers the risk of intracranial entry.[21]

Once the trephination site is localized, a 4-mm burr is used to drill the anterior table and enter the frontal sinus in an area that is strategic and will provide the greatest access to the disease. Bone-cutting instruments can be used to enlarge the opening if desired. Endoscopes are introduced through the trephine and the sinus cavity and drainage pathways are evaluated. Instruments are inserted through the trephine and the pathology is removed. If the frontal recess anatomy is distorted, cannulating or irrigating through the trephine while visualizing the recess endonasally may find the opening to the frontal sinus. A frontal sinus stent may be placed through the trephine or endoscopically. The periosteum is approximated with absorbable sutures and the skin incision sutured.

The combined use of a frontal sinus trephine with endoscopic frontal sinus surgery spares the patient the need for more invasive procedures. Benoit and Duncavage found no statistically significant difference in symptom improvement and patency rate after a combined approach versus an endoscopic Lothrop procedure. They found a patency rate of 79% and 82% for the combined approach and the endoscopic Lothrop, respectively.[22] A trephine also allows for preservation of natural frontal outflow drainage pathway, facilitates endoscopic and radiographic surveillance postoperatively and is cosmetically appealing.[23]

A disadvantage of the frontal sinus trephininination is external scar formation. There should be gentle soft tissue manipulation and the trephine should not be larger than 0.5 cm to avoid soft tissue prolapse and poor cosmetic results.[24] Minor complications have been reported including facial cellulitis and wound infection.[23] Other rare but potential complications are penetration of the posterior table, cerebrospinal fluid leak, forehead hypesthesia and ophthalmologic injury.

Illustrative case: This 24-year-old gentleman had previous sinus surgery prior to visiting us. He presented with significant frontal sinus disease with symptoms of pressure and pain. On endoscopic examination, no clear frontal sinus tract was identifiable. Evaluation of his CT scan (Figs. 53.8 and 53.9) demonstrated that on the left side, his frontal sinus was blocked by neo-osteogenic bone formation, and we could not safely drill from below using

Fig. 53.7: Position of the frontal trephine skin incision.

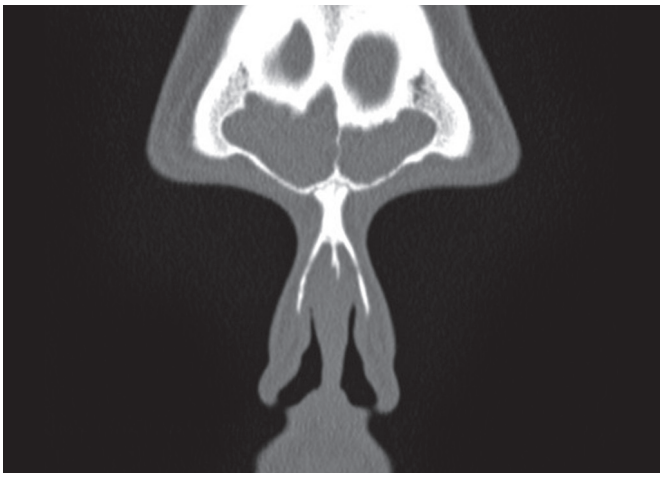

Fig. 53.8: Coronal view of the opacified frontal sinus of the illustrative case.

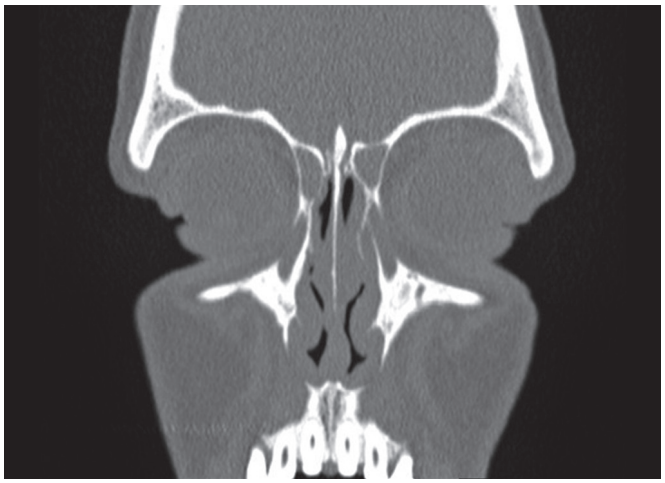

Fig. 53.9: Coronal view of the scarred and narrowed frontal outflow tract of the illustrative case.

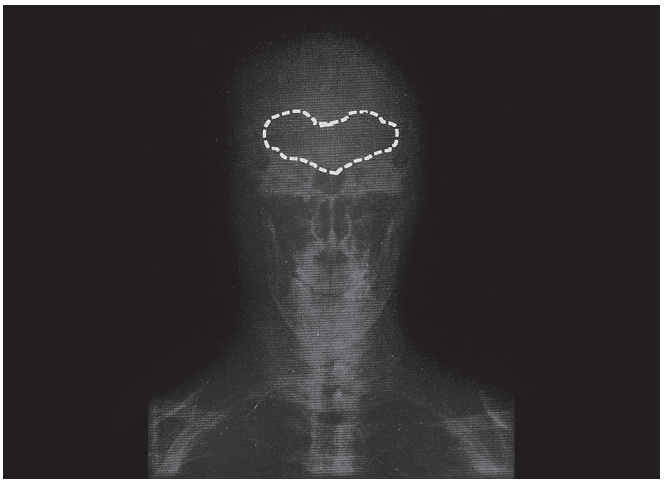

Fig. 53.10: Six-foot Caldwell with the frontal sinus outlined.

the endoscope. Via a trephination approach, we identified the left frontal sinus and then, using the image guidance, we were able to create a passage from above and remove the bone with curettes and kerrisons. The frontal duct was then stented (Figs. 53.7 to 53.9).

Osteoplastic Flap with or without Obliteration

The osteoplastic flap was originally described in 1894,[25] and achieved prominence in the late 20th century. Functionally, one must differentiate between the osteoplastic flap approach and the obliteration technique for refractory chronic frontal sinusitis. This distinction is important in that the flap itself is simply an approach to the frontal sinus. It may be used for disease processes other than chronic sinusitis, most often for benign and malignant tumors of the frontal sinus when endoscopic access is insufficient and the posterior table of the frontal sinus is uninvolved. Obliteration was utilized by many surgeons to treat chronic frontal sinusitis prior to advanced endoscopic techniques. Because diseased mucosa was believed to be untreatable by medical therapy, the mucosa was removed and the dead space filled with fat, hydroxyapatite, or allowed to scar via secondary intention.

The technique has been described for both bilateral and unilateral disease.[26,27] Prior to the image guidance era, a six-foot Caldwell frontal sinus X-ray was obtained (Fig. 53.10). Using this X-ray, a template of the frontal sinus is cut out and sterilized for use in surgery. Alternatively,

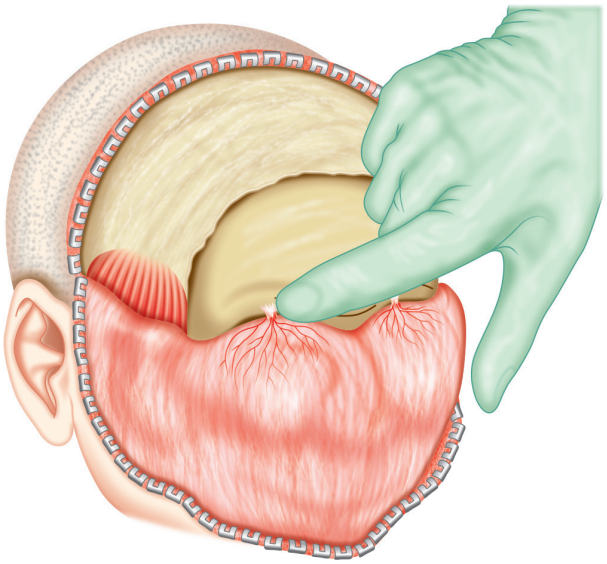

Fig. 53.11: Identifying the supraorbital notch and the supraorbital neurovascular bundle. Redrawn from Kim and Duncavage.[26]

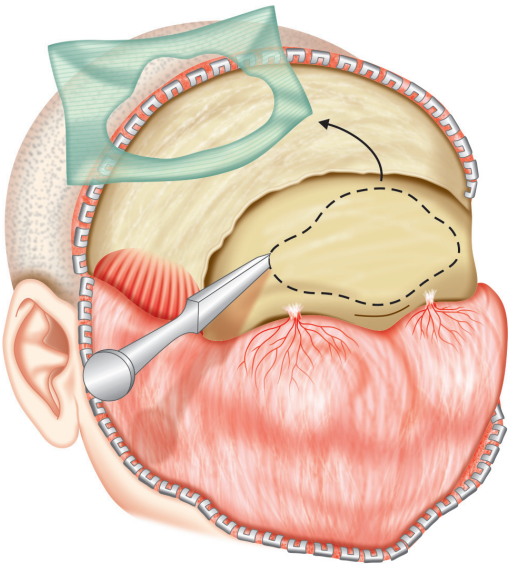

Fig. 53.12: Template from the six-foot Caldwell positioned to outline the frontal sinus. Redrawn from Kim and Duncavage.[26]

image guidance can be used to outline the osteotomies for the osteoplastic flap. The hair is then parted for a bicoronal incision, no shaving is necessary. One percent lidocaine with 1:100,000 epinephrine is injected into the planned bicoronal incision site. The scalp is incised through the galea aponeurotica, preserving the pericranium. Raney clips are used to control bleeding. Laterally, the temporalis fascia is not incised, thereby protecting the frontal branch of the facial nerve. The supraorbital notch is palpated prior to elevating at the supraorbital rim (Fig. 53.11). Care is taken to elevate the supraorbital neurovascular bundle intact with the scalp (Fig. 53.12). The six-foot Caldwell template or the image guidance is used to outline the planned frontal bone cut. Here, the surgeon is encouraged to be conservative, planning the cut smaller than the frontal sinus itself so that accidental intracranial entry is prevented. The pericranium is then incised with the bovie electrocautery in the pattern of the planned bone cut. It is then elevated approximately 5 mm inferiorly from the planned bone cut. An oscillating saw and chisel are used to perform the osteotomies, typically after pilot holes are drilled in the line of the cut (Figs. 53.13 and 53.14). The inferior cut can be achieved by using the saw, or by levering the osteoplastic flap up with osteotomes after a cut is made through the glabella. Care must be taken to separate the bone flap from the intersinus septum.

With the frontal sinus exposed, attention is then turned to the disease process. In patients undergoing obliteration, the diseased mucosa would be removed with curettes, and then the bone flap and frontal sinus drilled with a diamond drill to burr away the mucosal cells that remained in the invaginations of the foramina of Breschet. With the sinus mucosa gone, obliteration was then performed with fat, hydroxyapatite, cancellous bone, or methylmethacrylate.[26,28–30] The bone was replaced and secured with titanium plates.

The osteoplastic flap with obliteration has fallen out of favor for two reasons: better endoscopic techniques and the long-term complications. In particular, the formation of delayed mucoceles within the obliterated space up to 10 years postoperatively has necessitated revision surgery on some patients. However, the approach is still important as these patients may need to be reobliterated if the sinus cannot be "rescued" endoscopically. The endoscopic rescue has been described; however, if the mucoceles are particularly high or lateral in the obliterated cavity, reobliteration may be the best option. It should be noted that obliteration may still be a valid treatment in some cases when the modified endoscopic Lothrop procedure has not alleviated symptoms.

Illustrative case: A 44-year-old male presented to us with severe frontal headaches. He had previously undergone open and endoscopic resection of anterior skull base fibrous dysplasia 10 years prior to evaluation. He then developed a frontoethmoid mucocele that was treated with an osteoplastic flap with fat obliteration 1 year after his resection. He presented 9 years later with CT scans

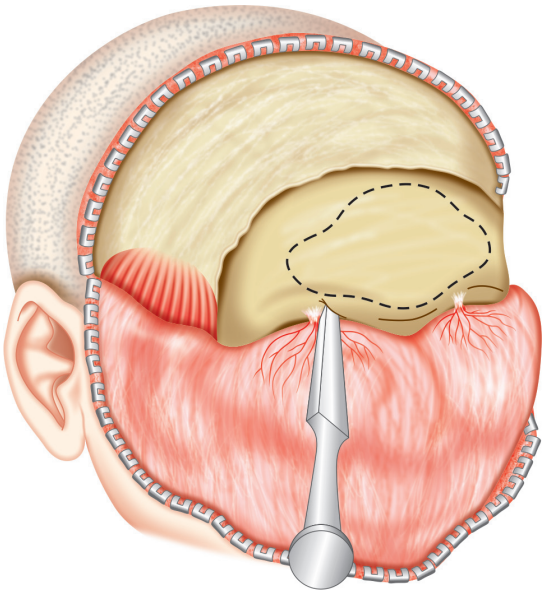

Fig. 53.13: Osteotome used to make pilot holes for the oscillating saw. Redrawn from Kim and Duncavage.[26]

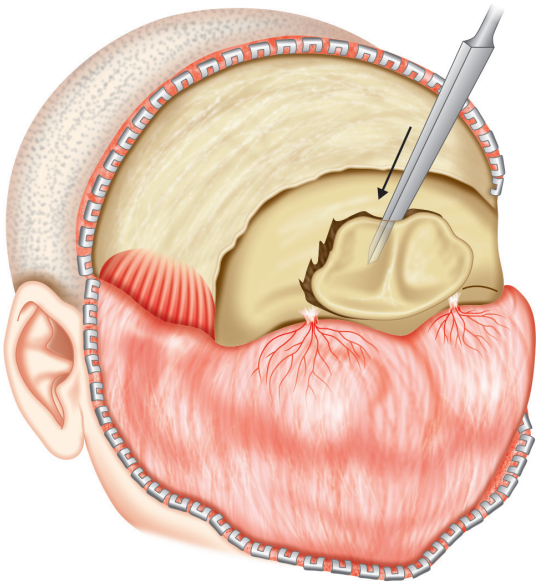

Fig. 53.14: Oscillating saw to complete the frontal osteotomy. Redrawn from Kim and Duncavage.[26]

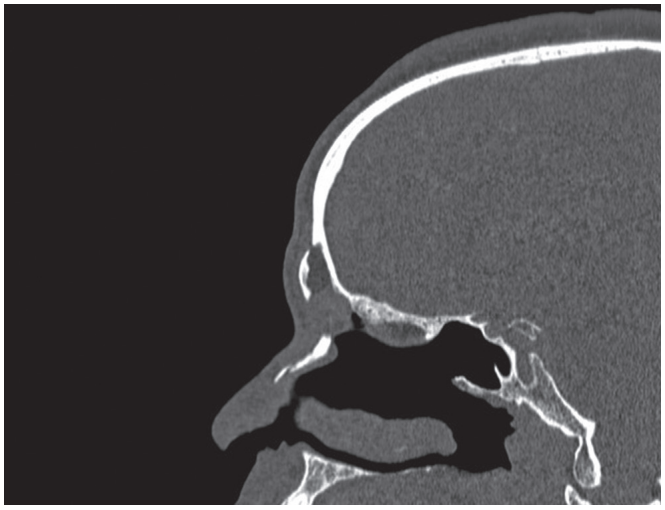

Fig. 53.15: Sagittal CT demonstrating mucocele.

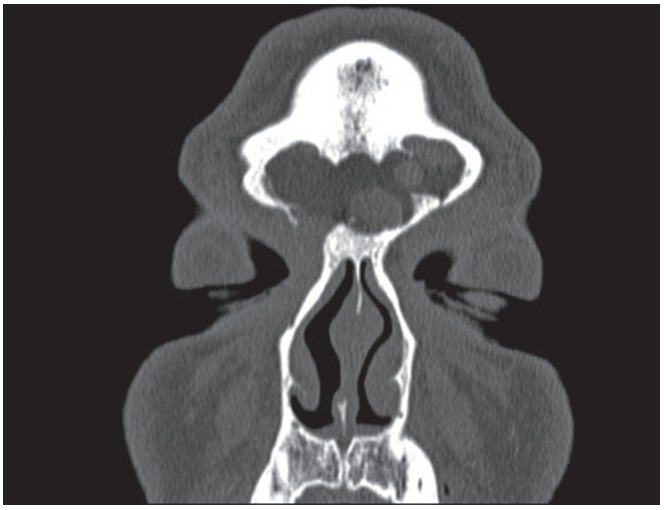

Fig. 53.16: Coronal CT demonstrating multiple mucoceles.

demonstrating multiple mucoceles present in the previously obliterated frontal sinus (Figs. 53.15 to 53.18). Given the multiple sites and the presence of mucoceles high in the frontal sinus, the patient underwent reobliteration via an osteoplastic flap approach. This case demonstrates both how the obliteration procedure can fail, and also that it may be used to rescue that failure.

ETHMOID SINUS

External approaches to the ethmoid sinus have largely fallen out of favor given the excellent visualization and techniques associated with the endoscopic approach.[31,32] Superior visualization of the fovea ethmoidalis and its relationship to the cribiform plate make the endoscopic approach safer in most cases of chronic sinusitis. However, there are some cases where an external approach may facilitate improved access and improved treatment. The approach to the ethmoid sinus can be combined with access to the inferior aspect of the frontal sinus and the frontal duct. They can be categorized as approach to primary disease, approach to frontal-ethmoidal junction, and approach for complications of sinus surgery.

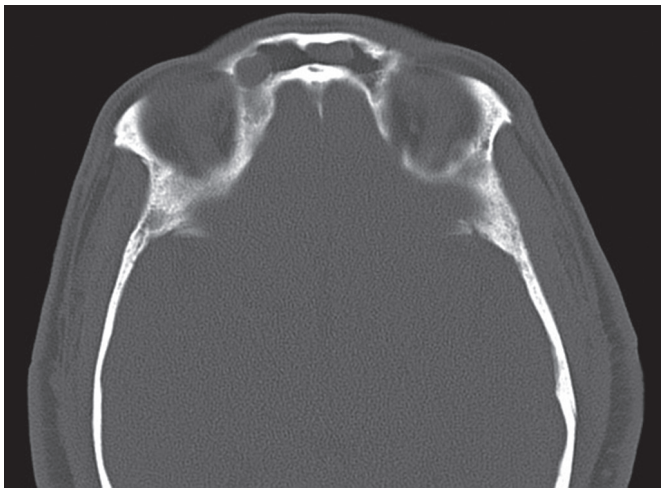

Fig. 53.17: Axial CT demonstrating multiple mucoceles.

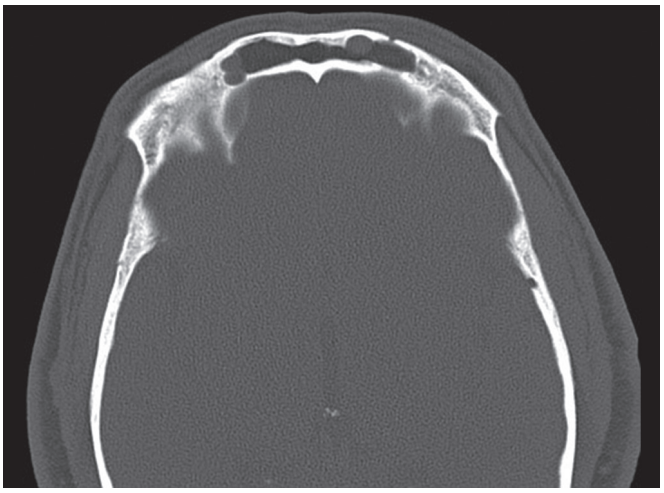

Fig. 53.18: Axial CT demonstrating multiple mucoceles along the periphery of the original dissection.

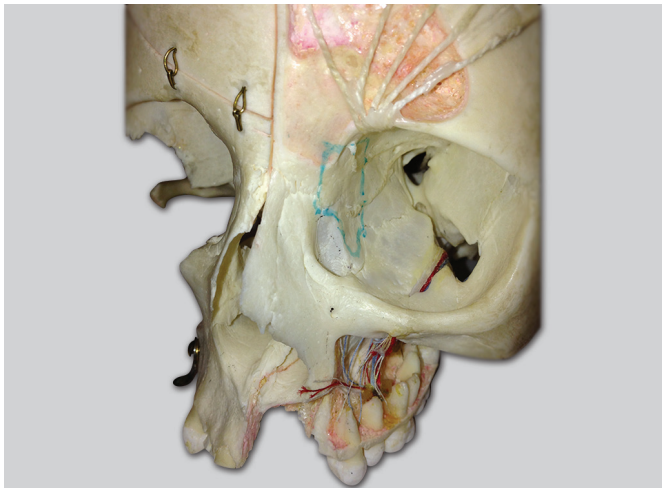

Fig. 53.19: Approximate outline of the bone removed during an open ethmoidectomy.

The approach in all cases is similar. The approach was originally described using a Lynch incision midway between the medial canthus and the nasion. The incision can incorporate a Z- or W-plasty to hide the scar. The incision is kept anterior to the lacrimal sac and inferior to the eyebrow. Dissection through the soft tissue will result in exposure of the angular artery, which may be ligated. Once the nasal bone has been encountered, dissection in the subperiosteal plan is performed such that the lacrimal system can be pushed inferolaterally out of its bony seat. The periorbita is then identified and preserved, pushed laterally such that the lamina papyracea is isolated. Depending on the depth of dissection, the anterior and posterior ethmoid arteries are then identified and either clipped or bipolared. The classic description of a 21–24 mm distance between the lacrimal crest and the anterior ethmoid artery, 12–14 mm from the anterior ethmoid artery to the posterior ethmoid artery, and 6–7 mm from the posterior ethmoid artery to the optic nerve holds true in most cases, although significant variability may exist. In the posterior dissection, careful attention must be paid to the identification of the frontoethmoid suture line, as this line allows the surgeon to predict the relative height of the anterior skull base. Once the sinus cavity is entered, one must be below this line to prevent skull base injury. The ethmoid partitions themselves are then taken down with through-biting instruments or curettes. Once the excision is completed, the medial canthus is repositioned in its original position with a tacking suture. The orbit is allowed to return to its original position and the subcutaneous tissue and skin are closed accordingly. Figure 53.19 shows the approximate outline of the bony resection. Note that the frontoethmoid suture line is above the superior border within the orbit.[32]

Approach to the frontal–ethmoidal junction may be necessary in the case when endoscopic tools are insufficient to access the frontonasal tract secondary to bony anatomy. The Sewall-Boyden modification involves extension of the bony resection to involve the inferior portion of the frontal bone and dorsum of the nasal bone to expose the inferior portion of the frontal sinus and the frontonasal duct. The frontal beak can then be resected with a drill or rongeurs. This may be useful when the anatomy of the frontal duct is restricted secondary to vertically long beak, a prominent beak or extensive osteitis. The challenging

portion of this procedure is elevating and rotating the medial mucosal flap from the nasal bones and septum to recreate a mucosal-lined frontal sinus tract. This flap can be pedicled laterally, medially, or with two attachments. The complications of this procedure are the same as for the external ethmoidectomy, including bleeding, infection, orbital and intracranial injury, and epiphora. However, the most common complication is stenosis of the fronto-nasal tract. Often a stent will be used in conjunction to maintain patency of the tract. Perhaps the best description of this procedure is found in Murr's 2010 article.[33]

For primary or even revision surgery, these techniques are rarely indicated. Narrow nasal anatomy between the orbit and the middle turbinate or septum that prevents endoscopic tools from reaching the superior ethmoid sinus and frontal recess may require an external approach in order to move the orbital contents laterally, but this is rare. More importantly, these techniques are useful in dealing with complications from sinusitis and sinus surgery. Orbital abscesses are easily accessible via the external ethmoidectomy approach.[34] One must be careful to evaluate the lamina papyracea on the preoperative CT scan and intraoperatively to ensure that the ethmoid sinuses themselves are treated appropriately. Bleeding from the anterior or posterior ethmoid artery after sinus surgery may be vision-threatening if an orbital hematoma develops. An external ethmoidectomy approach may be needed to control the bleeding and may be more timely in case of lack of endoscopic instrumentation.[35,36]

CONCLUSION

External approaches to the paranasal sinuses are not simply historically interesting. As we have shown in this chapter, they can be quite useful for select patients. Unfortunately, they are rare, and increasingly absent in otolaryngology training programs. Familiarity with these procedures is necessary for rhinologists and for any otolaryngologist who treats patients with sinusitis.

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CHAPTER

54

Odontogenic Disease and Oral–Antral Fistula

Richard A Kraut

INTRODUCTION

Odontogenic etiology accounts for at least 10%[1] and perhaps as much as 40%[2] of cases of maxillary sinusitis. The spread of dental infections into the maxillary sinus is due to the close relationship of the maxillary posterior teeth to the maxillary sinus. Routine dental procedures such as endodontic therapy or tooth extractions can result in foreign bodies being introduced into the sinus. Tumors originating in the palate often erode the palatal bone and the maxillary alveolar process and advance into the sinus. The relatively frequent occurrence of odontogenic pathology and its influence on the maxillary process warrants an overview of odontogenesis, a review of dental anatomy, and the management of dental infections. This chapter includes a review of selected cysts and tumors (Table 54.1) including diagnosis and treatment. Contemporary topics of dental implant reconstruction and bisphosphonate-related osteonecrosis of the jaws (BRONJ) and their impact on the maxillary sinus will be reviewed.

ODONTOGENESIS

Odontogenic cysts and tumors that affect the jaws and oral cavity are derived from the tissues associated with tooth formation. These tumors and cysts can arise long after tooth formation is complete. Formation of teeth in different shapes and sizes and at defined locations is a result of sequential and reciprocal interactions between epithelial and mesenchymal tissues. Tooth development begins at approximately 4 weeks in utero and extends into the late teen years. At approximately 4 weeks, the mandibular and

Table 54.1: Odontogenic cysts and tumors

Cysts		
Radicular cyst		
Dentigerous cyst		
Residual cyst		
Calcifying odontogenic cyst		
Nasal palatine cyst		
Tumors		
Included		
Ameloblastoma	Epithelial	Benign
Odontogenic keratocystic tumor	Epithelial	Benign
Central giant cell tumor	Epithelial	Benign
Calcifying epithelial odontogenic tumor	Epithelial	Benign
Odontoma	Mixed epithelial and mesenchymal	Benign
Not included		
Adenomatoid odontogenic tumor	Epithelial	Benign
Squamous odontogenic tumor	Epithelial	Benign
Malignant ameloblastoma	Epithelial	Malignant
Clear cell odontogenic carcinoma	Epithelial	Malignant
Odontogenic carcinoma	Epithelial	Malignant
Odontogenic fibroma	Mesenchymal	Benign
Cementoblastoma	Mesenchymal	Benign
Odontogenic myxoma	Mesenchymal	Benign
Cementifying fibroma	Mesenchymal	Benign
Ameloblastic fibrosarcoma	Mesenchymal	Malignant
Ameloblastoma fibroma	Mixed epithelial and mesenchymal	Benign
Ameloblastoma fibro-odontoma	Mixed epithelial and mesenchymal	Benign

maxillary arches are formed. The teeth are formed from cells that migrate from the neural crest to the primitive alveolus at about 6 weeks. In this initiation stage of development, the ectoderm thickens and extends strands into the underlying mesenchyme forming the dental lamina. In the bud phase of development, the lamina grows into small rounded structures overlying the area of condensing connective tissue and beginning the development of the enamel organ. In the cap phase of development, the bud becomes indented and covers the condensing mesenchymal cells of the dental papilla. The rest of the mesenchymal cells will form the dental follicle. The cells of the cap differentiate into four layers: an inner and outer enamel epithelium, the stratum intermedium, and stellate reticulum. They signal the overlying epithelial cells to send down a cord of cells (the dental lamina) that becomes the enamel organ. Together these cells are known as the tooth germ.

In the next stage of development, the enamel organ becomes a bell-shaped structure overlaying the papilla that has the shape of the future tooth. The appositional stage sees formation of the crown and the beginning of calcification. Preameloblasts from the inner enamel epithelium induce cells from the papilla to become odontoblasts producing the dentin matrix that in turn induces the preameloblasts to become ameloblasts that produce the enamel matrix. Ameloblasts are responsible for enamel production and eventual crown formation. After the crown forms, the inner and outer layers of the enamel organ squeeze out the two middle layers: the stratum intermedium and stellate reticulum. At the cervical area of the papilla, the inner and outer enamel epithelium forms a root sheath, which in turn induces the odontoblasts to form the root dentin. Cells from the dental sac contribute to the formation of the periodontal ligament. Cementoblasts and fibroblasts from the dental follicle deposit cementum on the root surface and form the periodontal membrane. The penetration of these cells through Herwig sheath at the edge of the enamel organ gives rise to epithelial rests of Malassez within the periodontal ligament. The enamel organ becomes squamoid and ultimately fuses with the gingiva during eruption.

When tooth formation is complete, remnants of odontogenic epithelium remain in the periodontal ligament and gingiva. In the gingiva, they are called rests of Serres and in the periodontal ligament they are known as the rests of Malassez. Odontogenic tumors arise from the Serres and Malassez rests.[3-5]

Clinical Evaluation

Dental radiographs obtained during a routine office visit may lead to incidental discovery of cysts or tumors. A panograph will often confirm clinical suspicions. In addition, cone beam scans that are used for dental implant treatment planning increase the likelihood of incidental findings and subsequent diagnosis.[6]

Management of odontogenic pathology requires obtaining a complete history and thorough physical examination. The age and general health of the patient are often important considerations in both the diagnosis and the treatment. The examination should include careful inspection, palpation, percussion, and auscultation of the affected part of the jaw and overlying dentition. The patient should be questioned about pain, loose teeth, occlusal problems, delayed tooth eruption, swelling, or intraoral bleeding. In addition, paresthesia, trismus, and significant malocclusion may indicate a malignant process. To the extent possible, the onset and growth rate of a lesion should be elicited. The patient should be queried about medications, particularly bisphosphonate-based medications.

In general, well-demarcated lesions outlined by sclerotic borders suggest benign growth, while aggressive lesions tend to be ill-defined radiolucent lesions with possible root resorption. With larger more aggressive lesions, computerized tomography may more clearly identify bony erosion and/or invasion into adjacent soft tissues.

Once a problem is detected, a differential diagnosis is developed and tissue is obtained for histologic identification. Fine-needle aspiration is excellent for ruling out vascular lesions prior to open biopsy and may be helpful to diagnose inflammatory or secondarily infected lesions. Open biopsy may be incisional (preferred especially for larger lesions prior to definitive therapy) or excisional (for smaller cysts and unilocular tumors).[7]

RADICULAR CYST

Odontogenic cysts are characterized by epithelium lining a fibrous cyst wall. Radicular cysts arise from proliferation of epithelial cells in the rests of Malassez, while dentigerous cysts arise from the rests of Serres. Both cystic lesions are noteworthy in their potentially destructive nature.[8]

Radicular cysts are localized at the periapical region of a tooth. In the maxilla, proximity of the cyst to the sinus floor may lead to invasion of the sinus and development of sinusitis. Arising from inflamed epithelial cells of the rests

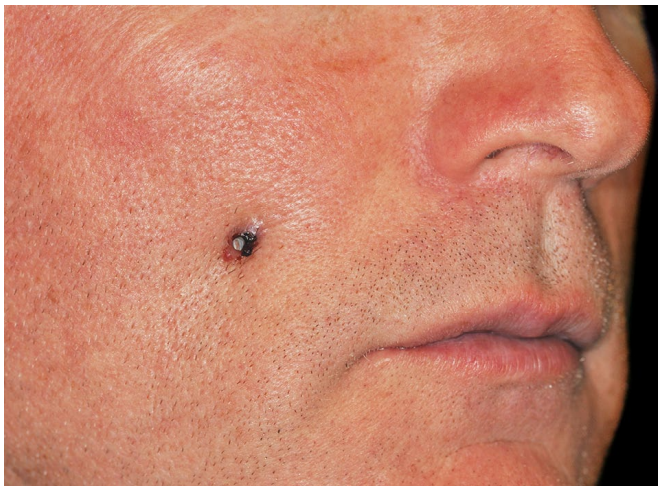

Fig. 54.1: Gutta-percha placed in facial fistula to determine the etiology of the fistula.

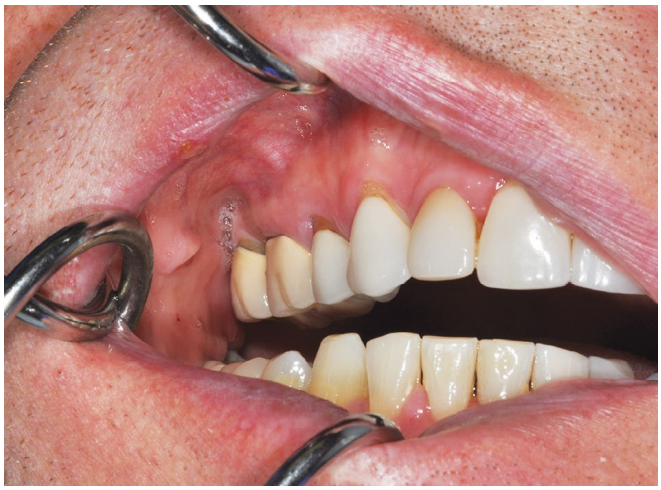

Fig. 54.2: Buccal mucosa is intact and did not reveal first molar as the source of the facial fistula.

of Malassez, the radicular cyst is the most common of the inflammatory cysts, accounting for approximately 50–65% of all cysts.[9] Most radicular cysts originate in pre-existing periapical granulomas.

During the past few decades, some authors have perpetuated the notion that nearly half of all periapical lesions are radicular cysts.[10] However, studies, based on meticulous serial sectioning of periapical lesions completely retrieved, have shown that the actual incidence of radicular cyst is only about 15% of all periapical lesions. Equally significant was the discovery in 1980 that radicular cysts exist in two structurally distinct classes. Those containing cavities completely enclosed in epithelial lining (periapical true cysts) and those containing epithelium-lined cavities that are open to the root canals (periapical pocket cysts). From a clinical point of view, a periapical pocket cyst may heal following conventional root canal therapy whereas a periapical true cyst is less likely to be resolved.[9]

Radiographically, a radicular cyst presents as a small well-defined periapical lucency at the root apex of a nonvital tooth. Radiographic differentiation of granulomas and radicular cysts has minimal impact on treatment as shown in Figures 54.1 to 54.3.

Large cysts may involve a complete quadrant with some of the teeth mobile, some root resorption, and some nonvital pulps. Although the cyst is painless when sterile, it will be painful when infected. Histologically, the cyst has a connective tissue wall that may vary in thickness, a stratified squamous epithelium lining, and foci of chronic inflammatory cells within the lumen. Radicular cysts that violate the sinus are surgically excised and the area curetted in conjunction with, or prior to, definitive treatment of sinusitis. Otherwise, affected teeth are extracted and cyst excised.

Alternately, endodontic therapy can be performed if the tooth can be preserved. Endodontic therapy removes of the pulp from within the internal chamber and canals of the tooth. This void is obturated with an inert material and isolates the internal component of the tooth from the oral environment. The successful completion of root canal therapy with appropriate removal of vital pulp prevents progression of the infection. Endodontic therapy is effective, though not without failure as shown in Figures 54.4 to 54.6. Due to differences in root anatomy, long-term outcome for posterior dentition is more guarded when compared to the anterior dentition. Proximity of the posterior dentition to the floor of the antrum is critical with regard to direct extension of the cyst into the maxillary sinus.

The vast majority of radicular radiolucencies resolve following endodontic therapy. The mechanism involved in this resolution may be the dissolution of epithelial lining due to the inflammatory exudate. Residual periapical lesions are typically treated with apicoectomy.

DENTIGEROUS CYST

This is the most common developmental cyst, accounting for 20–25% of all odontogenic cysts.[11] It originates from the separation of the follicle from around the crown of an unerupted tooth. This cyst develops via the accumulation of fluid between reduced enamel epithelium and a

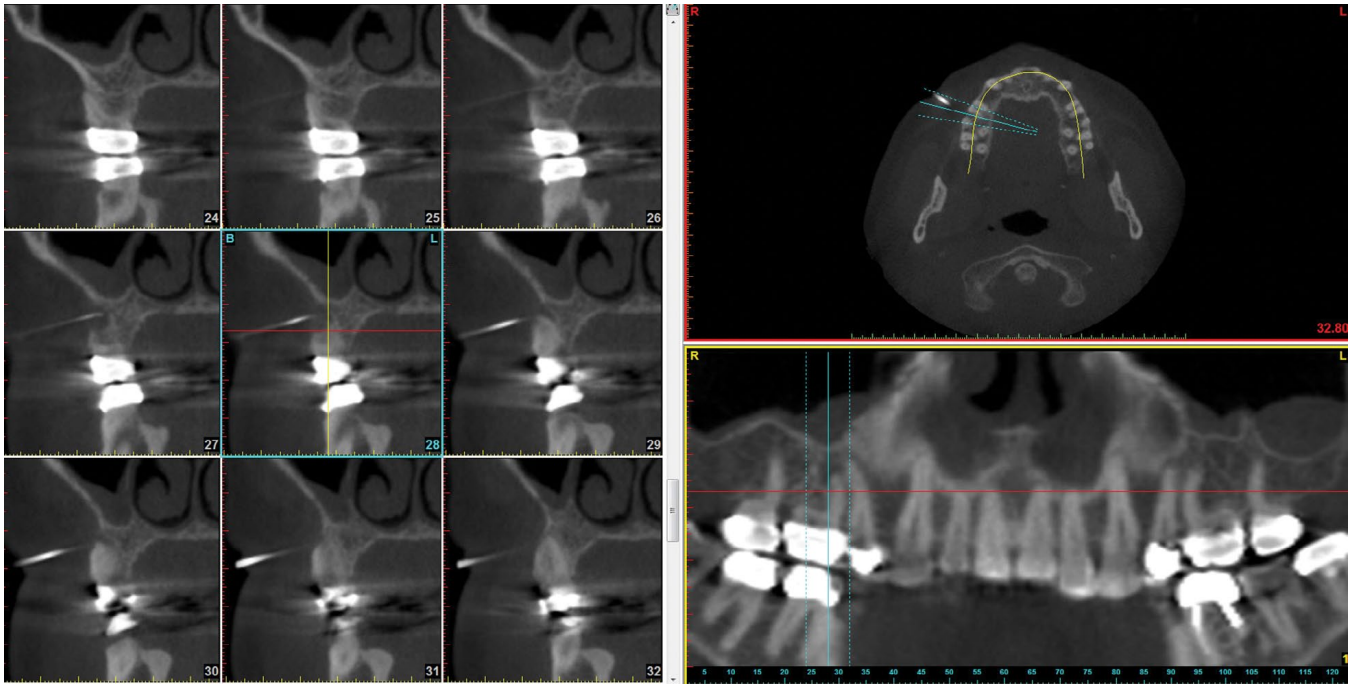

Fig. 54.3: Gutta-percha points to maxillary first molar that has a periapical radiolucency indicating need for endodontic therapy secondary to a necrotic pulp that has caused an infected granuloma.

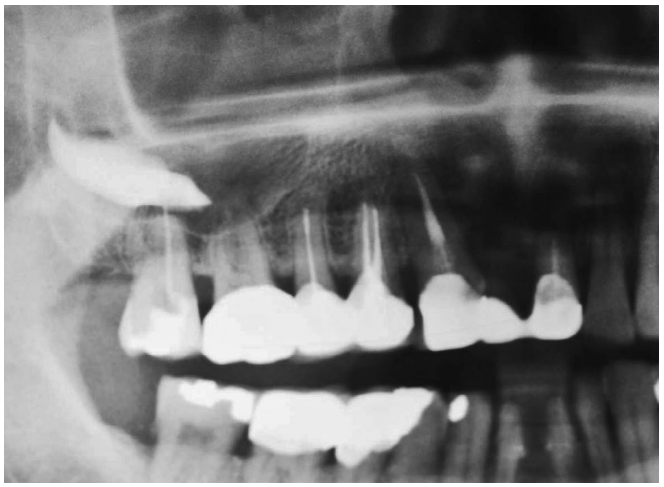

Fig. 54.4: Image showing massive extrusion of root canal filling material into the right antrum causing sinusitis.

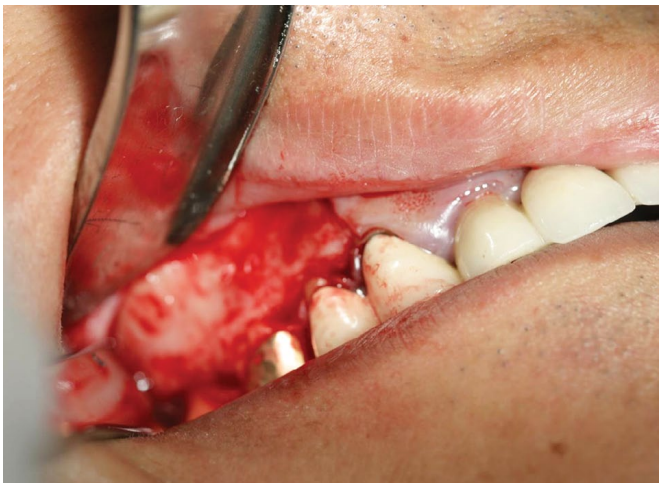

Fig. 54.5: The lateral wall of antrum was exposed to gain access to the antrum for removal of the foreign body.

completed tooth crown. It is most commonly associated with mandibular third molars, although maxillary canines and third molars may be affected. Dentigerous cysts are rarely associated with unerupted deciduous teeth. These cysts are most prevalent in the second to fourth decades and are more prominent in white males.

Most dentigerous cysts are asymptomatic, but large lesions can cause displacement or resorption of adjacent teeth and pain. The maxillary sinus is most usually affected by cysts involving one of the maxillary canines or third molars as shown in Figure 54.7. Maxillary anterior teeth may be displaced into the floor of the nose and maxillary posterior teeth may move through the sinus to the floor of the orbit. As the lesion extends into the sinus, bone deformity or infection may occur. The cyst may also cause resorption of the roots of adjacent teeth.

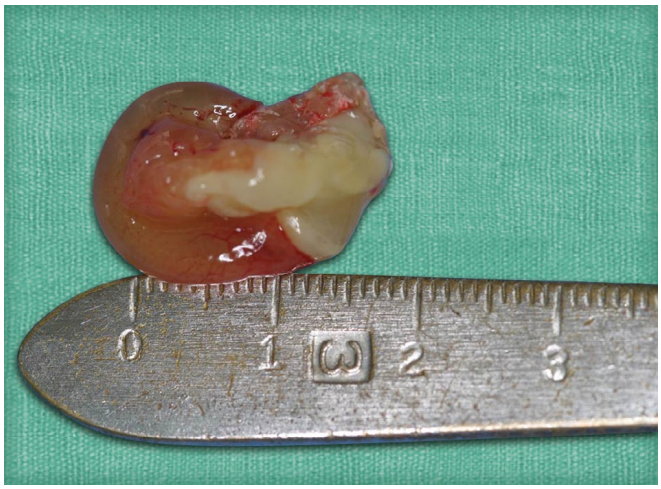

Fig. 54.6: Coronal aspect foreign body removed from infected sinus showing granulation tissue above the zinc oxide and eugenol.

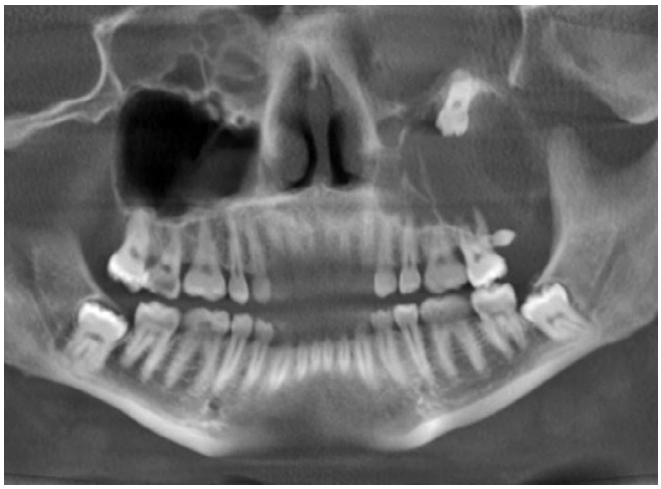

Fig. 54.7: Cone beam panoramic radiograph showing opaque left antrum secondary to a dentigerous cyst displacing the maxillary left third molar just below the orbit. A supernumerary tooth can be seen posterior to the maxillary second molar.

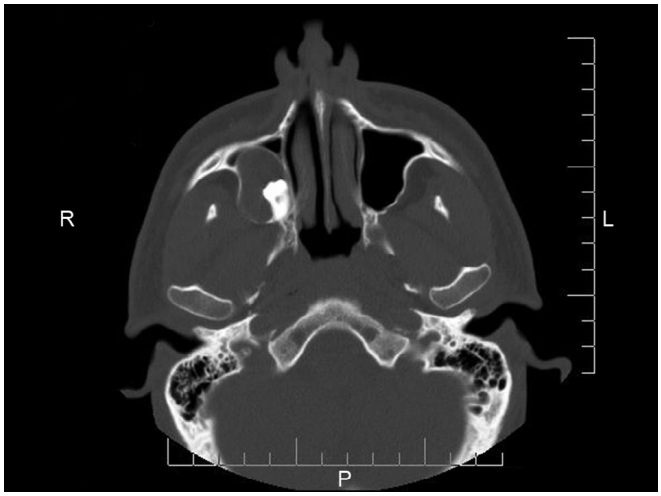

Fig. 54.8: Dentigerous cyst has displaced the maxillary third molar to the medial wall of the antrum.

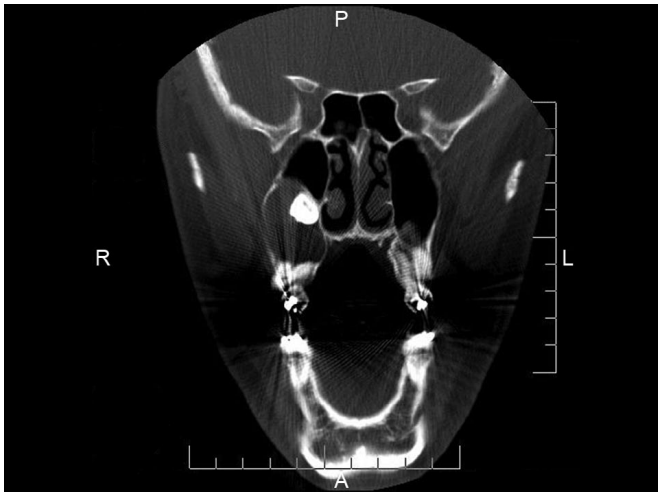

Fig. 54.9: Coronal computed tomography of dentigerous cyst that has displaced the right third molar; the cyst is below the Schneiderian membrane.

Radiographically, the cysts appear as expanded unilocular radiolucencies with a well-defined mucoperiosteal border as shown in Figures 54.8 to 54.10. However, an infected cyst may show ill-defined borders. Oftentimes the border of the lucent area will originate at the cementoenamel junction of the tooth. It can be difficult to distinguish between a dentigerous cyst and an enlarged follicle. Further-more, other odontogenic tumors such as unilocular ameloblastomas and OKTs have similar radiographic features.

The histology of the cyst varies, depending on whether the cyst is inflamed. The noninflamed cyst is composed of thin connective tissue walls loosely arranged and contains considerable glycosaminoglycan ground substance. The fibrous walls may include islands of inactive odontogenic epithelial rests. The epithelial lining consists of two to four layers of nonkeratinizing epithelium. Treatment is with enucleation and extraction of the unerupted tooth. Large dentigerous cysts may be marsupialized that allows decompression followed by excision of the cyst. Recurrence is rare.[12,13]

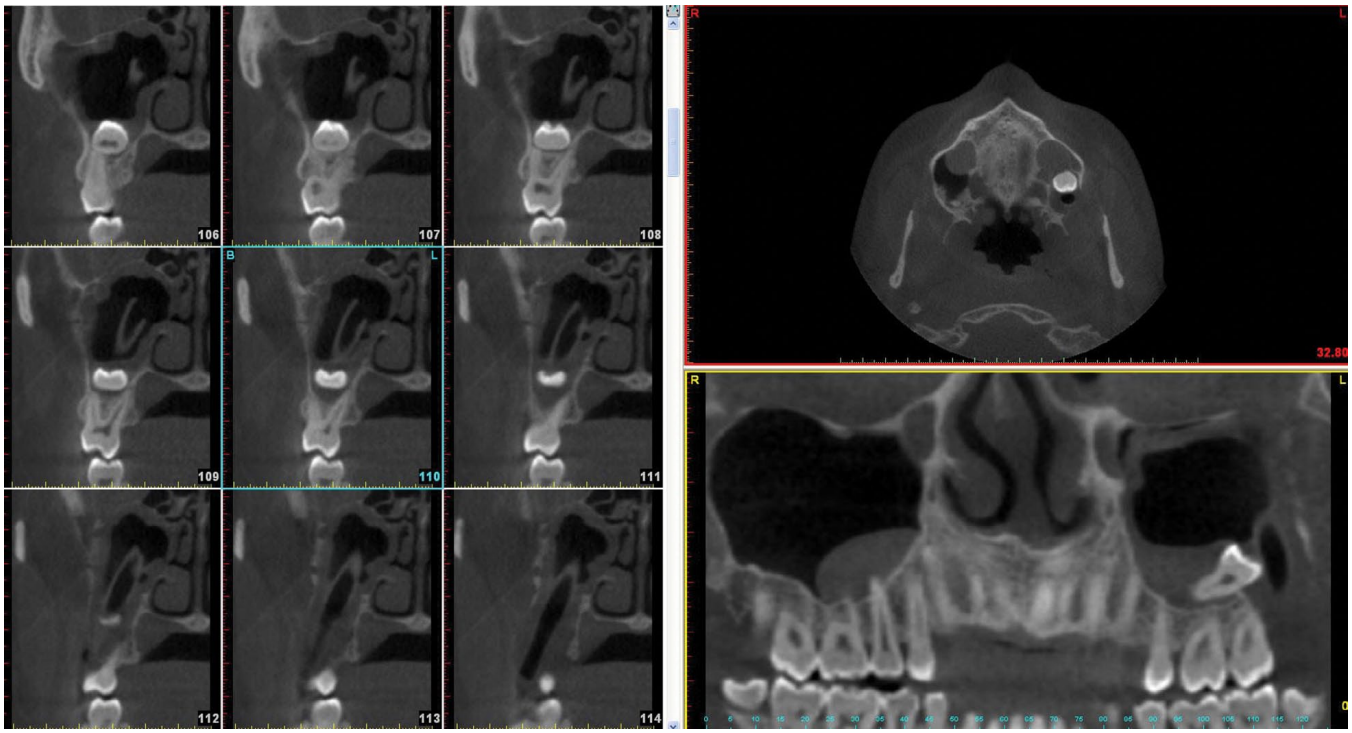

Fig. 54.10: Dentigerous cyst associated with upper left wisdom tooth has caused tooth to migrate to the antral floor.

RESIDUAL CYST

A residual cyst is an inflammatory cyst that fails to resolve after root canal therapy or tooth extraction. Most often the cysts occur following endodontic therapy that did not eliminate the initial cause of inflammation or that did not treat all canals. Radiographically most present as an enlarged and darkened radiolucency with no bony expansion. Residual cysts rarely occur after tooth extractions so other causes should be considered for any subsequent radiolucency. A primordial odontogenic keratocyst, ameloblastoma, myxoma should be considered. Pulp testing of adjacent teeth is recommended to rule out a radicular cyst, followed by enucleation and removal of any inflammatory stimulus. Endodontic therapy, apicoectomy, and tooth removal may also be required.[14]

CALCIFYING ODONTOGENIC CYST (GORLIN CYST)

The calcifying odontogenic cyst is much less aggressive than the odontogenic keratocystic tumor (OKT) and has a low incidence of recurrence following the usual treatment of curettage and enucleation. This cyst is very rare but occurs most frequently in the maxilla of females, particularly in teenagers. Most often, the cyst is identified as part of a routine dental exam. The cyst varies in size from 1 to 8 cm with 3 cm being the average. The cyst is asymptomatic unless growth causes significant expansion. The calcifying odontogenic cyst is primordial in origin arising from the rests of Serres. They are not associated with an impacted tooth.

At first the cyst will be radiolucent but as it matures it develops calcifications that have a mixed radiolucent-radiopaque appearance. These cysts can exhibit one of three radiographic patterns: one is a salt and pepper pattern of flecks, the second is a fluffy cloud-like appearance, and the third is a crescent-shaped pattern on one side of the radiolucency. Because of these three patterns of radiographic appearance, three different list of differential diagnosis must be considered. A unilocular radiolucency could suggest an OKT, an ameloblastoma, an adenomatoid odontogenic tumor (AOT), or an ameloblastic fibroma. However, a radiolucent-radiopaque lesion with a salt and pepper flecked pattern suggests the AOT, an odontoma, an ossifying fibroma, or a calcifying epithelial tumor. If the cyst presents as an extraosseous cyst, the differential diagnosis includes a gingival cyst, a peripheral ossifying fibroma, and a chronic periodontal abscess.

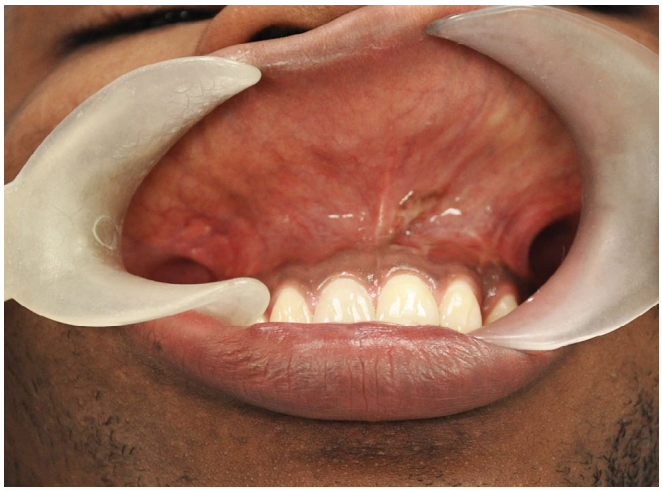

Fig. 54.11: Nasopalatine duct cyst has obliterated the subnasal sulks.

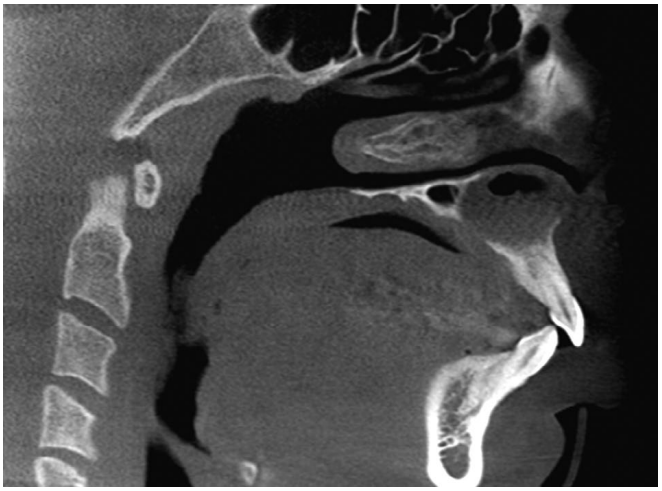

Fig. 54.12: Sagittal view of nasopalatine duct cyst showing destruction of the hard palate and obliteration of the nasal labial fold and destruction of the buccal bone.

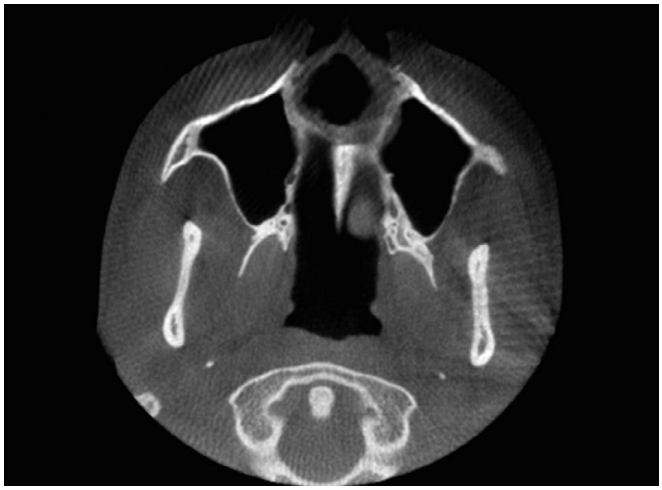

Fig. 54.13: Nasopalatine duct cyst has eroded the labial premaxilla and the anterior portion of the hard palate.

Histologically, the calcifying odontogenic cyst is usually a unilocular cyst with a lining is composed of stratified squamous epithelium with a basal layer that may be polarized away from the basement membrane. The lumen contains eosinophilic keratinized cells (ghost cells) in which the nuclei have degenerated, sometimes completely.[15,16]

Nasal Palatine Cyst (Incisive Canal Cyst)

The nasal palatine cyst is a nonodontogenic developmental cyst derived from embryonic epithelial remnants of the nasopalatine ducts. It usually occurs in adults 30–60 years of age with twice as many occurrences in males as opposed to females. It is usually a well-delineated, heart-shaped unilocular radiolucency located between, and apical to, the maxillary central incisors in the midline. Cysts may form at any point along the duct's course from the posterior palatal midline to the soft tissue palatine papilla as shown in Figures 54.11 to 54.13. Cells may be activated by an infection similar to branchial cysts or may activate spontaneously. The cyst usually presents as a soft tissue swelling along the midline. Palatal swelling is common, as is root resorption. Cysts limited to the palatine papilla exhibit swelling behind the maxillary central incisors. The cyst is often discovered as part of a routine dental exam and is usually asymptomatic. Histologically the cyst may be lined by stratified squamous epithelium, pseudostratified columnar epithelium, with or without cilia, or both. Mucous cells may be present. Treatment consists of enucleation from a labial approach, after which recurrence is rare. With large lesions, careful dissection is required to prevent a palatal tear since the cyst wall may adhere to the periosteum.

Ameloblastoma

Odontogenic tumors can be classified by their tissue of origin: epithelial, mesenchymal, or a mixed lesion. Studies reveal that there may be no clear divisions among many types of tumors, but rather a transition from one to another. Tumors may show areas that resemble different types of tumors within a single lesion.

Odontogenic tumors comprise a small percentage of the lesions found in the jaw. The majority are benign,

although the more primitive the dental structures from which they arise, the more aggressive they tend to be.[17] In some cases, the relationship to teeth is histologically and radiographically clear. In other cases, the odontogenic origin is less clear in that histologically tissues resembling dental tissues are not found. Nevertheless, they are identified as odontogenic because they are only found in the jaws.

Ameloblastomas are the most common odontogenic tumor, second only to odontomas. Ameloblastomas account for 11% of all odontogenic neoplasms/hamartomas. Ameloblastomas are found exclusively in the jaw and are usually benign but locally invasive. Ameloblastomas are so named because the cells of the tumor are epithelial in origin and can express amelogenin (a precursor of enamel). However, the cells of the ameloblastoma are incapable of making enamel matrix. The tumor occurs approximately equally in males and females, usually when they are in their 40s and 50s. Ameloblastomas may occur in any part of either jaw but approximately 85% occur in posterior mandible, specifically the molar-ramus area. About 15% occur in the maxilla, with the majority of these in the posterior maxilla. Ameloblastomas of the maxilla recur more frequently and behave more aggressively than those of the mandible, often invading the maxillary sinus. Maxillary ameloblastomas develop more frequently in older patients and in those cases, the prognosis is significantly less favorable.

Ameloblastomas are always purely radiolucent and may be unilocular but frequently become multilocular as they increase in size. Approximately 15% of ameloblastomas arise from the lining of a dentigerous cyst. Ameloblastomas are characterized by a progressive growth rate and, when untreated, may reach enormous proportions. In early stages of development, patients may be asymptomatic, but later patients typically present with a complaint of swelling and facial asymmetry. Occasionally, small tumors may be identified on routine radiography. Maxillary tumors can perforate the antrum and may extend into the nasal cavity, ethmoid sinuses, and skull base.

Although ameloblastomas are locally invasive, they rarely metastasize. When they do, histologically, they are identical to ameloblastomas that do not metastasize. There are no criteria identified to predict which ameloblastomas have the potential to metastasize. A malignant ameloblastoma spreads through the lymphatic system with the lungs being the most common site, followed by cervical lymph nodes and the spine. There is usually a long interval between diagnosis of the primary tumor and development of metastasis.

Radiographs show a well-circumscribed, expansile radiolucency with clearly demarcated scalloped borders that have been described as resembling a honeycomb or soap bubble. The unilocular lesion is indistinguishable from an odontogenic cyst. The extent of root resorption may indicate a neoplastic process.

Histologically, most ameloblastomas have the follicular or plexiform pattern, although basal cell or granular cell variations may also be seen. Classic features are sheets and islands of tumor cells showing an outer rim of columnar ameloblasts with nuclei polarized away from the basement membrane. The center of these nests is composed of stellate-shaped epithelial cells that mimic the stellate reticulum. Rarely, they can exhibit cytologic features of malignancy with squamous differentiation (<1%). Those tumors are diagnosed as ameloblastic carcinoma and patients have a poor prognosis.

Prior to 1992, the World Health Organization recognized the existence of three distinctive clinicopathologic variants of ameloblastoma: conventional/solid/multicystic ameloblastoma, unicystic ameloblastoma, and peripheral ameloblastoma. Subsequent studies identified important clinical and radiographic differences between ameloblastomas comprised exclusively of the desmoplastic pattern and solid lesions. In 2005, a reclassification excluded the desmoplastic pattern from the histological spectrum of solid ameloblastomas and placed it as a distinctive variant called desmoplastic ameloblastoma.[18]

The solid type is the most common and is further subtyped histologically into follicular (most common subtype), acanthomatous, plexiform, granular cell, and basal cell. The follicular type has epithelial islands with peripheral columnar cells with reverse polarity and central areas that resemble stellate reticulum. Cyst formation is common and the stroma may be fibrous.

The acanthomatous variant shows abundant keratin formation and should not be mistaken for squamous cell carcinoma. The plexiform variant shows long anastomosing plexiform epithelial cords. It is more commonly found in the maxilla and is considered to be more aggressive. The basal cell variant is least common; peripheral columnar cells can be lacking and there may be little stellate reticulum present. The granular cell variant shows cells whose cytoplasm is granular and the change may be focal or widespread. Diagnosis of ameloblastomas is often initially made from a panograph, followed by CT scans. Although benign, these tumors are locally aggressive.

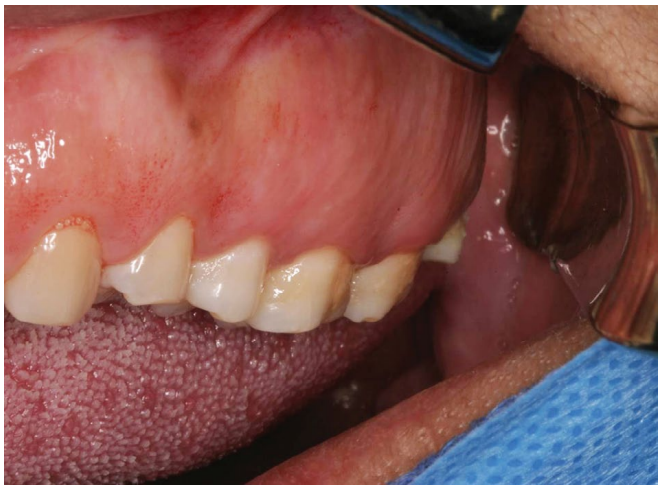

Fig. 54.14: Buccal expansion of left maxilla was caused by the odontogenic keratocystic tumor.

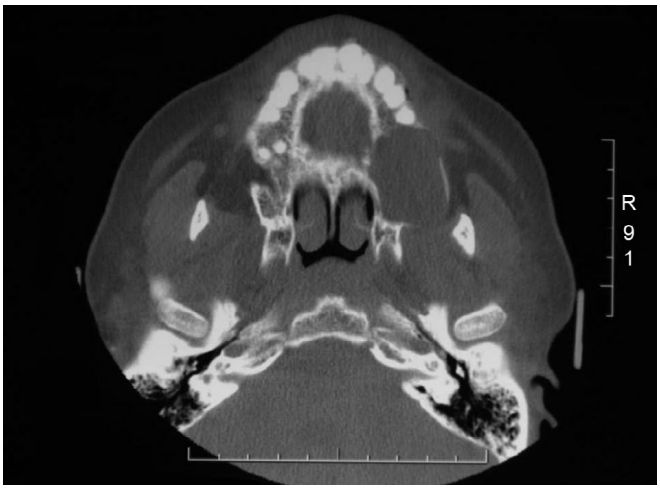

Fig. 54.15: Computed tomography axial view showing expansion of the right maxillary sinus secondary to an odontogenic keratocystic tumor.

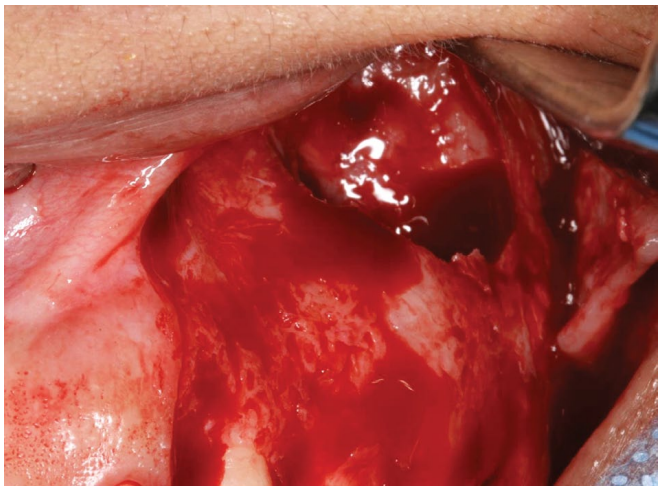

Fig. 54.16: Lateral osteotomy of the left antrum to gain access to the odontogenic keratocystic tumor within the antrum.

Recurrence rates for maxillary ameloblastomas between 60% and 80% are associated with simple enucleation, so more aggressive treatment is mandated. Histologically, they are identical to mandibular ameloblastomas but involvement of the maxillary sinus and nasal cavity may occur and spread through the posterior wall of the maxilla into the pterygomaxillary space. Infiltration of the greater palatine canal up to the base of the skull is not unknown. Treatment often includes a maxillectomy guided by CT or magnetic resonance imaging to achieve 1 cm margins. Removal of pterygoid plates is often necessary. Complete reconstruction of this area usually requires a skin graft and prosthetic obturator. Full prosthetic reconstruction can be achieved with autogenous reconstruction of the palate with microvascular free flaps and subsequent dental implants.

Odontogenic Keratocystic Tumor

OKT (formerly odontogenic keratocyst) is the most aggressive and recurrent cyst of odontogenic origin. It is a microscopically distinct form of cyst that may assume the character of other odontogenic cysts. Approximately 60% of OKTs are of primordial origin, developing from the dental lamina rests or from basal cells of oral epithelium. The remaining 40% are of dentigerous origin developing from the reduced enamel epithelium of the dental follicle. Cysts of primordial origin recur more frequently than those of dentigerous origin.[19]

OKTs comprise approximately 11% of all cysts of the jaws; twice as many appear in the mandible as opposed to the maxilla. Most, in both the maxilla and the mandible, develop in the third molar region. The peak years for appearance are the teens and in 20s, but they occur at all ages. It may be associated with the crown of a tooth appearing as a dentigerous cyst or may represent a keratinizing variant of the lateral periodontal cyst. Children who have basal cell nevus syndrome often develop multiple cysts at one time or develop new cysts over time.

Radiographically, it may appear as a well-marginated, inter-radicular radiolucency, pericoronal radiolucency, or a multilocular radiolucency similar to other odontogenic cysts as shown in Figures 54.14 to 54.18. Most OKTs are asymptomatic, although larger cysts may cause jaw

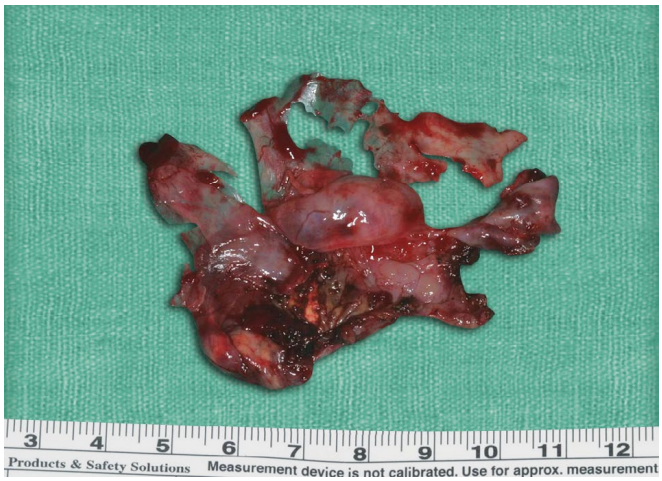

Fig. 54.17: Thin-walled odontogenic keratocystic tumor removed from left antrum.

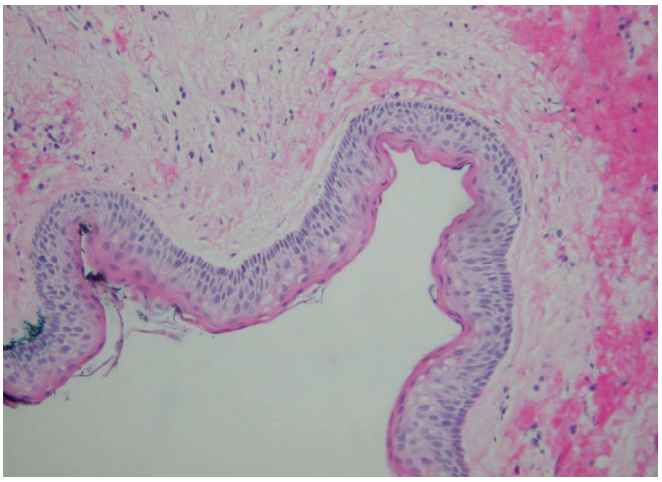

Fig. 54.18: Medium power photomicrograph of OKT showing palisading of nuclei and a 5–7 cell layer of epithelium lining of the odontogenic keratocystic tumor.

expansion and tooth displacement or mobility. The cysts often resorb the roots of adjacent teeth. They expand more from the anterior to the posterior rather than buccolingually. However, in the maxilla there is more buccal expansion than palatal expansion since the cyst tends to extend through bone with the least density.

Small unilocular lesions can be diagnosed and treated with periapical and panoramic radiographs. Large or multilocular lesions should have an incisional biopsy and a CT scan to define the margins for surgical removal.[20]

Histologically, OKTs have a thin epithelial lining with underlying connective tissue composed of a thin collagen layer with islands of epithelium that may represent other early cysts. Secondary inflammation may mask characteristic features of odontogenic keratocystic tumor, resulting in misdiagnosis of a dentigerous, lateral periodontal, or other more benign cyst.

Treatment depends on the extent of the initial lesion. If the entire cyst lining can be removed, small OKTs may be treated with enucleation. Any associated impacted teeth must be removed. The most problematic clinical aspect of the odontogenic keratocyst is the high frequency of recurrence, up to 60–70%. Most recur within the first 5 years after treatment. The thin and friable lining of the cyst wall often makes complete removal with enucleation difficult. Satellite cysts within the fibrous cyst wall may lead to recurrence if they are not completely removed.

When an OKT is present in the maxilla, it often invades the maxillary sinus and may adhere to the sinus membrane, actually replacing the membrane in some instances. Treatment of OKTs infiltrating the maxilla is similar to treatment of mandibular cysts. Cone beam scans are necessary to check for recurrence in the maxilla, since standard radiographs do not provide sufficient data.

To decrease recurrences, some advocate removal of overlying soft tissues that may contain remnant epithelial elements. However, the most common treatment is total enucleation, with or without a "peripheral ostectomy," to excise the entire specimen. A study by Bataineh promotes complete resection without continuity defects through an intraoral approach.[21] They advocate resection of cortex bone approximately 1 cm around the lesion with sacrifice of any teeth associated with the lesion. When perforation of the cortex occurred, the overlying mucosa/soft tissues were also excised. The osseous walls of the defect were abraded with course surgical burs and the defect was packed with Whitehead's varnish on iodoform (triiodomethane) gauze for 5–8 days. The inferior alveolar nerve was free of pathologic tissue and spared in all cases. With a follow-up from 2 to 8 years, no recurrences were found. Long-term follow-up with periodic cone beam scan is recommended, as OKTs have been known to recur 20–40 years after initial treatment.

Central Giant Cell Tumor

The lesion formerly known as a central giant cell reparative granuloma is actually a benign tumor of osteoclast precursors and is now categorized as a central giant cell tumor. Giant cells in these lesions are osteoclast precursors; they develop the ruffled borders typical of osteoclasts and they

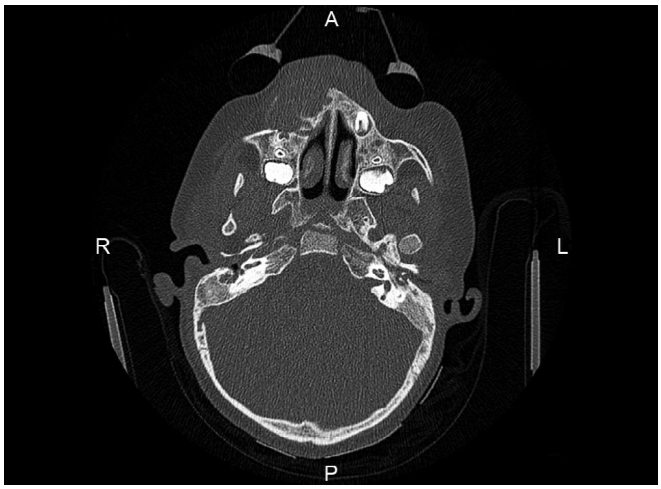

Fig. 54.19: Central giant cell lesion has eroded right premaxilla and displaced tooth buds.

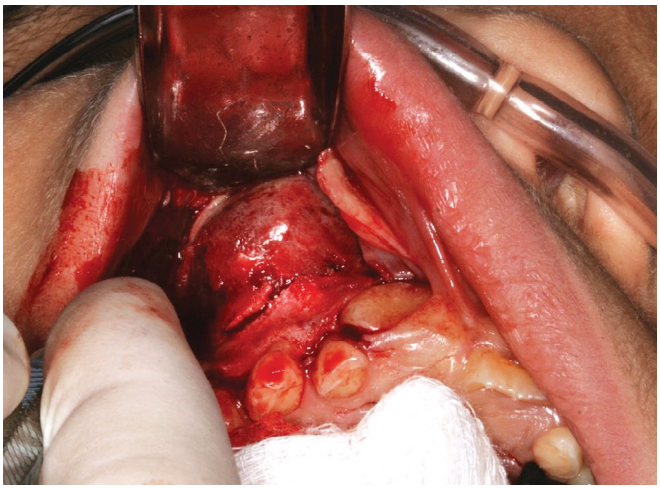

Fig. 54.20: Giant cell lesion has destroyed the premaxilla and displaced permanent tooth bud within the lesion that required excision and peripheral ostectomy.

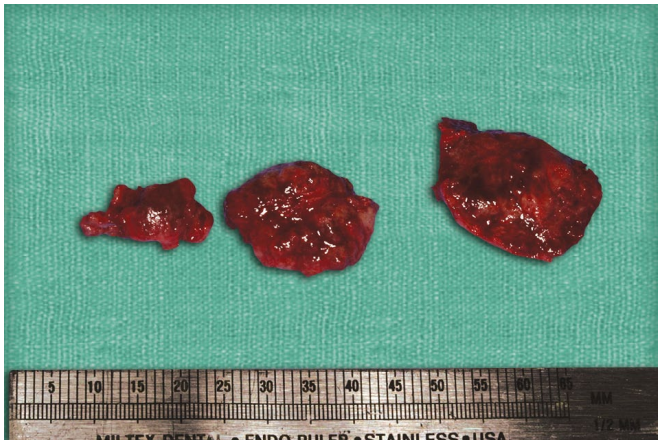

Fig. 54.21: Giant cell lesion specimen, tissue is friable and cannot be removed in one piece.

resorb bone just like osteoclasts. But they are destructive rather than reparative. The giant cell lesion is not a granuloma. A granuloma is a reaction to an infectious or inflammatory agent; the giant cell lesions are not. In addition, the lesion formerly known as an aneurysmal bone cyst is now categorized as a variant of a central giant cell tumor because it has macroscopic rather than microscopic spaces. Significant hemorrhage can arise from this tumor because all giant cell tumors have a venous pressure bleeding quality and those with larger blood-filled spaces exhibit a greater bleeding tendency.[22]

Central giant cell tumors of the jaws are benign but aggressive lesions with biologic activity identical to that in the long bones. They usually present as a painless lesion that may develop quickly over period ranging from 2 weeks to 2 months (Figs. 54.19 to 54.21). However, patients will report pain If the periosteum is stretched. The lesion may appear blue because of cortical and mucosal thinning and internal vascularity. These lesions are found most often in children between 5 and 15 years, three times more often in the mandible than the maxilla, and twice as frequently in females as opposed to males. The lesions usually occur in the anterior portion of the jaw, occasionally cross the midline but posterior regions may also be affected.

Radiographically, a central giant cell tumor usually appears as a multilocular, radiolucent lesion that thins the cortices, including the inferior border. It may scallop the inferior border, displace teeth, resorb inter-radicular bone, and tooth roots. Diagnostically, it is important to rule out a high-pressure vascular lesion. In addition, both primary and secondary hyperparathyroidism should be considered. Histologically, the central giant cell tumors cannot be distinguished from those lesions nor can they be distinguished from cherubism. The tumor is red or brown in color with a mass of a spindle cell stroma that may include varied sizes of multinucleated giant cells distributed irregularly throughout, often concentrated in an area of hemorrhage. Extravasated erythrocytes and hemosiderin will usually be evident. Giant cells are unencapsulated but are usually delimited.

The variant of the giant cell formerly known as an aneurysmal cyst develops within another lesion of the bone, most often with giant cells. Areas of the tumor consist of central giant cell tumor with cellular fibrous tissue, multinucleated giant cells, and extravasated blood.

Nonsurgical treatment options include six weekly injections of triamcinolone 10 mg/mL using 1 mL for each 1 cm of tumor. Alternately, 9 months to a year of daily subcutaneous injections of calcitonin (Miacalcin, Novartis) may be attempted. The FDA has recently expressed concerns about Miacalcin with regard to possible cancer risk so the benefit of such therapy should be considered. Lesions that respond to either therapy with complete bone regeneration or that leave a static radiolucency over several years are considered to be cured. If the remaining radiolucency grows or shows additional radiolucency, retreatment is indicated. Both nonsurgical treatments have the advantage of being associated with low morbidity and neither precludes additional therapies if they are not successful. However, a great deal of patient and parent cooperation is required for significant periods of time. Given the usual age of the patients this may be difficult.

Surgical treatment of central giant cell tumors usually consists of curettage of the lesion and the bone cavity with recurrent lesions or ones that have led to significant bone resorption, requiring resection. High rates of recurrence — as much as 50% – are associated with large lesions that encompass large areas and many teeth. Complete removal of lesions is difficult in those circumstances.

CALCIFYING EPITHELIAL ODONTOGENIC TUMOR (PINDBORG TUMOR)

In 1955, Dr. Pindborg described four cases of an unusual odontogenic tumor.[23] Calcifying epithelial odontogenic tumors (CEOTs) are extremely rare, accounting for <1% of odontogenic tumors. Fewer than 200 have been reported in the literature.[24] They are benign, though morbidity can be associated with bony expansion. They recur at a rate of approximately 15%, as compared with a 90% recurrence rate for ameloblastomas. Most occur in the fourth to sixth decade of life with approximately even distribution between males and females. Some are mildly invasive while others can be moderately invasive. They appear three times more frequently in the mandible than the maxilla, especially in the mandibular ramus. Most often CEOTs are associated with the crown of an impacted tooth. Root resorption and displacement of the impacted tooth are common findings. Pain is seldom a primary complaint. Especially in maxillary lesions, early tumors may not be identified because of expansion into the sinus. Facial asymmetry or incidental findings of palpable bony expansion during routine dental exams may be the first indication of the lesion.

CEOTs are unencapsulated tumors with sheets, nests, and cords of epithelial cells that may have distinct intercellular bridges.[25] Histologically, diagnosis is based on the distinct epithelium with abundant amyloid, varied amounts of calcification, and seldom clear cells. Small concentric calcifications called Liesegang rings are seen in the epithelial islands.

Radiographically it most commonly appears as a mixed radiolucent—radiopaque lesion similar to a calcifying odontogenic cyst. As the tumor grows and matures, it may become more radiopaque but some remain completely radiolucent. Radiographic appearance varies ranging from a unilocular radiolucency to a multilocular "soap bubble" one. Demarcation between the lesion and normal bone also varies with some showing distinct, well circumscribed borders and other showing virtually no differentiation with adjacent bone. The variations in radiographic appearance and in the extent of invasiveness, both panoramic and CT scan are recommended for diagnosis and treatment.

There is no consensus on treatment of CEOTs due to several factors including the fact that lesion is slow growing, the degree of invasiveness is variable and because it is sufficiently rare that long-term follow-up data is not available. Resection appears to have a very low recurrence versus enucleation and curettage for which recurrence ranges from 15% to 30% after as few as 2 years.

Odontoma

Odontomas are hamartomas, benign tumor-like nodules of mature dental tissues, enamel, dentition, cementum and pulp. They arise from the odontogenic epithelium that produces enamel and the mesenchyme that produces dentin. There are two types of odontomas; the compound odontoma forms small tooth-like structures while the complex odontoma forms a calcified mass. Compound and complex odontomas contain both epithelial and mesenchymal cells. Most compound odontomas develop anterior to the mental foramen but complex odontomas develop more often posterior to the mental foramen. Radiographically the compound odontoma will have a "bag of marbles" or gravel-like appearance.[26] The complex odontoma will appear as a large, irregularly shaped mass. Both will have a well-demarcated border. Odontomas are found almost exclusively in children and young adults under the age of 25. Treatment consists of enucleation and curettage. It is important to assure all calcified masses have been removed. Usually bone regeneration will occur within a year.[27]

Oral–Antral Communication and Oral–Antral Fistula

Oral–antral communications (OACs) are sequelae of extractions, cyst removal, or implant placement. An OAC that is not properly diagnosed and treated may become an oral–antral fistula (OAF) with subsequent development of chronic sinusitis. The majority (93%) of OACs are the result of dental extractions due to the proximity of the roots of the maxillary bicuspids and molars to the maxillary sinus. Third molar extractions account for 41% of the OACs, second molars were involved in 18% of the cases, second premolars account for 9%, and first premolars are involved in the remaining 5%. Pathological lesions in the sinus and trauma account for another 5.7%, periodontal infections cause only 0.93% of communications with various other factors accounting for the remaining 0.65%.[28]

When an OAC occurs with no indication that the sinus was infected prior to the procedure, a collagen plug is placed in the communicating tooth socket. A figure eight suture is used to stabilize the soft tissue and to retain the collagen plug.[29] The patient is then placed on 5 days of antibiotic therapy (amoxicillin–clavulanate acid 875 mg) to prevent infection of the blood clot in the socket. The patient is advised to avoid dislodging the clot by blowing their nose or sneezing with the mouth closed. If the OAC is larger than 5 mm or if sinusitis is present, an OAF may develop. Acute sinusitis is associated with aerobic bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Chronic sinusitis associated with an OAF exhibits a polymicrobial process with mostly anaerobic bacteria such as *Peptostreptococcus*, *Prevotella*, *Bacteroides*, *Propionibacterium*, or *Fusobacterium* species. Surgical intervention to aerate the sinus may be required in addition to antibiotic treatment for periods of 3 weeks or more. In the case of chronic sinusitis, twice daily irrigation should continue until the infection has been resolved with no purulence evident when the OAF is irrigated. If purulence persists after 2 weeks of irrigation and antibiotic therapy, the sinus should be cultured aerobically and anaerobically to determine what additional antibiotics should be prescribed. Empiric antibiotics targeting sinonasal and oral cavity bacteria most commonly include amoxicillin–clavulanate acid and clindamycin.[30]

A number of methods of surgical repair of OACs have been documented, but only a few are widely accepted and routinely utilized. Methods include the palatal rotation flap, the buccal flap, the buccal sliding flap, and the buccal fat pad (BFP) flap. The choice of technique depends on the amount and condition of the tissue available for repair, the size, and location of the defect and the requirements of subsequent dental restorations.[31] All of the techniques for closure of OAFs depend on excision of the fistula and on bone being present on the roots of the all teeth within the fistula. Attempts to close the OAF with root exposure within the fistula result in failure, since the soft tissue used to close the OAF cannot adhere to the root surface. Imaging, preferably cone beam studies or CT scans, is necessary to determine the extent of the sinus disease and also to measure the size of the defect since the bone defect is always larger than the soft tissue defect.

REPAIR OF ORAL–ANTRAL DEFECTS USING THE BUCCAL FAT PAD

The use of the BFP for surgical closure was first reported by Egyedi in 1977. Subsequent case reports and research have modified the initial technique particularly with regard to dismissing the necessity of covering the flap with a split thickness skin graft. The BFP is an anatomically rounded and biconvex structure that is important in establishing the facial contour. It is adipose tissue surrounded by a thin capsule. The BFP is located in both masticatory spaces. It has a central body and four extensions; pterygopalatine, temporal, pterygoid and buccal. Blood is supplied by the maxillary, superficial temporal and facial arteries thus ensuring a rich blood supply for the flap.[32] The technique involves developing a buccal mucoperiosteal incision cranial to the osseous opening of the OAC. One this mucoperiosteal flap is developed, the periosteum is incised and BFP is allowed to emerge until adequate tissue exists for obturation of the OAC. The fat is then sutured into position as shown in Figures 54.22 to 54.25.[33]

Rapidis et al. have posited that BFP closure should not be used with maxillary defects greater than 4 × 4 × 3 cm due to the possibility of flap necrosis or the potential to create a new communication. However, some have had success with larger defects. Hao reports that maxillary defects are particularly suitable for this technique because of the close proximity of the BFP to the maxilla. A significant disadvantage of the BFP technique is that fact that it can only be used once. The use of the BFP is contraindicated in patients who have prior radiation therapy, malar hypoplasia, thin cheeks, or Down syndrome.

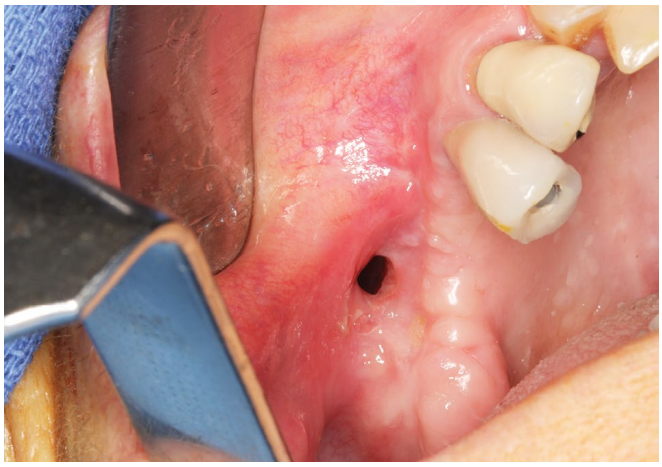

Fig. 54.22: Oral–antral fistula secondary to bisphosphonate necrosis of the maxilla.

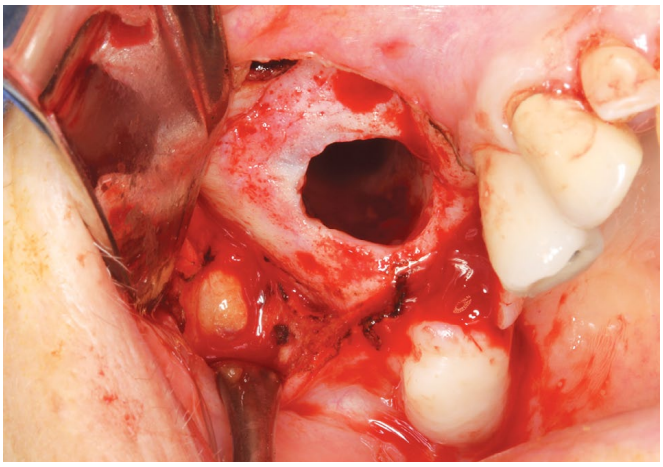

Fig. 54.23: The osseous defect is four times larger than the soft tissue fistula. Upper right corner buccal fat pad prior to its being used to obturate the fistula.

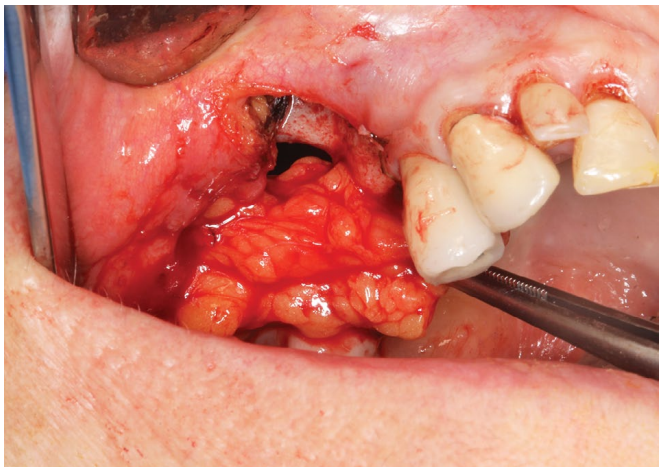

Fig. 54.24: Buccal fat pad obturating the osseous defect.

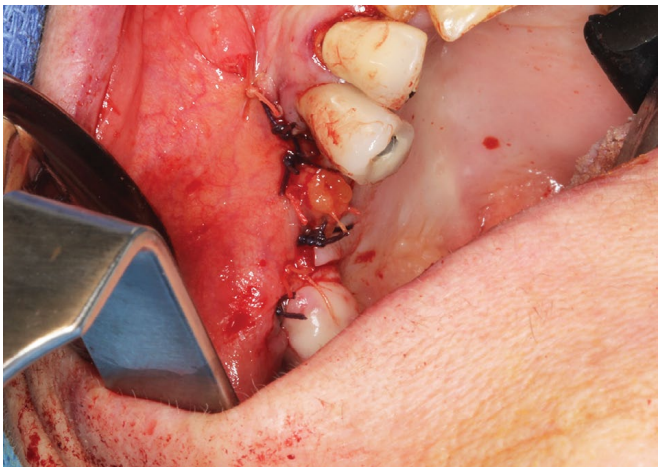

Fig. 54.25: Closure of flap with small amount of buccal fat pad still exposed. The exposed fat will be covered with epithelium in approximately 3 weeks.

REPAIR OF ORAL–ANTRAL DEFECTS USING THE BUCCAL SLIDING FLAP

In 1936, Rehrmann introduced the buccal sliding flap for closing OACs. This flap is developed by making two buccal divergent vertical incisions extending into the buccal vestibule from the OAC. The trapezoidal flap is elevated and brought across the defect and sutured to the palatal margins of the defect. In order to decrease the tension on the flap, the buccal periosteum can be scored high in the vestibule that allows the flap to move passively to the site as shown in Figure 54.26. There is minimal sulcular distortion with this procedure, but it leaves an area to heal by secondary intention that is uncomfortable for the patient as shown in Figure 54.27. This technique is particularly useful when a moderate soft tissue defect exists in the posterior maxilla.[30,34]

REPAIR OF ORAL–ANTRAL DEFECTS USING PALATAL FLAPS

The palatal rotation flap was first described by Ashley in 1939. Although palatal tissue is thicker and less elastic than the buccal tissue, it can be mobilized and rotated to close OACs particularly in or anterior to the second

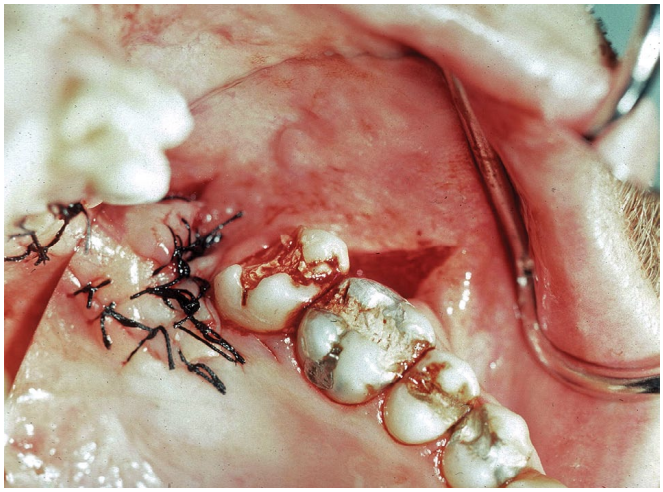

Fig. 54.26: Lateral buccal flap closing an oral–antral fistula.

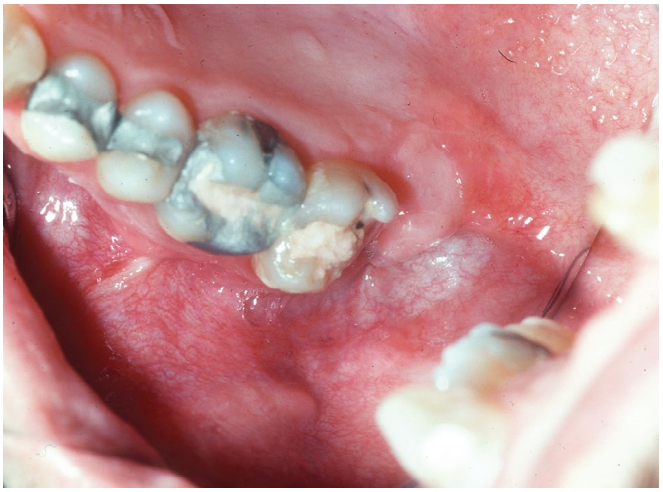

Fig. 54.27: Healed lateral buccal flap closing an oral–antral fistula. Buccal vestibule has been decreased in order to close the fistula.

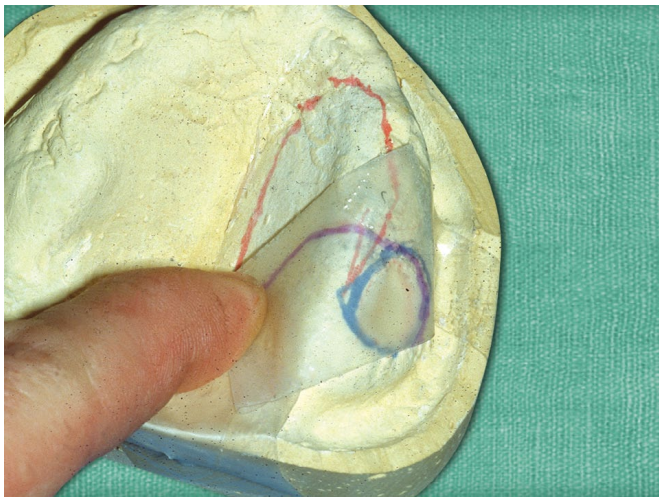

Fig. 54.28: Diagnostic cast of patient with oral–antral fistula used to plan palatal rotation flap. Flap must be one-third larger than the area to be obturated since it will contract when released from the palate.

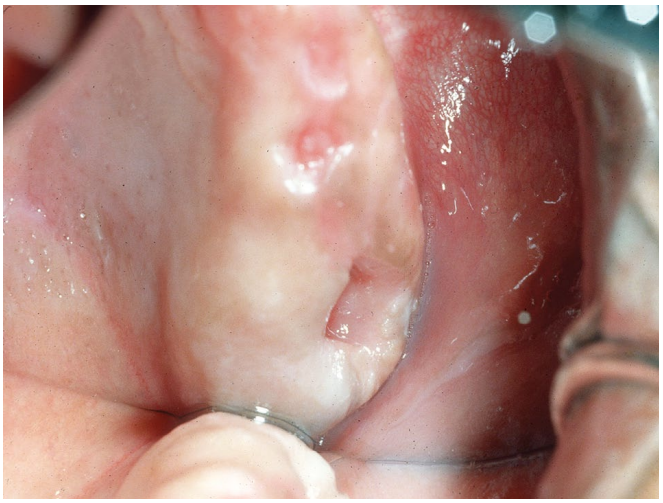

Fig. 54.29: Oral–antral fistula in an edentulous maxilla. A palatal flap was used to preserve the buccal vestibule for proper denture retention.

molar region. Closure in the third molar region is impeded by the vascular pedicle. Blood is supplied by the greater palatine artery.[35,36]

The most practical palatal flap design is that of a rotational flap that has a wedge removed near its base to facilitate rotation. Integrity of the palatine artery should be preserved if at all possible. The exposed palatal bone with heal by secondary epithelialization. The area of the palate from which the flap is taken may be left exposed or closed with a bolster sutured in place or with a plastic palatal stent. If the palatal flap does not reach the lateral alveolus, a secondary buccal flap is also utilized.

When planning a rotational palatal flap, it is advantageous to prepare a diagnostic model to determine the exact dimension of the flap that will be required as shown in Figure 54.28. This technique is particularly useful in edentulous areas of the mouth since there is no vestibular distortion, as shown in Figures 54.29 and 54.30. Shortly after surgery a relieved denture may be contoured and utilized during the healing process. A palatal flap is preferred to

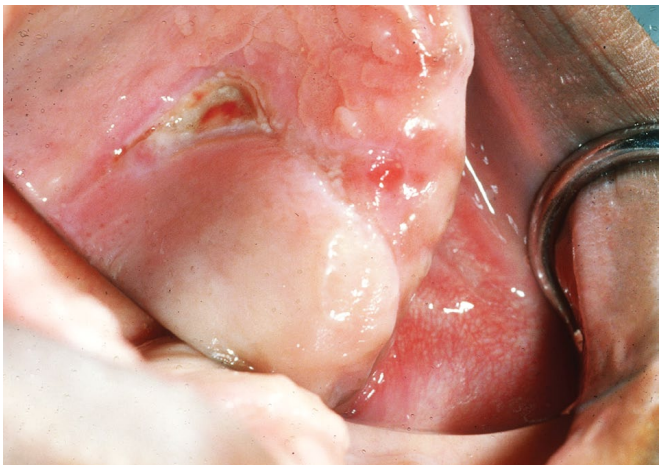

Fig. 54.30: Palatal flap healing 3 weeks postoperative.

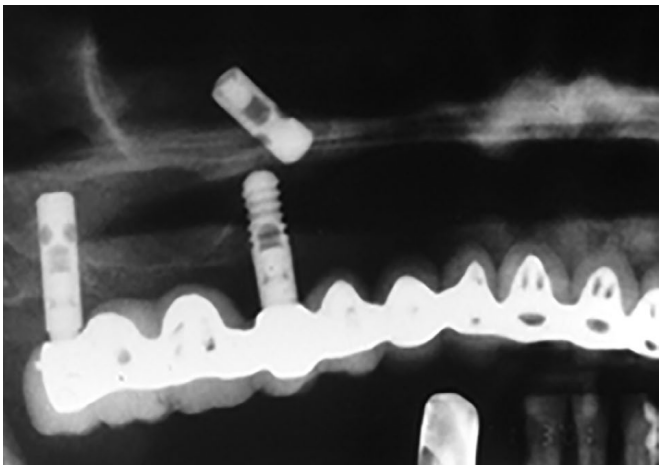

Fig. 54.31: Dental implant has migrated into the maxillary sinus.

buccal flaps in edentulous patients because the palatal flap does not reduce the maxillary buccal vestibule needed to obtain a suction fit of an upper denture.

ORAL–ANTRAL COMMUNICATION OR ORAL–ANTRAL FISTULA SECONDARY TO IMPLANT PLACEMENT OF BONE GRAFTING INFECTION

Patients presenting for reconstruction of the posterior maxilla following the loss of premolar and molar teeth often lack adequate bone height to support endosteal dental implants. Generally 10 mm is considered minimal height for implant placement in the posterior maxilla. Patients with 3–5 mm or more of bone often undergo simultaneous bone graft augmentation of the antral floor with implant placement. Those with <3 mm of native bone in the posterior maxilla undergo grafting followed by graft maturation of 6 months before implant placement. Sinus grafting is most often accomplished via a lateral osteotomy of the maxillary sinus wall and elevation of the Schneiderian membrane. When the Schneiderian membrane is perforated, there is an increased risk of the bone graft becoming infected. If the graft becomes infected, the sinus must be cultured then irrigated until clear. At that point the flap should be closed. Empiric antibiotics should be prescribed pending culture results. Antibiotics should be continued for at least 2 weeks guided by culture results. Often the graft will survive and the implants will become functional. If after one series of culture, irrigation, and appropriate antibiotic therapy, the infection does not resolve removal of all graft material and implants should be considered if the infection does not resolve after antibiotic therapy.

Further attempts at reconstruction should be delayed for 3–6 months. A full or partial denture may be placed over the mucosa of the posterior maxilla during the integration period for esthetics and masticatory function. Pressure from the prosthesis can cause an implant to migrate into the sinus. After 6 months, when the implant is scheduled to be uncovered the implant may be found to have migrated into the sinus a shown in Figures 54.31 to 54.34. When an implant is in the sinus, use a cone beam radiograph to guide the removal of the implant via a lateral antral osteotomy.

BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW (BRONJ)

Bisphosphonate drugs inhibit bone resorption and renewal by suppressing osteoclastic activity. Table 54.2 includes a list of the drugs most often prescribed in the United States.[37] The drugs are widely prescribed; in 2011, bisphosphonate-based drugs had $4.2 billion in US sales.[38] Orally administered bisphosphonates and intravenously administered Reclast are used for prevention and treatment of osteoporosis, particularly in postmenopausal women. They are also prescribed for patients with osteopenia and Paget disease. Most intravenously administered bisphosphonates are used to treat bone loss associated with metastatic bone disease in patients with breast, lung, prostate, and other cancers as well as those with and multiple myeloma, giant cell lesions, osteogenesis imperfecta, and fibrous dysplasia.[39]

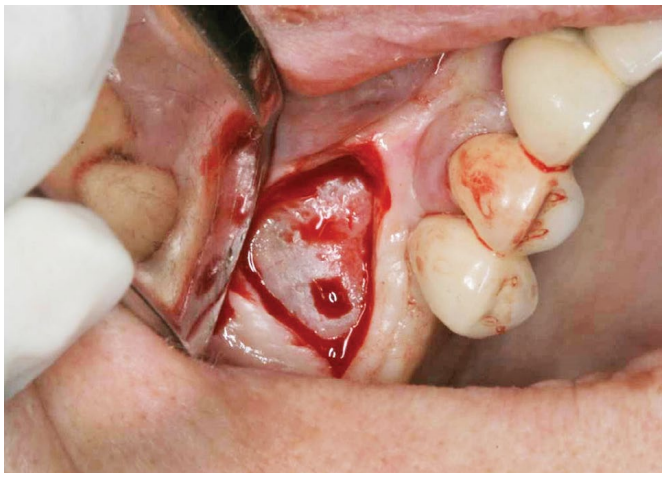

Fig. 54.32: Lateral approach to antrum to retrieve displaced implant.

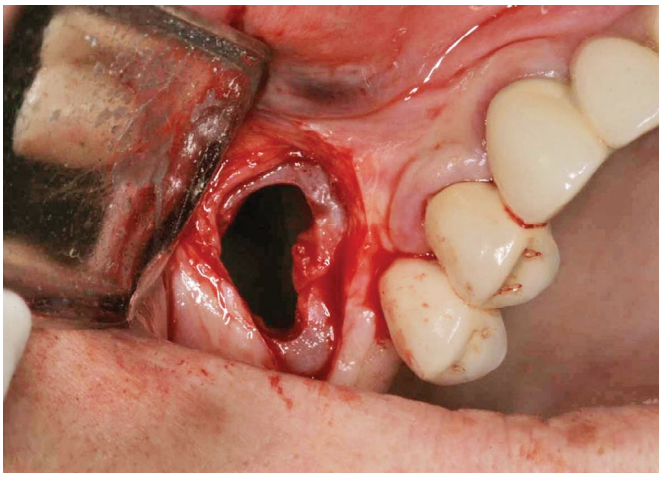

Fig. 54.33: Lateral access to retrieve displaced implant.

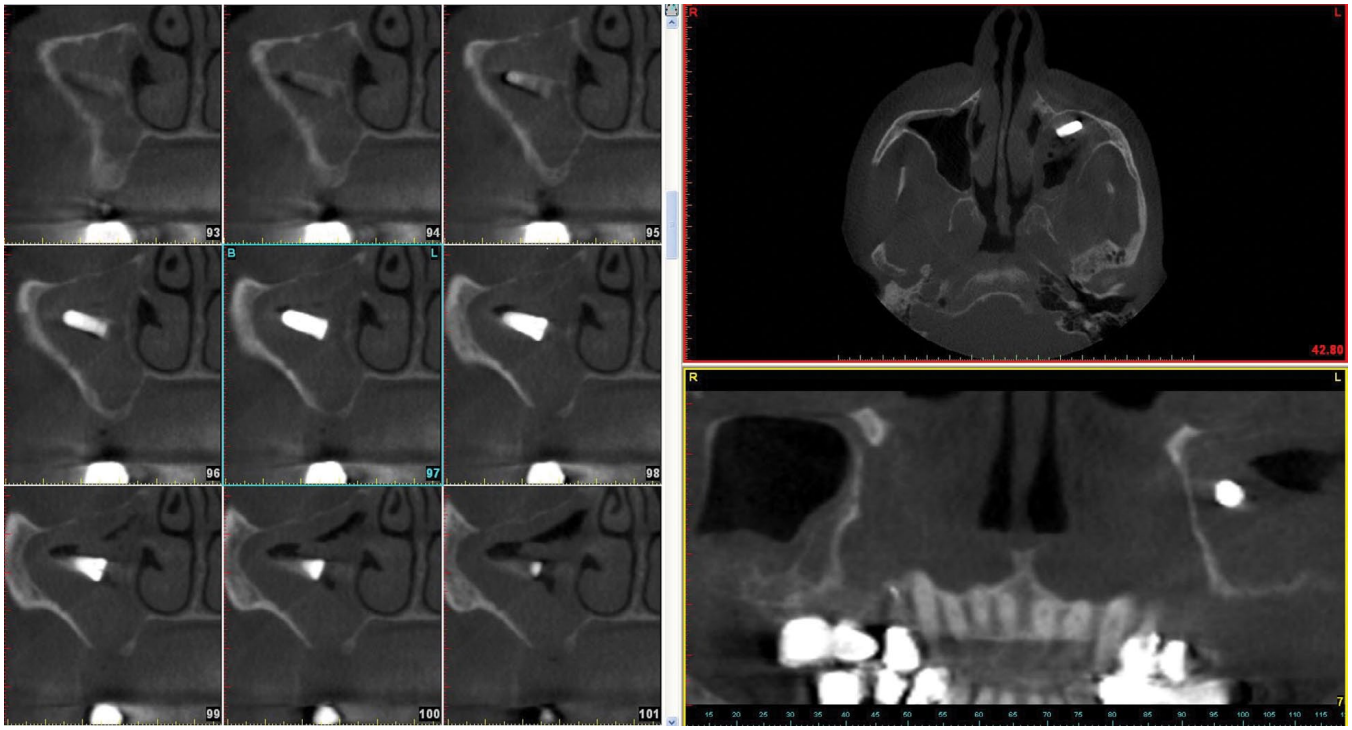

Fig. 54.34: Dental implant displaced into the left antrum. The patient had worn a partial denture while the implant was theoretically integrating. The alveolar defect is an oral–antral fistula.

The most commonly prescribed oral bisphosphonates are Alendronate (Fosamax), Risedronate (Actonel), and Ibandronate (Boniva). The most commonly prescribed intravenous (IV) bisphosphonate is Zoledronate (Zometa and Reclast). To date, only bisphosphonates containing nitrogen have been associated with osteonecrosis of the jaw.[40]

During normal bone remodeling, osteoclasts resorb the bone but this is inhibited by bisphosphonates. Without the resorption and subsequent release of bone inducing protein, old bone is not removed and new bone is not produced. Alveolar bone depends more on osteoclastic bone resorption/remodeling than any other bone in the adult body. Bisphosphonates become highly concentrated

Table 54.2: Bisphosphonates commonly prescribed in the United States

Brand name	*Manufacturer*	*Generic name*	*Administration*	*Primary indication*	*Contain nitrogen*	*Potency relative to etidronate*
Didronel	Proctor & Gamble Pharmaceuticals	Etidronate	Orally	Paget disease	No	1
Skelid	Sanofi Pharmaceuticals	Tiludronate	Orally	Paget disease	No	50
Actonel	Warner Chilcott PLC	Risedronate	Oral	Osteoporosis	Yes	1000
Boniva	Roche Laboratories	Ibandronate	Oral/IV	Osteoporosis	Yes	1000
Fosamax	Merck & Co.	Alendronate	Oral	Osteoporosis	Yes	1000
Fosamax Plus D	Merck & Co.	Alendronate	Oral	Osteoporosis	Yes	1000
Aredia	Novartis	Pamidronate	IV	Bone metastases	Yes	1000–5000
Zometa	Novartis	Zoledronic acid	IV	Bone metastases	Yes	10,000+
Reclast	Novartis	Zoledronate	IV	Osteoporosis	Yes	10,000+

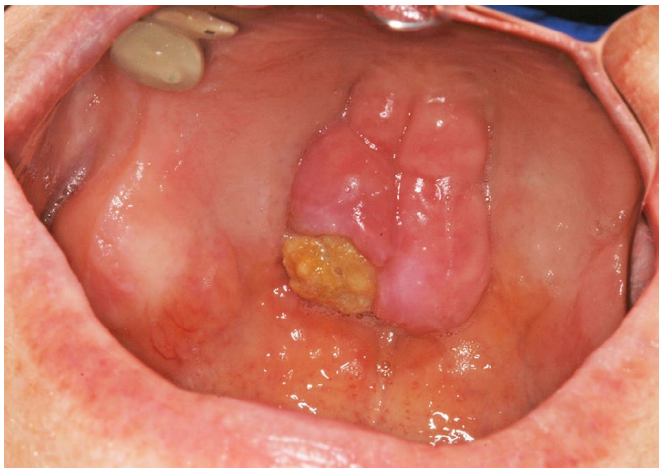

Fig. 54.35: Sixty-five-year old female with a history of taking alendronate for 4 years with spontaneous exposed bone on her maxillary torus.

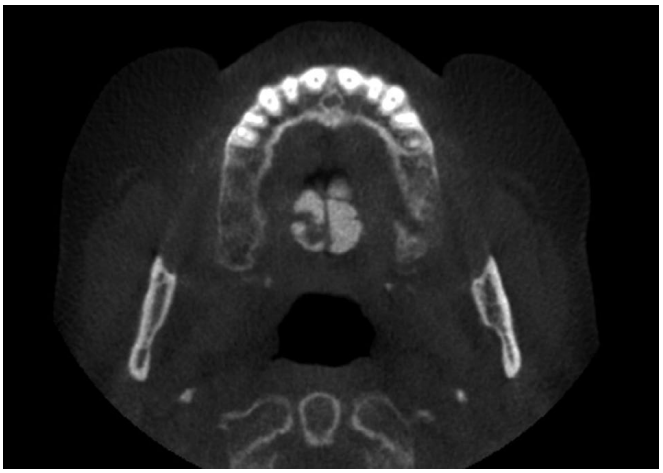

Fig. 54.36: Axial cone beam with clear necrotic area of the maxillary torus.

in the jaw because the jaws have a greater blood supply than other bones and because of the presence of teeth that require daily bone remodeling around the periodontal ligament. Alveolar bone remodels at 10 times the rate of the tibia.[41]

In 2003, Dr Robert E Marx submitted a letter to the editor of the Journal of Oral and Maxillofacial Surgery identifying 36 cases of bone exposure in the jaws. In all 36 cases, the exposed bone did not respond to standard surgical or medical treatments. All patients were receiving IV bisphosphonate treatments. Since that initial correspondence, numerous studies have been published, most of which indicate a relationship between the bisphosphonate therapy and painful, exposed bone in the jaw.[42]

Most cases of BRONJ are associated with the use of IV bisphosphonates, but there are reports of cases involving only oral bisphosphonates. Both jaws may be affected, although the majority of the cases involve the mandible. Based on available data, the risk of BRONJ is significantly higher for those receiving IV bisphosphonates, those taking more potent versions of the drugs and those taking oral versions for >3 years. The half-life of the drugs is 11 years so the effectiveness of longer term therapy is being studied.[43] Spontaneous appearances of BRONJ, as shown in Figures 54.35 and 54.36, have been reported, but to date, reports indicate that the majority of patients who develop BRONJ had recent dental surgery including extractions, periapical surgery, periodontal surgery, and implant placement.[44] The risk of BRONJ for patients taking oral bisphosphonates for fewer than 3 years is relatively low; however, millions of patients take these drugs. There are no reliable data on the incidence of BRONJ.[45]

In 2006 and 2009, the American Association of Oral and Maxillofacial Surgeons issued position papers regarding the diagnosis and proposed treatment for BRONJ. According to AAOMS, patients may be considered to have BRONJ if all of the following three characteristics are present: current or previous treatment with a bisphosphonate; exposed bone in the maxillofacial region that has persisted for >8 weeks; and no history of radiation therapy to the jaws.[46]

Patients sometimes present with obvious symptoms of BRONJ but more often present complaining of temporomandibular pain, sinusitis, soft tissue swelling, loosening of the teeth, and exposed bone. BRONJ is sometimes misdiagnosed as osteomyelitis that presents as black necrotic bone or as a white alveolar ridge or lingual cortex exposure.[47] Even if specifically asked about bisphosphonate use during routine medical or dental visits, patients may not list bisphosphonates among their medications, particularly if the medication was provided intravenously as part of oncology treatment.

AAOMS developed a classification system for identifying risk factors and symptoms.

At risk patients have no apparent necrotic bone but have been treated with oral or IV bisphosphonates.

Stage 0 patients are those with no clinical evidence of necrotic bone, but with some nonspecific clinical findings and symptoms of pain in odontalgia not explained by dental pathology.

Stage 1 patients have exposed and necrotic bone that is asymptomatic without signs of infection.

Stage 2 patients have exposed and necrotic bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage.

Stage 3 patients have exposed and necrotic bone with pain, infection, and one or more of the following:

Exposed and necrotic bone extending beyond the region of the alveolar bone (i.e. inferior border and ramus in the mandible maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture; extraoral fistula, oral–antral or OAC or osteolysis extending to the inferior border of the mandible or the sinus floor.[46]

Treatment of bisphosphonate-induced jaw necrosis requires careful management of the exposed necrotic bone with 0.12% chlorhexidine rinse three times a day for the duration of exposed bone. PenVK 500 mg is prescribed four times a day to resolve the infection and consequently to reduce pain. Motrin (800 mg) can also be prescribed to alleviate pain. If the necrotic bone becomes reinfected, further antibiotic therapy should be instituted. When maxillary necrosis progresses through the alveolar process, the patient will develop either an oral nasal or an OAF. These fistulas can be obturated utilizing a prosthesis or closed with a BFP flap, discussed elsewhere in this chapter and as shown in Figures 54.37 to 54.40.[47]

Researchers have discovered recently that three additional drugs may be associated with jaw necrosis.[48] Denosumab is an osteoclast inhibitor used in orthopedics and oncology. Case reports suggest that it is associated with

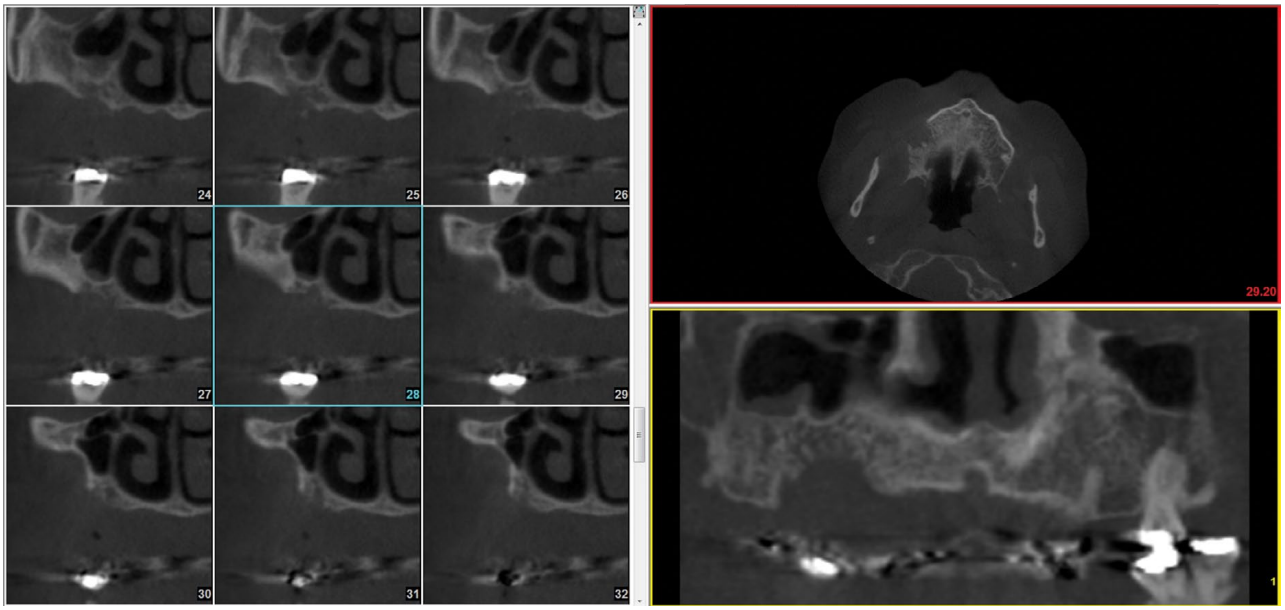

Fig. 54.37: Cone beam shows significant destruction of right maxillary alveolar process.

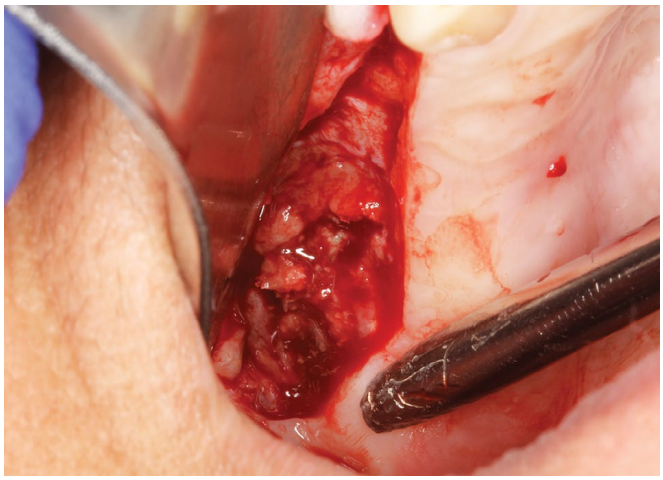

Fig. 54.38: Right maxillary ridge exposed revealing necrotic bone secondary to bisphosphonate-related osteonecrosis of the jaws.

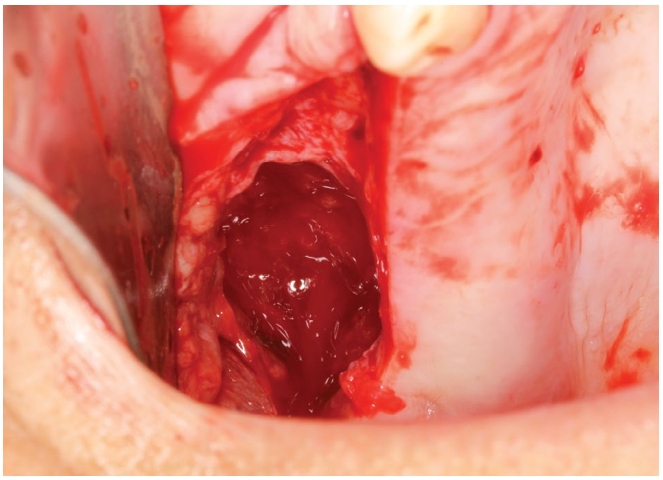

Fig. 54.39: Large oral–antral fistula after debriding the necrotic bone.

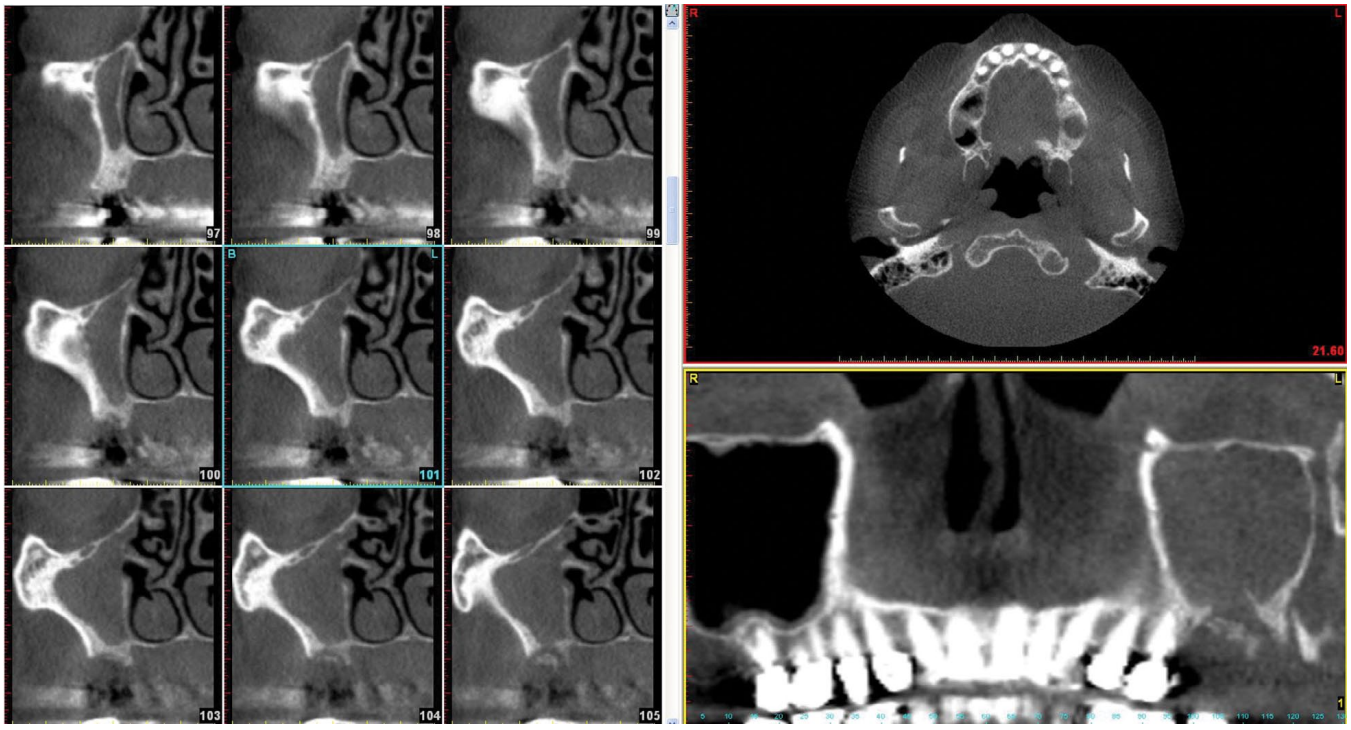

Fig. 54.40: Stage 3 bisphosphonate-related osteonecrosis of the jaws with necrosis through maxillary alveolar process resulting in oral–antral fistula.

osteonecrosis at approximately the same rate as IV bisphosphonates. As stated earlier, osteoclasts and osteoblasts are responsible for bone resorption and apposition. Osteoclasts originate from the monocyte-macrophage lineage influenced by growth factors, specifically macrophage colony-stimulating factor (M-CSF), receptor activator of nuclear factor K-b ligand (RANKL), and vascular endothelial growth factor (VEGF). Osteoclasts are primarily reliant on exposure to RANKL. Denosumab inhibits formation and activity of the osteoclasts. It is used to treat osteoporosis and bone metastases. Bevacizumab targets VEGF and is used to treat advanced colon, lung, renal, and central nervous system tumors. It also has a role in treatment of breast and ovarian cancers. Bevacizumab acts by

preventing the growth of blood vessels. Sunitinib is a tyrosine kinase inhibitor that inhibits angiogenesis by interfering with the VEGF receptor and the M-CFS receptor and other metabolic pathways.

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CHAPTER

55 Complications in Endoscopic Sinus Surgery

James A Stankiewicz

COMPLICATIONS IN ENDOSCOPIC SINUS SURGERY

Successful endoscopic sinus surgery (ESS) requires adequate preoperative planning including medical therapy, endoscopic examination, and thorough review of radiographic studies, computed tomography (CT) scans, and occasionally magnetic resonance imaging (MRI) studies. The surgery must be landmark based with an understanding of how each landmark is a guide to safe surgery. Image guidance is used as a confirming tool, not to thoughtlessly allow surgical performance. Close endoscopic observation and course checking throughout the surgery provide safe surgery and immediate recognition of problems with solutions. It is important to recognize immediately any breech of skull base or orbit; evaluating and treating any problems as they occur. Careful postoperative management and observation allow early discovery of any problems and timely management.

SAFE ENDOSCOPIC SINUS SURGERY

Elsewhere in this textbook the techniques of ESS will be discussed. This section discussion will concentrate using landmarks to prevent complications and perform safe surgery.

Middle Turbinate and Uncinate Process

The middle turbinate is a guide to the antrostomy and the maxillary line (line between maxillary bone and lacrimal bone). The uncinate process inserts anteriorly on the maxillary line. No dissection is necessary anterior to the anterior end of the middle turbinate in the creation of maxillary antrostomy. Making punch cuts across the maxillary line, while making a maxillary antrostomy as was done early on in ESS increases the risks of injury to the nasolacrimal duct. Today the antrostomy is opened posteriorly not anteriorly preventing this complication.[2,3]

Maxillary Antrostomy

The maxillary antrostomy provides not only drainage to the maxillary sinuses but also identification of the orbit and the way to the sphenoid sinuses. The superior rim of the maxillary sinus is the lower part of the lamina papyracea and the beginning of the orbit. Identifying the orbit early on in the dissection allows for complication prevention. Following that same line (through the upper rim of the antrostomy) posteriorly points to the lower vertical basal lamella. Once through the basal lamella, the line runs to the anterior wall of the sphenoid sinus.

The Sphenoid Sinus

Identifying the anterior wall of the sphenoid sinus establishes the posterior skull base. Remember that the distances between sinus lamella (maxillary line, bulla ethmoidalis, basal lamella, sphenoid sinus) are measured at 1 cm intervals as the surgeon moves back in the line through the antrostomy over the basal lamella described above. The maxillary line is at 4 cm, the bulla at 5 cm, the basal lamella at 6 cm, and the sphenoid in regular size adults at 7 cm.[4,5] Using a measuring tool of some sort

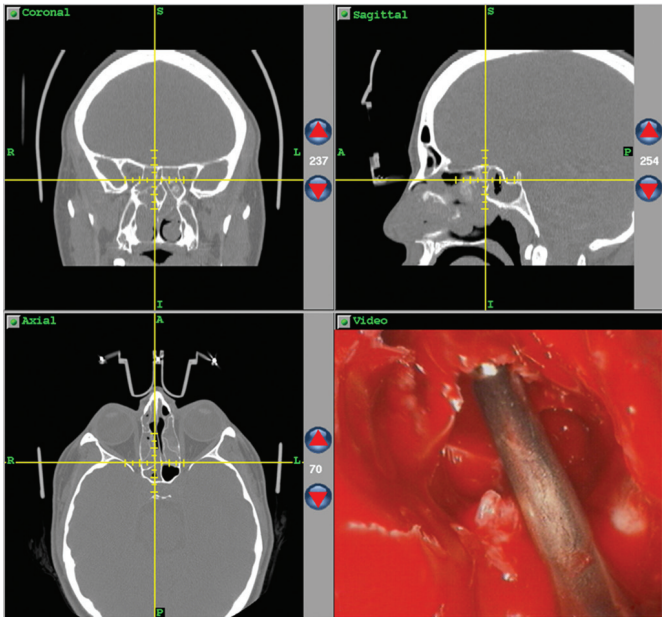


Fig. 55.1: Image guidance figure showing sphenoid ethmoid angle to indicate superior skull base.

(beaded probe, microdebrider blade, etc.) keeps the surgeon safe as the anterior wall of the sphenoid sinus and ostia are approached. The spheno ethmoid angle is a key landmark for it is where the superior roof of the ethmoid begins at the skull base. As one looks at this angle, it is important to recognize the differences in endoscopic appearance. The sphenoid anterior wall comes forward toward the surgeon, and the ethmoid skull base moves away from the surgeon, creating the angle (Fig. 55.1). It is at this point, a posterior to anterior superior ethmoid dissection begins.

Ethmoid Skull Base

One of the most confusing and treacherous area to open in ESS is the ethmoid skull base. The lateral ethmoid "fovea" ethmoidalis at the junction with the lamina papyracea (orbit) is much thicker, perhaps 10 times thicker, than the medial ethmoid against the middle turbinate lamella, the lateral lamella.[6,7] This is the most common site of iatrogenic cerebrospinal fluid (CSF) leak. This medial thin area runs on a line from behind the frontal recess to the sphenoid sinus. Injury can occur anywhere along this line. Normally, the fovea ethmoidalis and the cribriform plate are at the same level near the top of the orbit. However, this may vary. The fovea may be low lying with the cribriform. The fovea may be in normal position with a long lateral lamella and low-lying cribriform plate that lends itself to the development of CSF leak. The brain is more accessible here and is below the fovea ethmoidalis at the lateral lamella. The fovea and cribriform plate abnormality may be asymmetrical between right and left sides. It is very important these anatomical variants are noted in viewing coronal CT scans prior to and during surgery to be safe (Figs. 55.2A and B).

Vascular Anatomy of Concern

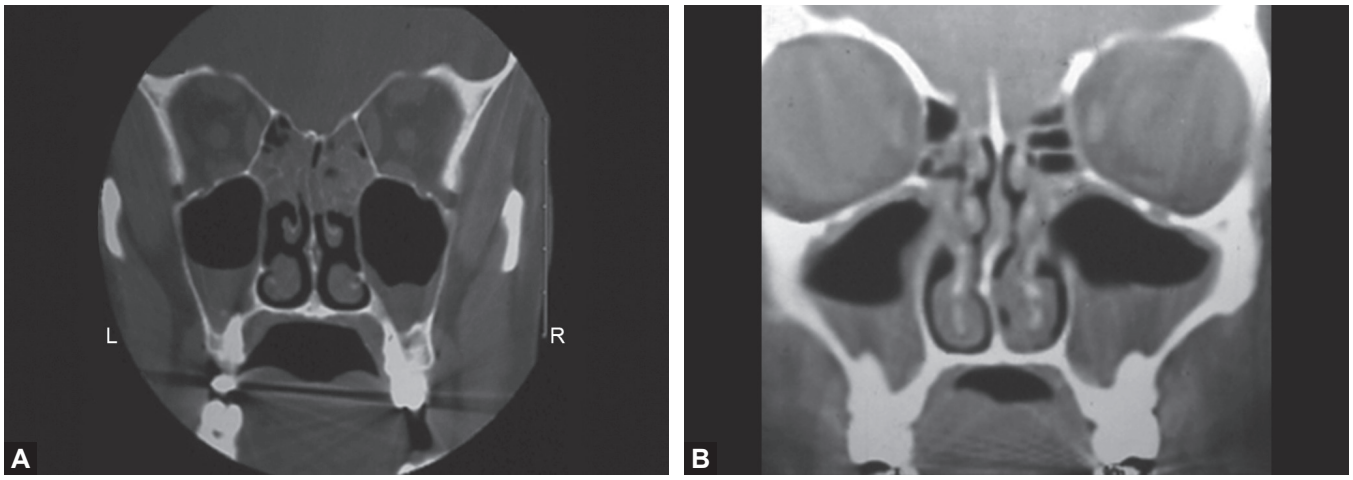
The horizontal basal lamella of the middle turbinate receives the blood supply from the sphenopalatine foramen (Figs. 55.3A to C). The posterior septal artery follows a course from the internal maxillary artery and its sphenopalatine artery branch through the sphenopalatine foramen to just inferior to the sphenoid sinus. It often gives off branches inferior medial and inferior lateral to the sphenoid ostia. These vessels can be injured by disrupting the horizontal basal lamella partially or totally or during the opening of the sphenoid sinus. Since they are arteries, bleeding can be brisk and sometimes confused for the carotid artery. Bleeding postoperatively is usually from one of these arteries as well and constitutes the most common reason for postoperative hemorrhage requiring packing or cautery.

The ethmoid arteries are not commonly injured since in most cases they are located in the ethmoidal skull base. The posterior ethmoid is the rarest vessel injured. The anterior ethmoid artery, however, can exist anatomically below the skull base in a sling and can be injured when performing upper ethmoid frontal recess surgery (Fig. 55.4). The bleeding can be brisk as well and may mirror bleeding that occurs when the skull base is breached. The biggest danger, however, is disruption of the anterior ethmoid artery at the lamina papyracea allowing for intraorbital bleeding and an orbital hematoma to occur that can be catastrophic.

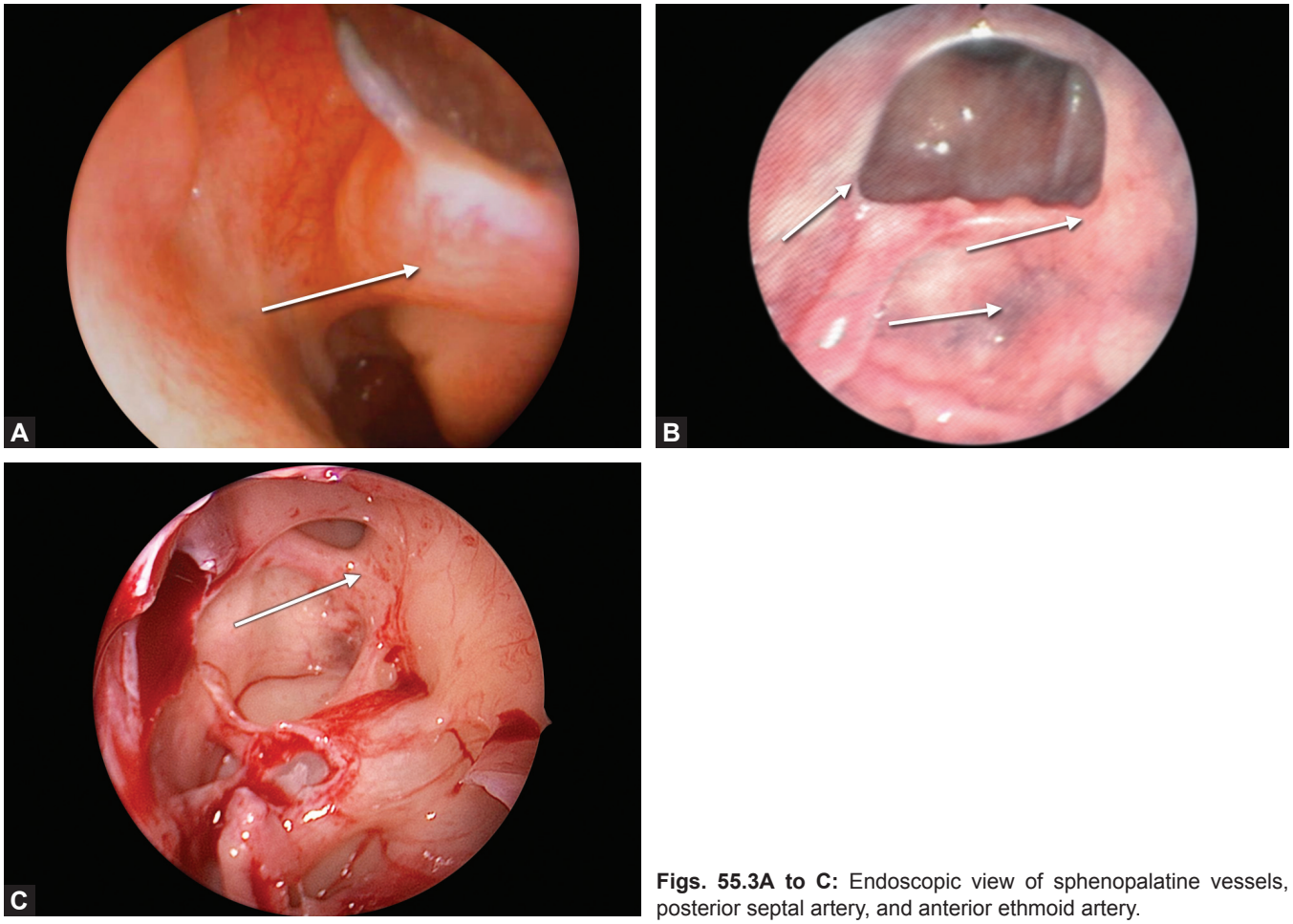
MANEUVERS AND INSTRUMENTATION, AND PLANNING, LEADING TO SAFE ENDOSCOPIC SINUS SURGERY

Perioperative Planning

The extent of disease needs to be ascertained using endoscopy and CT scanning. Whether a patient has had previous ESS and what anatomical structures remain along with disease is most important. Endoscopy and CT scan review can also show evidence of skull base abnormalities,



Figs. 55.2A and B: Low lying skull base images on computed tomography (CT) scan.



Figs. 55.3A to C: Endoscopic view of sphenopalatine vessels, posterior septal artery, and anterior ethmoid artery.

dehiscences, scarring, and osteitic bone changes. A safe plan for surgery cannot happen without this effort. Understand that in revision surgery, in most cases, more diseased anatomy will become apparent as surgery progresses. With this, the risk of complication increases. Visualization is paramount during ESS. Poor visualization equals

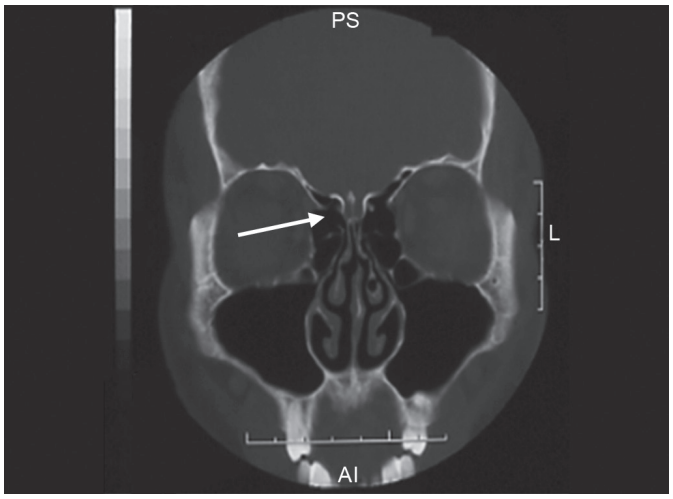
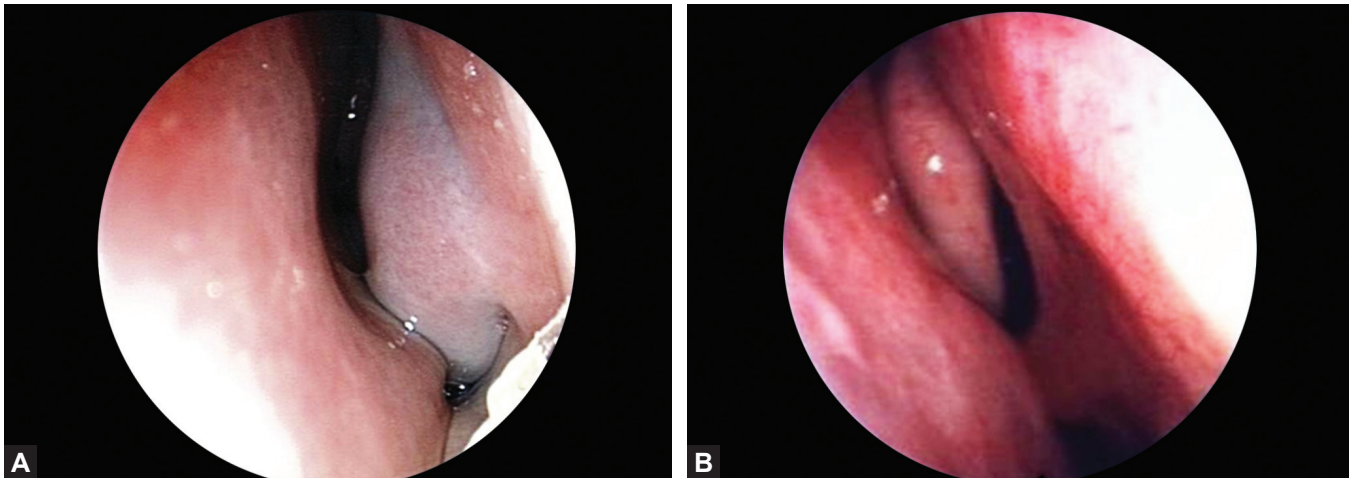


Fig. 55.4: Computed tomography (CT) scan showing low lying anterior ethmoid artery from orbit to ethmoid.



Figs. 55.5A and B: Endoscopic view showing severe septal deviation making endoscopic sinus surgery problematic.

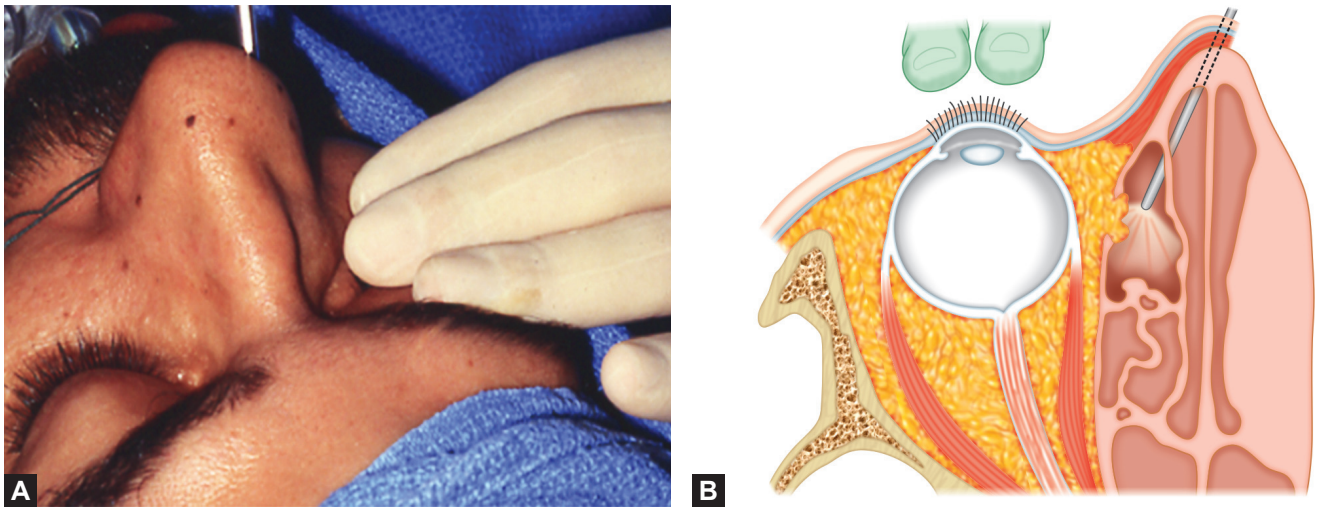
higher risk of complications. Bleeding has to be controlled during surgery or surgery should not proceed. Cocaine and pledgets with epinephrine placed before and during surgery can help improve visualization and reduce bleeding.

Operative Planning and Complication Prevention

Prior to surgery, the eyes need to be uncovered so they can be viewed by the surgeon and nursing staff during surgery. Viewing the eye during surgery may be the first sign the lamina papyracea is dehiscent and orbital hematoma is forming.

During surgery, as mentioned above, bleeding control is necessary to allow adequate visualization. Exposure is key and septoplasty is necessary if the septum obstructs visualization. Traditional or endoscopic septoplasty is very helpful toward safe visualization. If a septoplasty is not done and vision is partially obscured, the surgeon's endoscopic view is more lateral in the ethmoid increasing risk of injury to the laminar papyracea and possible orbital complications (Figs. 55.5A and B).

A simple procedure described several times before to aid in determining if the lamina papyracea is dehiscent is the Bulb Press Test.[2,4] Described in 1987, it is perhaps the most useful nonimage-guided technique helping to avoid causing any injury to orbital tissue. While viewing into the ethmoid sinus laterally, the orbit is gently pressed repeatedly (Figs. 55.6A and B). Any dehiscence, periorbita, or orbital fat will show movement of the orbital tissue. Periorbita is white and orbital fat is "greasy" yellow.



Figs. 55.6A and B: Bulb Press Test—pressing eye bulb and looking at lamina papyracea endoscopically.

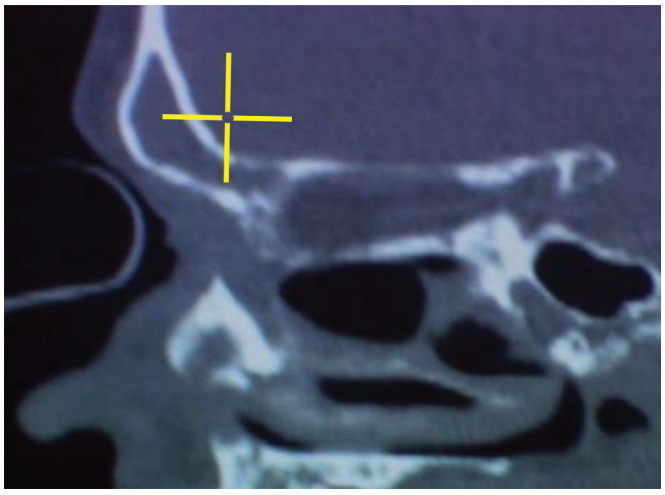


Fig. 55.7: Image guidance view showing error in calibration.

Other concerns during surgery is the use of 1:1000 or 1:10000 epinephrine for bleeding control or the use of concentrated alcohol-based liquid to keep the endoscope clean and clear. The containers holding these solutions need marking and/or the solutions colored so they are not inadvertently injected into the nose or even into the orbit. Dangerous, life-threatening arrhythmias can occur with concentrated epinephrine. The alcohol-based liquid can act as a sclerosing agent if injected into the orbit causing muscle and/or nerve damage.

If minimal bleeding occurs during superior ethmoid surgery and suddenly bleeding increases, the skull base may have been entered. Appropriate endoscopic examination is necessary to determine if this is the case.

POSTOPERATIVE CONSIDERATIONS

The recovery room staff needs to be aware of orbital or brain-related complications and their presentation. Any orbital changes noted in the operating room not requiring decompression need close observation in the recovery room to make sure significant orbital hematoma does not occur. Vision and extraocular mobility need checking. If there is any concern, evaluation by the surgeon is obtained. An ophthalmologist may help monitor the patient's vision. Any mental status change, severe headache, or unilateral clear liquid drainage is consistent with possible skull base injury and needs radiologic CT evaluation. This plan continues once patient is discharged from recovery room to home care. Clinic or emergency room evaluation needs consideration for any of these complaints day 1 or day 30.

IMAGE GUIDANCE

Image guidance is established as very useful during ESS. Indications for image guidance are listed in the American Academy of Otolaryngology-Head and Neck Surgery website among its clinical indicators grouping. However, complete reliance of image guidance may be hazardous (Fig. 55.7). If not properly calibrated and this calibration error is not picked up by the surgeon, catastrophic skull base, orbital, or vascular injury may occur. Image guidance should be used to corroborate location not dictate the surgery.[9,10] While it may seem intuitive that image guidance reduces complications, in a study by Ramakrishnan, complications in ESS with or without image guidance were

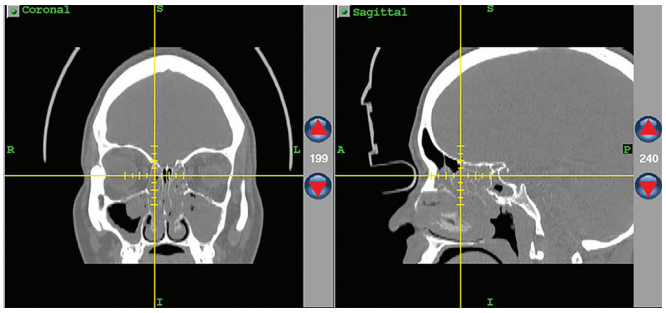


Fig. 55.8: Skull base "cushion" when performing endoscopic sinus surgery (ESS) with image guidance.

not significantly different.[11] Image guidance is used by most surgeons in more difficult ESS cases, but it is not a guarantee complications will not happen. Often times, any movement by the patient or even by the surgeon changing head position can cause calibration errors to occur. The image-guided CT scan may be inadequate. Comparing image guidance location against known anatomy is a good way to pick up calibration errors. The surgeon should allow a cushion away from the skull base or orbit. Rarely, is it necessary to remove pathology right up to skull base or orbit. This 2–3 mm "cushion" can insure against inadvertent orbital or skull base entry (Fig. 55.8).

COMPLICATION IN ESS AND THEIR MANAGEMENT

Table 55.1 lists complications that can occur during ESS. The complications are listed in four categories: orbital, skull base/brain, vascular, and others, which are a good starting point for a discussion of ESS complications.

Orbital Complications

Orbital Hematoma

There are two faces of orbital hematoma: slow and fast orbital hematoma.[12] Slow (venous) orbital hematoma can occur with bleeding into the orbital cavity due to injury of the veins lining the lamina papyracea, periorbita, or orbital fat. There is a slow leakage of blood into the orbit over hours. Eye lid swelling and ecchymosis occurs with chemosis and conjunctivitis. The eye feels firm to palpation and the pupil can dilate. If 5cc or more blood accumulates in the orbit, intraorbital pressure can increase from normal 15 to 20 mm H_2O to 50 or more. At this level, the optic nerve venous drainage can obstruct causing ischemia to the optic nerve. According to the literature, the optic nerve can

Table 55.1: Complications of ESS

Vascular injury
Carotid artery
Anterior communicating artery
Carotid cavernous fistula
Ethmoidal arteries (anterior and posterior)
Sphenopalatine artery
Septal branch of the sphenopalatine artery
Deep vein thrombosis
Orbital disorders
Blindness
Diplopia
Nasolacrimal duct injury
Nasolacrimal sac injury
Injury to Hasner valve
Orbital hematoma
Orbital emphysema
Periorbital ecchymosis
Lid edema
Anisocoria
Skull base/brain
Cerebrospinal fistula
Meningitis
Frontal lobe injury
Hyposmia, dysosmia, anosmia
Pneumocephalus
Anterior cerebral artery injury
Subarachnoid hemorrhage
Brain abscess
Death
Other
Nerve injury
Infraorbital hypesthesia
Infraorbital paresthesia
Supraorbital and supratrochlear hypesthesia
Supraorbital and supratrochlear paresthesia
Inferior alveolar hypesthesia
Inferior alveolar paresthesia
Facial disorders
Facial edema
Subcutaneous emphysema
Packing related
Displaced packing
Aspiration
Infection
Increased orbital pressure
Toxic shock syndrome
Myospherulosis
Scar tissue formation
Other
Cardiac shock
Myocardial infarction
Pulmonary embolism

only tolerate this increased pressure for 60–90 minutes before blindness occurs.[12] In most cases, accumulation of blood in the orbit is minimal, never reaching dangerous levels. Periorbita or orbital fat can be exposed or removed with no hematoma or even ecchymosis. However, intraorbital bleeding can be insidious with slow progression of symptoms and signs. Postop recovery room nurses and family cooperation is necessary to monitor this situation closely. Progressive changes and especially vision loss requires urgent or emergency treatment as will be outlined below.

Fast (arterial) orbital hematoma occurs as a result of a traumatized artery bleeding into the orbit, either the posterior (very rare) or the anterior ethmoid artery (most likely). When working superiorly in the ethmoid and frontal area, the anterior ethmoid artery is partially or totally transected at its entrance through the lamina papyracea causing bleeding in the orbit. In this circumstance, an arterial hematoma forms quickly with high pressures compressing the optic nerve vasculature. Immediate eye lid swelling, pupil dilation, chemosis, and ecchymosis develops. The eye is very firm to palpation. This is an emergency situation. The optic nerve can only tolerate these immediate high pressures for 15–30 minutes before blindness will occur.[13]

Treatment Principles: Immediate lowering of eye pressures is warranted. The easiest maneuver to try is orbital massage. By gently massaging the orbit medial to lateral or inferior to superior, blood in the orbit can be redistributed lowering pressures and softening the eye to palpation.[2,12,13] If not successful, the next procedure is a lateral canthotomy with cantholysis to achieve mechanical decompression.[2,12,13] This is a procedure that is performed by the Otolaryngologist in most cases due to the unavailability of an ophthalmologist and may be vision saving. Given the short time period for action, delays such as sending the patient for a CT scan, which is not helpful in this circumstance, should be avoided and may jeopardize vision. While the use of Mannitol or high dose steroids has been suggested as possible treatment, no data exists regarding success in this clinical circumstance. These medications are not immediate acting and will not lower pressure soon enough to avoid blindness. In this clinical scenario, it is better to act surgically then delay treatment.

Regarding the fast arterial orbital hematoma, special considerations are necessary. If lateral canthotomy/cantholysis does not reduce pressure indicating continued bleeding into the orbit, control of the anterior ethmoid artery is necessary. If it is not controlled, vision is jeopardized. An external Lynch approach is the best way to control the artery, visually with hemoclips.[2,12,13] The orbit can also be decompressed through this approach. Endoscopic intranasal approaches are difficult because of the anatomic location of the anterior ethmoid vessel. The vessel is located at the junction of lamina papyracea with the skull base. Only the most experienced endoscopic surgeon should attempt this with the Lynch procedure as backup. Minimally, the orbit should be decompressed that can be done endoscopically and may be very helpful.

Postoperatively vision needs monitoring with the assistance of an ophthalmologist. Canthotomy incisions usually close nicely without need for wound revision. External Lynch incision also heals well cosmetically. Any vision deficit is addressed with Ophthalmology for best treatment.

Blindness

Blindness during ESS occurs in several ways: (1) direct injury to the optic nerve, (2) compression of blood supply to the optic nerve (orbital hematoma), (3) vascular spasm or particle deposition in blood supply to the optic nerve.

Direct injury to the optic nerve can occur intraorbitally where instrumentation contacts or injures the optic nerve. Usually, this happens at the orbital apex, the narrowest and most complex anatomical area of the eye. Often this injury will be accompanied by signs of orbital hematoma and should be treated as noted. The patient's continued loss of vision on examination is verified by vision testing and a Marcus Gunn pupil.[13] A dehiscent optic nerve can be present in an Onodi cell located above and lateral to the sphenoid sinus (Fig. 55.9). If the Onodi cell is not recognized in preop CT scanning and entered with instrumentation, a dehiscent optic nerve can be directly injured. Signs of orbital hematoma will not appear.

Blindness due to orbital hematoma was discussed along with treatment options. Vision loss due to injections at the time of surgery is possible. Any injection of Xylocaine with epinephrine occurring in the face, nose or sinus area runs the very rare risk of vasospasm of optic nerve and vessels with blindness.[14] Injections into the greater palatine foramen are known to cause rare blindness since the injection, usually xylocaine with epinephrine, can go directly to the orbital apex causing arterial vessel contraction or spasm. Injection of nasal polyps or turbinates with corticosteroids is known to rarely cause blindness due to particulate matter getting into the eye circulation.

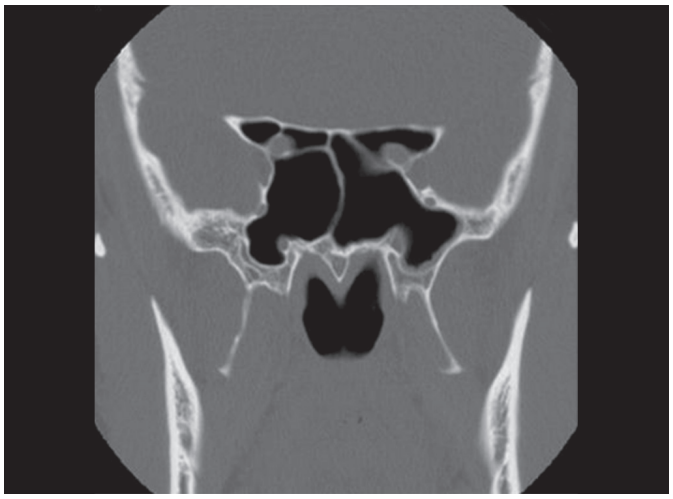
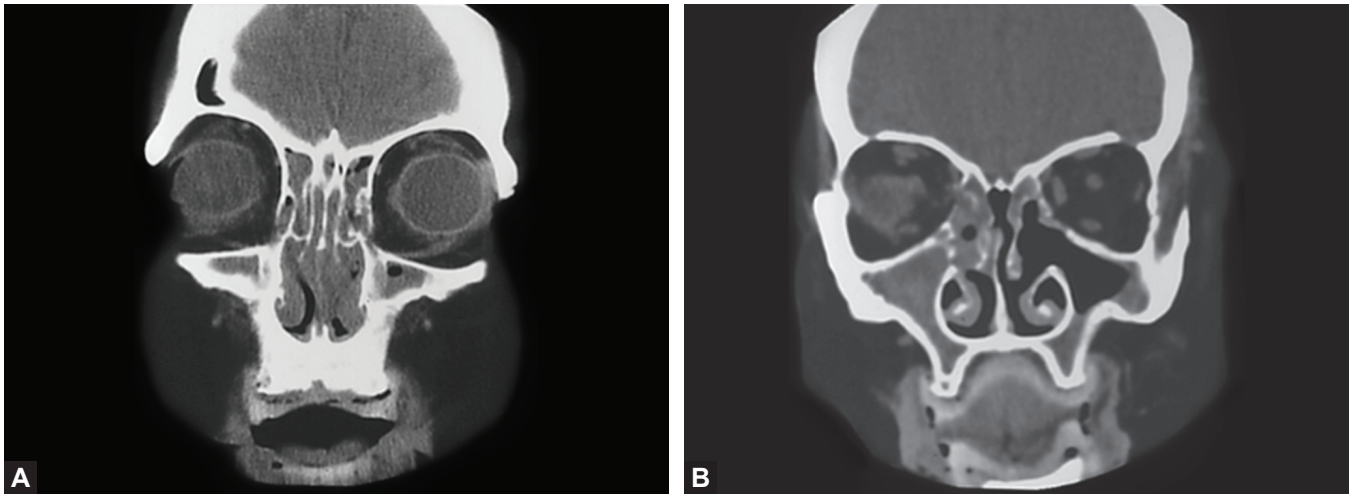


Fig. 55.9: Dehiscent optic nerve in an Onodi cell on computed tomography (CT) scan.
Courtesy: Kevin Welch, MD.



Figs. 55.10A and B: Before and after injury computed tomography (CT) scans of medial rectus muscle.

Treatment Philosophy: Direct injury to the optic nerve is not treatable and blindness cannot be avoided. Likewise, injected material causing vessel spasm or clogging with particulate matter are not treatable in most cases. An emergency ophthalmology consultation is needed in both scenarios. Only fast action in treating blindness due to orbital hematoma can reverse the process and save vision as previously noted.

Double Vision (Diplopia)

If during ESS the lamina papyracea is dehiscent, naturally or iatrogenically, there is potential for not only orbital hematoma but also eye muscle/nerve injury. When the eye muscle is injured, double vision, diplopia, occurs. The most commonly injured eye muscle is the medial rectus.[2,15] However, medicolegal case review will show that the inferior rectus, inferior oblique, superior oblique, and the lateral rectus have all been injured during ESS. It is paramount the orbit be identified during ESS, above the antrostomy. Anatomically, as the orbit narrows to its apex, the posterior ethmoids extend laterally. The medial rectus muscle is closest to the surgeon at the basal lamella attachment to the lamina papyracea, the junction between the anterior and posterior ethmoid (Figs. 55.10A and B). The lamina can be disrupted by any instrument used for ESS. With non powered instruments, the lamina and orbit are entered and injury to any muscle occurs in the orbit. This can also happen with the microdebrider. However, the most common mechanism of injury with the microdebrider is for the suction action of the instrument to pull periorbita, orbital fat, and sometimes the medial rectus muscle into the ethmoid sinus.[15] The cutting

action of the microdebrider removes orbital fat injuring the medial rectus muscle if present. With any orbital injury, orbital hematoma may also occur as discussed.

Another possibility for medial rectus or other muscle injury is the injection of medications for control of bleeding before or during surgery. The needle can puncture the eye muscle and cause diplopia. Fortunately, the diplopia is usually temporary and the muscle will recover in most cases.

Treatment Principles: It is important to note the presence of orbital fat immediately and stop the dissection. If noted quickly, the patient may avoid any evidence of orbital hematoma or eye muscle injury. The Bulb Press Test noted earlier is very helpful here.[2,4,5] Be wary of the Fat Float Test where fat floats in saline and other tissues do not. Medial rectus muscle will not float, and a negative test in this case is not an indication to safely continue with the dissection. Indeed, this scenario has happened resulting in injury to medial rectus. Injury to the medial rectus muscle can be noted in the recovery room, but changes associated with orbital hematoma may prevent adequate examination. Double vision may be noted after the patient has been discharged one or more days later. While a visit to an Ophthalmologist is indicated once double vision is noted, most ophthalmologists including oculoplastic surgeons will defer a surgical treatment until any hematoma has cleared and proper examination is performed. Even then, unless a radiological examination or eye exam indicates a bone spicule is impaling the muscle, surgical treatment is deferred. Surgical correction of a paralyzed extraocular muscle is difficult with mixed results; especially, if the muscle is transected.

Nasolacrimal Duct Injury

As noted, this injury occurs rarely today and in most cases will repair itself.[1] If treatment is necessary, open or endoscopic procedures have a high degree of success in reopening drainage.[16] On occasion, endoscopic inferior antrostomy is performed. The opening of the nasolacrimal duct needs identification prior to beginning the surgery. Usually, it is easy to identify. The need to identify the duct also goes along for the creation of a mega-antrostomy or extended antrostomy. Rarely, in anteriorly pneumatized ethmoid cells, the lacrimal sac can be exposed since it can be contiguous with these cells. Normally, the bone over the sac is hard and thick enough to prevent this from happening. The Bulb Press Test described earlier can identify the sac. If entered, observation is necessary and may not require any surgery.

Subcutaneous Emphysema

Subcutaneous emphysema can occur by pushing air through an opening in the lamina papyracea.[5] Using an AMBU bag at the end of surgery, difficult extubation with straining, or blowing the nose, causes air to enter the orbit. Swelling of the eye lids usually occurs most often on the lower lid. Palpating the area reveals a "Rice Krispies" or crinkling sensation of air trapped under the skin. Additional features of orbital hematoma may be present and are managed as previously noted. While in most cases subcutaneous emphysema stays localized to the eye and cheek, rarely the emphysema can spread over the scalp and over the chest.[2]

Treatment Principles: If orbital hematoma is present, it should be treated as outlined. Otherwise observation is all that is necessary. Within 1 week, the subcutaneous emphysema will disappear. The patient has to be mindful not to blow their nose or strain so air does not reaccumulate.

CRANIAL COMPLICATIONS

Cerebrospinal Fluid Leak

As noted earlier, while uncommon (less than 1% of ESS patients), a CSF leak is a known complication of ESS.[2,17,18] It most commonly occurs medial in the ethmoid sinus adjacent to the lateral lamella of the medial skull base where the skull base is weakest from the frontal ostia to the sphenoid sinus.[2,7] Intraoperatively, the CSF leak may be proceeded by increased bleeding at the skull base. The surgeon may then notice pulsations from the brain through the dehiscent skull base and a "wash out" sign where the clear CSF has washed away blood. Endoscopes, microdebriders, suctions and other instrumentation have been passed through the dehiscence in the brain; unfortunately, creating further injury. It is important that the CSF leak is noted as early as possible, minimizing injury. Identification can be enhanced by using Valsalva, topical or intrathecal fluorescein, and image guidance. Intravenous ophthalmic fluorescein used topically on pledgets will turn from yellow to green in the presence of CSF.

If not discovered in surgery, the patient in the recovery room or at home may experience excruciating headache or mental status changes. Because of packing, clear fluid may not be apparent. Certainly if clear fluid drainage is present, CSF leak is present until otherwise disproven. Patients may complain of a "popping" or feeling of "something moving around" in their head that could be air

or pneumocephalus. A CT scan will delineate the presence of pneumocephalus. Very rare is the tension pneumocephalus where air increasingly accumulates intracranially due to ball valving. These patients are sicker, more symptomatic, and need immediate treatment.

Treatment Principles

As soon as the CSF leak is noted intraoperatively it should be repaired.[2,18] If the surgeon is inexperienced and feels uncomfortable with repair, the patient should be sent to a colleague who can perform the repair. Provided the skull base defect is small, 1–2 cm or less, the CSF leak is repaired in most cases by placing a graft overlay on the defect after preparing the skull base for grafting with a curette or other scraping instrument. A mucosal graft from the septum or middle turbinate is easy to harvest and works well. Temporalis fascia works well. Alloplastic tissue of dura or regenerated skin tissue matrix has also been used successfully. The graft is covered with a fibrin glue material and Gelfoam. A poly-vinyl alcohol sponge holds everything in place and is removed in 7–10 days. A large defect in the skull base is bridged with septal bone, cartilage, or turbinate bone. An intralay tissue graft is used by some surgeons for repair with equal success but requires more technical skill. Most CSF leaks will heal nicely treated in this fashion.

Intrathecal fluorescein or lumbar drains are not necessary in treating acute visualized CSF leaks. Topical fluorescein will usually suffice to identify the leak. Elsewhere in this book is a discussion more specific to the CSF leak and its overall management. Of course, any patient with a complicated CSF leak such as the tension pneumocephalus with mental status changes or hemorrhage requires consultation with a neurosurgeon for best management.

Brain Injury

Any time an instrument is placed past the skull base, brain injury can occur. While meningitis is a possible complication of CSF leak; it, in truth, is very rare. This is despite the fact the nose and sinus areas are not the cleanest environment. However, should meningitis occur, it can be devastating. Bordering on the skull base is the frontal lobe of the brain and the cerebral vessels. The frontal lobe has been injured in ESS (Fig. 55.11). The cerebral vessels, usually the anterior cerebral, have been injured. Aneurysms have developed of the anterior cerebral artery.

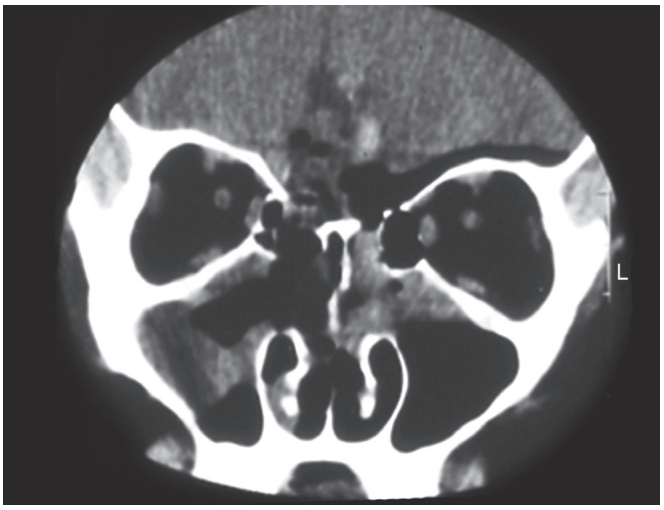


Fig. 55.11: Computed tomography (CT) scan of catastrophic complication and front lobe injury.

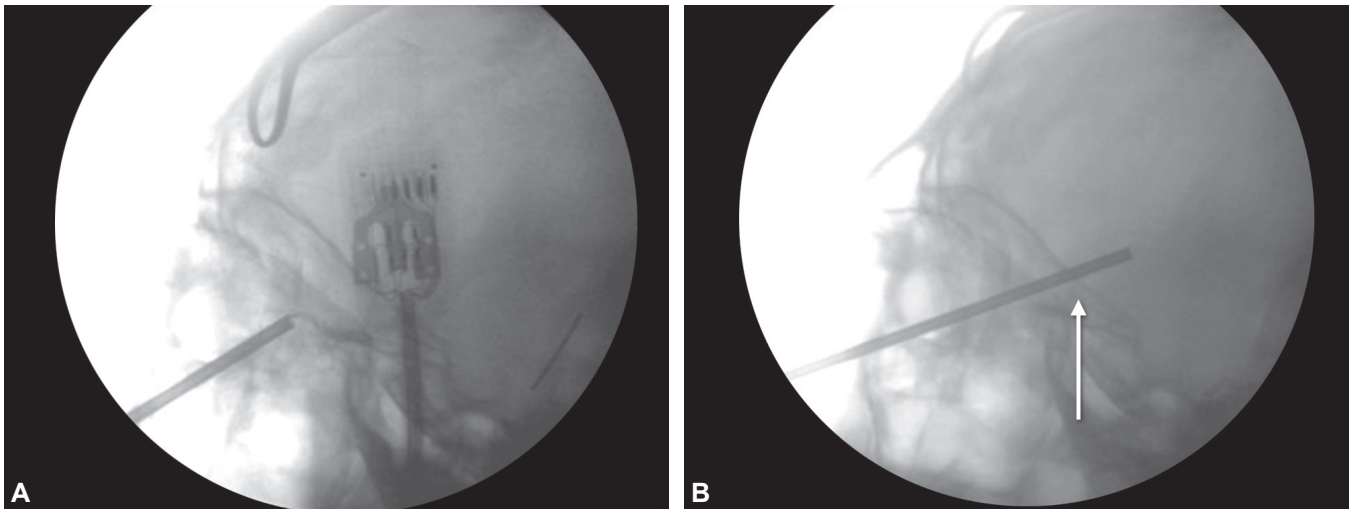
Subarachnoid hemorrhage has occurred with marked disability and death. Endoscopes have been placed intracranially with resultant brain damage (Figs. 55.12A and B). Microdebriders have removed significant brain tissue again with hemorrhage, disability, and death. Cerebellar herniation due to increased intracranial pressure due to meningitis or cardiac shock related to ESS resulting in cortical blindness is possible.[2]

Treatment Philosophy

Any intracranial injury or increased pressure requires management by Neurosurgery and ENT. These complications are very tough management problems often resulting in disability and sometimes death.

Vascular Complications

The most common complication during or after ESS is bleeding.[2] Increased bleeding during ESS compromises visualization and increases the risk of complication. The patient needs to be prepared preoperatively as much as possible to reduce bleeding. Highly inflamed infected sinuses should be treated with antibiotics and steroids prior to surgery reducing inflammation and decreasing bleeding. In nasal polyp surgery, especially in revision surgery, preop medication to reduce inflammation may be helpful.[19] Selection of anesthetic technique such as TIVA versus inhalation does reduce bleeding particularly if mean blood pressure levels are kept below 100 mg Hg.[20] Deliberate high and low CO_2 levels may also have an effect on intraoperative bleeding.[21] During surgery, bleeding



Figs. 55.12A and B: Endoscope located intracranially during endoscopic sinus surgery (ESS).

sometimes can be difficult despite the best preoperative and perioperative preparation.[22] Unsuspected underlying bleeding problems may rear their head. Surgery in these cases needs to stop and the cause determined. Bleeding may be due to medications the patient took either prescription or over the counter such as certain holistic medications and even vitamins. Platelet or coagulopathic disorders may emerge.

As noted in the beginning of this chapter most significant intraoperative or postoperative hemorrhage comes from two arteries and their arterial branches—the anterior ethmoid and sphenopalatine arteries.[2] Most often, during surgery, trauma to one of these arteries is indicated by pulsatile bleeding characteristic of an artery or brisk bleeding. Postoperatively, significant bleeding can occur up to 5 or 6 weeks after surgery. Bleeding is brisk, posterior in location making it difficult to control, and a very traumatic experience for the patient, family and emergency room staff.

Treatment Philosophy

Visualization is key to safe ESS. If bleeding cannot be controlled to adequately visualize, surgery should be stopped, the patient evaluated and scheduled for another day.

Any arterial bleeding occurring during surgery can be controlled with monopolar or bipolar cautery. Using monopolar cautery on the skull base especially in an area of dehiscence may cause a CSF leak. If the orbit is dehiscent near the medial rectus, monopolar cautery could theoretically cause injury, but this has not been reported. Any delayed hemorrhage should be treated by the endoscopic surgeon and not by posterior packing alone. On occasion, in clinic, a bleeding vessel is found, cauterized and packed with absorbable packing with or without Merocel. Any patient with vigorous hemorrhage requiring packing done in an emergency room should be taken back to surgery, cauterized, packed lightly, and discharged. The posterior septal artery and sphenopalatine vessels are the etiology. There is increased risk of bleeding if the middle turbinate was sacrificed and the branches from the sphenopalatine foramen not controlled at surgery.[2] An article looking at patient comfort, cost, and outcomes in posterior epistaxis for any reason argued strongly to treat posterior epistaxis endoscopically and avoid posterior packing and prolonged hospitalization.[23]

Carotid Artery Injury

The carotid artery sits at the posterior lateral wall of the sphenoid sinus. What is cause for concern is that the artery is dehiscent in up to 20% of patients. As noted earlier, the anterior wall of the sphenoid sinus in the normal size adult is 7cm, and the back wall 8 or 9 cm.[2,4] The carotid artery has been injured where distance relationships were not measured. The surgeon in these cases thought the sphenoid was actually the posterior ethmoid sinus. In an attempt to erroneously open the anterior wall of the sphenoid sinus that was actually the posterior sphenoid sinus wall, the carotid was injured. Removing any septa in the sphenoid sinus with grasping forceps is hazardous because often the sphenoid septa are attached to the

sphenoid wall at the carotid artery. Limited dissection is done in the sphenoid sinus to prevent entering a dehiscent carotid artery. The use of suction and irrigation clears most sphenoid pathology. If ESS surgery is contemplated in the sphenoid sinus, packing should be placed in the nasopharynx or the oral cavity so if bleeding does occur from the carotid it can quickly be controlled.

Treatment Philosophy

Obviously, the hallmark of carotid artery bleeding is remarkable hemorrhage. The first movement by the surgeon must be to pack off the nose anteriorly.[24] Hopefully, packing was placed preoperatively in the nasopharynx or oropharynx. This will control the hemorrhage. Normal blood pressure must be maintained to provide adequate brain circulation. If the patient is stable, the patient should be moved to the embolization suite for angiography and the placement of coils or sponges in the carotid artery if cross brain circulation is present on angiography.[24] If there is no cross brain circulation, the chances of stroke with embolization is very high. The neurosurgeon and invasive angiographer have to decide if a "trapping" procedure will work or embolization should proceed. An unstable patient in the operating room may need an intraoperative angiogram with embolization. If the carotid embolization is successful, packing can be safely removed within 7–10 days. Quick action as described above can save a patient's life with often no neurological sequelae.

OTHER COMPLICATIONS OF ESS

Although not common several other complications of ESS have occurred. Table 1 lists several not already discussed. These will be touched upon for completeness sake.

Facial numbness can occur and is related to injury to the inferior orbital nerve in the maxillary sinus.[2] Polyps or inverted papilloma removed superiorly in the maxillary sinus can traumatize the nerve; especially, if dehiscent or cautery is used to control bleeding. The numbness is usually permanent but over time the area of numbness may decrease.

Facial pain also is related to this same nerve injury.[2] Rarely, when an inferior antrostomy is performed endoscopically, pain from the branches of the second division of the 5th nerve are traumatized and cause pain. Again over time this pain diminishes and is tolerated. Of note, it is well known that in performing a Caldwell–Luc surgery, chronic numbness and/or pain may occur if the infraorbital nerve branches are traumatized when the maxillary sinus is entered.[25]

Anisocoria (dilated pupil) can happen and is quite disconcerting to the surgeon. If there are no signs of orbital entrance or orbital hematoma, the dilated pupil is most often caused by local anesthesia injected into the orbit and will resolve on its own. Persistent anisocoria is due to damage to the nerve supply to the pupil from hemorrhage or manipulation by instrumentation. This usually resolves with resolution of an orbital hematoma.[26]

Packing related complications are possible. A forgotten non absorbable packing or stent causing recurrent infection does happen. Nonfixed packing or stents can be aspirated and require removal from the trachea or bronchus. Packing or stents can be pushed up into sinuses and cause obstruction and infection. Over packing when the lamina papyracea is dehisced or decompressed can increase orbital pressure causing orbital pain, rarely vision loss. Simply reducing or removing the packing handles the problem. Toxic shock syndrome can occur with or without nasal packing if the patient has the toxic shock staphylococcal bacteria TSS 1 present. Large nasal crusts can act like packing harboring the bacteria. Patients present with high fever, hand rash, and mental status changes. Treating with antistaph IV antibiotics and removing the packing or crusting is usually successful treatment.[27]

Myospherulosis (fungal sinusitis related to packing) can occur if petroleum-based ointment is used to coat packing or is placed in the nose. It is not commonly seen today but is treated with debridement, irrigations, and observation.[28]

Synechia or localized scarring is not a complication of ESS if the patient does well without infection. Scarring causing persistent or recurrent sinusitis is not a complication of ESS but a failure of healing, technique and debridement. Patients failing medical therapy in these cases require revision ESS.

Deep vein thrombosis and pulmonary embolism can occur even when an ESS is done as an outpatient procedure.[2] Obviously, any patient noting calf pain and swelling requires diagnostic testing. Pulmonary embolism is an acute respiratory event with shortness of breath or respiratory emergency. Again, diagnostic studies are done to make the diagnosis and anticlotting drugs such as Heparin and Coumadin are used for treatment.

Any patient who has received radiation to the brain for a brain tumor and has evidence of brain necrosis

should be considered very carefully for head and neck surgery especially at the skull base. Surgery can accelerate the brain necrosis causing the patient to not wake up from anesthesia resulting in the need for major workup, and causing family and MD consternation. We have experienced three cases: two sinuses and one temporal bone. With neurosurgical assistance without need for surgery, these patients awaken from their coma and can do well. But it is a scary, unnerving situation.[2]

Open (Empty) Nose Syndrome

Since the initial publication from the Mayo Clinic by Kern et al, this diagnosis has been very controversial and problematic.[29] Essentially, the theory is that the nasal physiology is altered due to removal of inferior and middle turbinates along with extensive sinus surgery. The nose is open to perform its function. Patient symptoms include nasal obstruction, ear symptoms, loss of smell, bad smell, headache or nasal pain, chronic drainage, voice change, increased drainage, crusting or infection "uncomfortable" nose or dry nose, and vision changes. Most of the symptoms are subjective and objective documentation is difficult. While atrophic rhinitis with marked crusting and infection may be present, it is rarely seen. It is of interest that there are certain schools around the world that recommend in patients with extensive sinus disease with or without polyps that the nose should undergo "nasalization" with radical ESS. These groups have not reported postoperative symptoms consistent with open nose syndrome.[30] A good rule to follow is to avoid removing both inferior and middle turbinates at sinus surgery. This will greatly reduce the possibility of empty nose syndrome.[31]

Open nose syndrome is difficult to treat requiring local care with irrigations and topical medications. These patients are often distraught and may require psychiatric evaluation, counseling and medical therapy. Attempts at reconstructing the nose by placing grafts to act like turbinates are rarely successful. Open nose syndrome is a very tough problem to contend with and provide treatment for.

PEDIATRIC ESS COMPLICATIONS

After 1985, both adult and pediatric ESS were performed frequently. However, pediatric ESS was much less aggressive targeting the anterior ethmoid and maxillary sinuses.[32] In the age groups of 1–10 years, the sphenoid and frontal sinuses are not yet developed. As years went by, pediatric sinusitis began to mirror more chronic otitis with effusion with children getting better without surgery as they got older. Added to that knowledge was the success of adenoidectomy, clearing up over 50% of chronic sinusitis. As a result today, pediatric ESS is performed sparingly. Given the above, complications in pediatric ESS are seen minimally. CSF leak, orbital hematoma, and blindness have occurred but very rarely (probably in single digits) compared to the adult ESS patients. The surgeon should not become complacent in pediatric ESS. There are children and young adults with marked allergy and asthma, cystic fibrosis, and immunodeficiency who require aggressive ESS and are higher risk of complications. Case in point is the child with hypoplastic maxillary sinus where the uncinate process is contiguous with the orbit. These patients with maxillary sinusitis are at much higher risk of orbital injury.[2] So, it is just as necessary in this pediatric and adolescent population to use the same skills and preparation for ESS as in the adult to avoid complication.

Balloon Sinuplasty Dilation

Beginning in 2006, the technology of balloon sinuplasty emerged as an optional tool for the performance of ESS. Since balloon dilatation technology does not incorporate powered instrumentation or other cutting tools, the risks of complications are much lower than in standard ESS. In fact, not one skull base or orbital injury has been attributed to balloon sinuplasty dilatation alone. However, balloon sinuplasty and standard ESS ("hybrid" surgery) runs the same risks of complications as standard ESS. In short, the literature shows balloon sinuplasty is a safe surgery. Even then heightened awareness is always required, especially, with hybrid ESS.[2]

POWERED ESS

Powered instrumentation has revolutionized ESS and skull base surgery allowing the surgeon to go places in the skull base not previously thought possible. The drawback of powered instrumentation, as we saw in our discussion of microdebrider related orbital injuries, is that, if placed in the wrong area, powered instrumentation can cause a lot of injury in a very short period of time, literally seconds. This statement also applies not only for microdebriders but also drills, some of which can reach 50000 rpm or greater. Bone can be removed much more quickly. Skull base dehiscence with CSF leak has occurred along with vascular injury to the carotid artery and orbital

injury. Great care is necessary when using any powered instrument. The ESS complications are the same as with nonpowered instruments.

INCIDENCE OF COMPLICATIONS OF ESS

The overall incidence of complications in ESS was reported at 29% in 1987.[1] Major complications were reported at 8%. Two years later in 1989, the overall evidence was reduced to 9.3%.[2] May and Levine reported an overall complication rate at 8%.[33] Major complications were reported in 0.85% (most common CSF Leak) and minor complications at 6.9%. This is compared to a literature search of complications that showed an overall major complication rate of 5.4% (overall 6.5%). Keerl and Stankiewicz reported on the incidence of complications during the first 300 endoscopic sinus procedures of 55 surgeons (1500) performed.[17] Noted was a marked decrease in complications with surgical experience. Dural injury was more common during patient from surgery 1 to 30. Orbital injury was most common from surgery 30 to 180. Experienced surgeons doing more difficult cases had more serious complications. The learning curve is achieved at 100 and above surgeries. Stankiewicz in his summary of complications with ESS after 25 years reported an incidence of 0.86% for CSF leaks, 0.06% for orbital complications, 1.2% for hemorrhage, along with an overall complication rate of 3%.[2]

Ramakrishnan looking at a large computer database of 62823 patients found a nationwide incidence overall complications of 1%.[11] Orbital complication with and without computerized guidance was 0.07%, CSF leak at 0.17%, and hemorrhage with transfusion 0.76%. Of interest there was no statistically significant improvement in the complication rate in patients undergoing image-guided computerized sinus surgery. Orbital injury risk actually worsened (0.06% vs. 0.14%).

In summary, major complications of CSF leak, orbital hematoma, and major vessel injury occur in much fewer than 1% of patients. Overall complication rates are reduced below 5%. Any discussion of complication risk with patients should not only take these numbers into consideration, but also the personal experience of the surgeon. The use of image guidance does not guarantee complication free surgery. Constant vigilance, preparation, anticipation, and knowledge of anatomy are key to preventing complications.

CONCLUSION

Complications during and after ESS can and do occur even today with extensive experience using surgical techniques and enhanced technology. Proper surgical planning, preparation, technique, visualization, and instrumentation are necessary to avoid complications. However, even in the best hands, in difficult cases, with image guidance, complications will occur. Immediate recognition in these cases, can allow for treatment, reversing or minimizing possible injury to orbit or brain.

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SECTION 10

Endoscopic Skull Base Surgery

CHAPTER

56 Endoscopic Surgery of the Sella and Suprasellar Region

Osaama H Khan, Roheen Raithatha, Vijay K Anand, Theodore H Schwartz

INTRODUCTION

The world of brain tumor surgery has changed dramatically in the past century and is continually evolving. Neurosurgical oncology has been transformed by the capacity to do minimally invasive procedures. These techniques have changed our ability to do precise and safe surgery for brain tumors in complex areas. Perhaps the most successful application of a minimally invasive approach is the use of the endoscope in resecting pituitary tumors.[1,2] Herein, we describe an overview of the role of endoscopic endonasal surgery in the management of sellar and suprasellar tumors.

HISTORICAL PERSPECTIVES

The first endoscopic sinonasal examination was performed by Hirschmann in 1901 and the first surgery performed in 1903 for chronic sinus inflammation.[3,4] By the middle of the 20th century, the optical improvements described by Harold Hopkins and, subsequently, implemented by Karl Storz heralded the era of modern endoscopy. His medical instruments company in Tuttlingen, Germany, rapidly grew and integrated endoscopy into all fields of medicine.[5,6] By the early 1980s, endoscopy became an integral part of inflammatory sinus surgery, and physicians began to expand its application to other areas of sinus and skull base pathology. The extension of endoscopic technique past the sinus walls to access intracranial lesions was logical and natural.[3,7]

While intracranial approaches to the sellar region were being developed, several surgeons were seeking alternate routes to the pituitary gland. By 1910, the transnasal approach to the pituitary was becoming a viable option, and in June of that year Oskar Hirsch and Harvey Cushing performed two seminal transnasal operations on two different continents. Hirsch utilized a submucosal septal dissection with a traditional nasal speculum and a transethmoidal route to reach the sella.[8] Cushing performed a submucosal, sublabial approach to the sella via the sphenoid sinus.[9] In 1967, Hardy began to use the operating microscope for pituitary surgery and developed a set of instruments specifically designed for transsphenoidal microsurgery.[10]

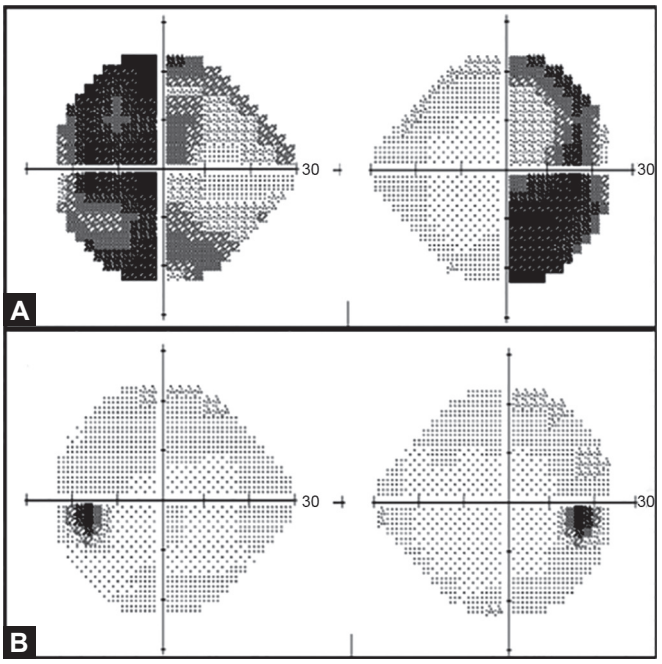
As endoscopy gained popularity among otolaryngologists performing sinus surgery, it was eventually adapted to transsphenoidal neurosurgery. The first neurosurgeon to explore the sella with the help of the endoscope was Guiot in the 1960s.[9,11,12] However, it was not until the 1990s that neurosurgeons began to actively implement endoscopy in sellar surgery. Yaniv and Rappaport reported on their experience with a combined microscopic and endoscopic method, using the endoscope to expose areas of the sella that are hidden from the limited line of sight of the microscope.[13] Cappabianca, with multiple associates, popularized the exclusively endoscopic transsphenoidal approach, obviating the need for the microscope. The last two decades have focused on development of instrumentation designed specifically for endoscopic pituitary surgery and on the adaptability of endoscopic transsphenoidal surgery for the treatment of a broad spectrum of skull base lesions.

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

Clinical presentation can be as benign as headaches but other symptoms are usually dependent on the location of the pathology. For example, lesions of the planum sphenoidale or tuberculum sella will likely present with visual changes, a pituitary adenoma can present with endocrinopathies whereas cavernous sinus masses would present with cranial nerve deficits. For this reason, a series of examinations and investigations are recommended prior to surgery. These include neurological, neuroendocrinological, neuro-ophthalmological, neuroradiological, and/or neuropsychological assessments. The rationale for including neuropsychological examination prior to surgery is that the basal forebrain structures and the medial temporal lobes may be affected after treatments, and hence it is prudent to determine, if possible, the preoperative neuropsychological status. This is especially recommended in young children who may be candidates for radiation therapy at a later stage.

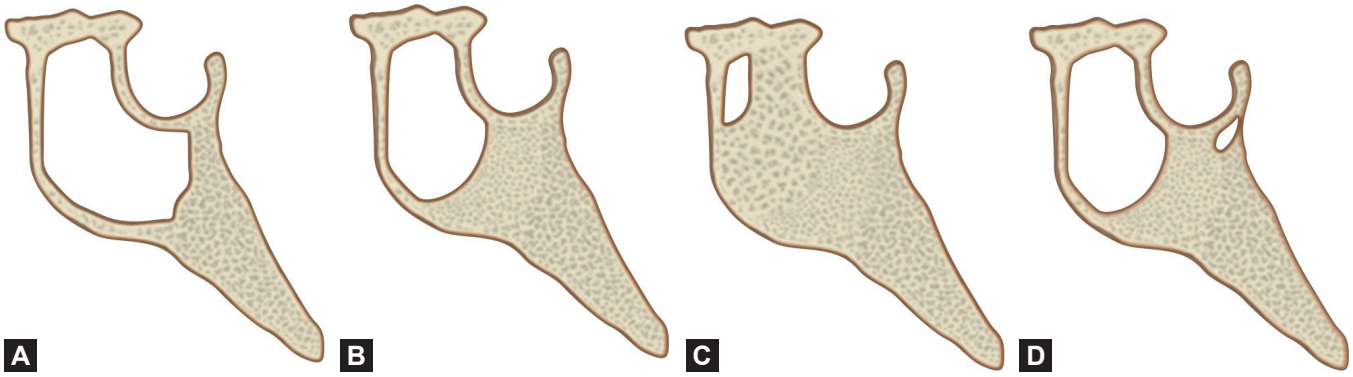
All lesions in the sellar or parasellar region require an endocrine evaluation to determine if the lesion is a secretory pituitary adenoma and, if so, what type of hormone is oversecreted. Also, even if the lesion is not a pituitary adenoma, a comprehensive endocrine evaluation will assess the pituitary function and whether any hormonal replacement is required. At our institution, we perform pre and postoperative endocrinological evaluation with free cortisol, ACTH, free thyroxine, thyroid-stimulating hormone (TSH), prolactin (PRL), growth hormone (GH), insulin growth factor-I (IGF-I), testosterone, estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) to assess for endocrinological derangements. The diagnosis of a prolactinoma is made based on serum PRL levels of >150 ng/mL in combination with typical clinical symptoms.[14] In patients with a prolactinoma, endocrinological remission is defined as postoperative PRL levels of <20 ng/mL in females or <15 ng/mL in males. The diagnosis of Cushing's disease is based on either abnormal 24-hour urinary-free cortisol or abnormal results on low-dose dexamethasone suppression tests, defined as failure of 1 mg of dexamethasone to reduce plasma cortisol levels to < 1.8 mg/mL the next morning.[15,16] The diagnosis of acromegaly is based on abnormal basal fasting levels of GH and IGF-I.[17]

A formal neuro-ophthalmological examination is essential in all patients. The examination includes visual field testing (perimetry), both to confrontation and with Goldmann perimetry and/or semiautomatic perimetry. The classic bitemporal hemianopsia is found in chiasmatic compression (Figs. 56.1A and B). Early compression may lead to upper quadrantic defects. This results from inferior chiasmal fiber compression. Evaluation of visual acuity via a Snellen chart with and without correction is essential. Fundoscopy must be undertaken to evaluate the presence of optic nerve atrophy. Extraocular movements should be documented, especially in tumors extending into the surrounding cavernous sinus.



Figs. 56.1A and B: (A) Preoperative Humphrey visual field testing demonstrating bitemporal hemianopsia secondary to optic chiasm compression by tumor. (B) Postoperative Humphrey visual field testing in the same patient demonstrating resolution of the visual field deficits.

Computed tomography (CT) images provide important information about the bony anatomy of the skull base, paranasal sinuses, and sphenoid sinus pneumatization (Figs. 56.2A to D). Currently, magnetic resonance imaging (MRI) is the modality of choice for the diagnosis and characterization of a pituitary lesion. The standard protocol for MRI of the pituitary and parasellar region consists of sagittal T1- and T2-weighted images performed with and without intravenous contrast.[18] Contrast enhancement may differentiate the adenoma from the displaced pituitary gland, may detect cavernous sinus invasion, appreciate narrowing of the intracavernous internal



Figs. 56.2A to D: Sphenoid pneumatization. (A) Sellar, (B) Presellar, (C) Conchal, and (D) Postsellar.

Table 56.1: Pathology of sellar and suprasellar region

Abscess
Aneurysms
Arachnoid cysts
Astrocytoma – low and high grade
Cavernous sinus thrombosis
Craniopharyngiomas
Clival neoplasms – chordoma, chondrosarcoma
Dermoid tumor
Epidermoid tumor
Germ cell tumors
Hypothalamic hamartomas
Lymphoma
Meningioma
Metastasis
Optic pathway glioma
Pituitary adenoma (micro- and macroadenomas)
Pituitary apoplexy
Rathke's cleft cyst
Schwannoma
Sphenoid sinus neoplasms

carotid artery (ICA), and is helpful in the differential diagnosis of sellar and parasellar lesions. Angiography may be indicated preoperatively if carotid artery compromise is suspected or the functional integrity of the circle of Willis requires assessment. CT or MR angiography generally provides sufficient information about the vascular anatomy for surgical planning.

COMMON PATHOLOGIES

Table 56.1 lists the differential diagnosis for sellar and suprasellar lesions.

Pituitary Neoplasms

Pituitary adenomas account for 25% of all intracranial tumors and are the most common lesion arising in the sellar region.[19] Interestingly, they are present in approximately 16.9% of the general population.[20] Morphologically, adenomas are classified based on size, with lesions 1 cm or greater referred to as macroadenomas and lesions smaller than 1 cm referred to as microadenomas. Classification is also based on hormone secretion—functional or nonfunctional adenomas. PRL producing adenomas are the most common type. One-third are not associated with hypersecretory syndromes; of these, the majority produce but do not secrete the gonadotropins FSH and/or LH. GH or adrenocorticotropin hormone (ACTH) producing adenomas each account for 10–15% of pituitary adenomas and TSH adenomas are rare.

Prolactinomas

Hyperprolactinemia is among the most common of pituitary disorders and accounts for 30–60% of pituitary tumors.[21] Physiological hyperprolactinemia is seen with physical and emotional stress, pregnancy, nipple stimulation, and after sexual orgasm. Iatrogenic elevation occurs by antagonizing dopamine action with such medications such as antiemetics, antidepressants, antipsychotics, and narcotics. The clinical findings, regardless of gender, can be associated with anxiety, depression, fatigue, emotional instability, and hostility.[22,23] Women of reproductive age include amenorrhea, galactorrhea, infertility, seborrhea and hirsutism. Low estrogen can result in loss of libido, and long-lasting effects include osteopenia. In men, the most common presentation is with loss of libido and impotency and less commonly with oligospermia and hypogonadism. Galactorrhea and/or gynecomastia present in 15–30% of male patients.[24]

Treatment goals are dependent on acuity and cause of presentation with the ultimate goal of normalization of PRL levels. Patients presenting with noniatrogenic hyperprolactinemia are usually treated medically with dopamine agonists to normalize serum levels but also to control tumor size and/or growth. A systematic review of the use of cabergoline and bromocriptine for prolactinomas showed that cabergoline was more effective at normalization of hyperprolactinemia and was associated with significantly less adverse events.[25] Those requiring surgery have either failed medical treatment or developed major adverse effects induced by all of the dopaminergic agonists. There still remains some controversy as to the use of cabergoline given the long-term adverse effects when a number of surgical series report remission rates of 85–89%[26-28] with recurrence rates of 18.7%.[29]

Acromegaly

Acromegaly is a disease of chronic overproduction of GH. The consequences of GH oversecretion are numerous and include, but not limited to facial changes (large lips, tongue, skin changes), laryngeal hypertrophy (low voice), bony hypertrophy (prognathism, thick skull, jaw, hands, cervical spine stenosis), hypertension, cardiomyopathy, barrel chest, high adrenocorticoid output, and chronic renal volume increase. Acromegaly is diagnosed by clinical features, an elevated serum IGF-1 level, and a serum GH level that does not decline to < 1 ng/mL after oral glucose (75 or 100 g). The definitive test for acromegaly is the GH response to an oral glucose challenge (oral glucose tolerance test or OGTT). The test must be performed correctly to interpret the results. Baseline serum glucose and GH are measured, the patient drinks a glucose solution (75 or 100 g), and the serum glucose and GH levels are measured every 30 minutes for 2 hours. The current guideline for a normal response is a serum GH level of < 1 ng/mL. Cardiac disease is the most important cause of morbidity and mortality in acromegalic patients.[30,31] This is followed by respiratory disease, with upper airway obstruction (obstructive sleep apnea) affecting up to 70% patients.[32]

Surgery remains the first-line therapy.[17] Whether microscopic or endoscopic, the surgical techniques are the same as with other adenomas. Remission rates vary between 46% and 85%, with microadenomas 75–100% and macroadenomas 50–80%.[33-36] Intraoperative biochemical testing to determine remission during resection has been employed in some centers, with successful measurement of intraoperative GH levels as a guide to remission.[37]

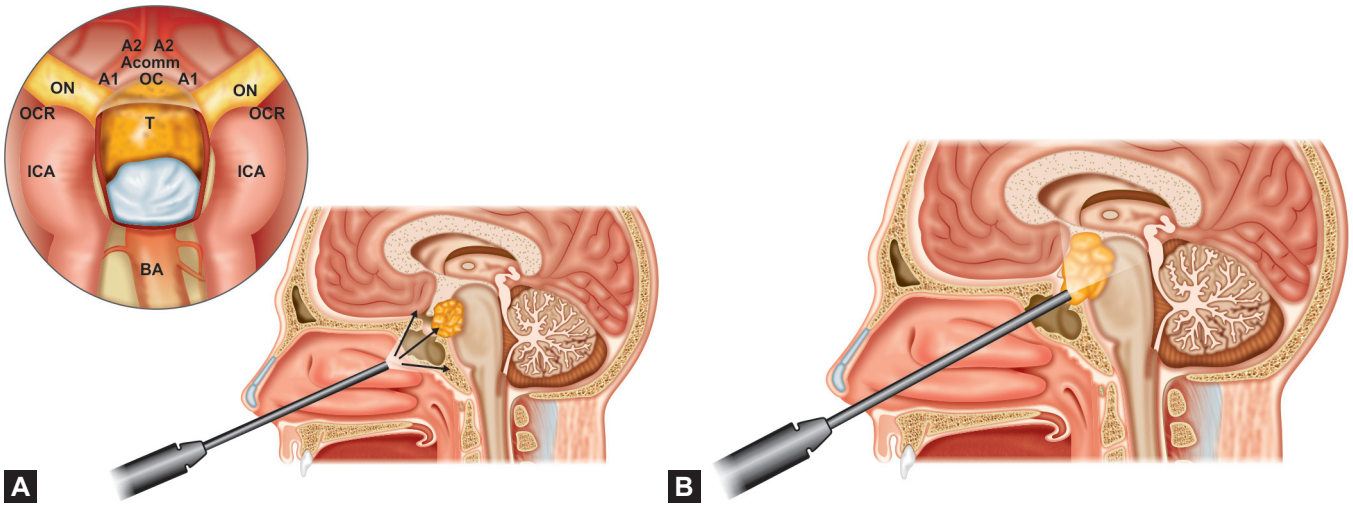
Cushing's Disease

Cushing's disease specifically results from the unregulated hypersecretion of ACTH by a pituitary adenoma and consequent hypercortisolism. Excess cortisol secretion was first described by Harvey Cushing in 1912.[38] Systemic hypertension is among the most common manifestations of Cushing's disease. As many as 80% of patients with Cushing's disease have systemic hypertension and 50% of untreated patients have severe hypertension with a diastolic blood pressure > 100 mm Hg. Weight gain, centripetal obesity, fat deposits over the cheeks and temporal regions, giving rise to the rounded "moon-facies", are commonly observed in Cushing's disease. Glucose intolerance occurs in at least 60% of patients with Cushing's disease, with overt diabetes mellitus present in up to one-third of all patients.[39] Many patients with Cushing's disease report depression, memory loss, generalized weakness, and a myopathy of the proximal muscles of the lower limb and the shoulder girdle.

Consistent overproduction of cortisol is demonstrated by three types of screening tests: Elevated 24-hour urine-free cortisol (preferably measured by tandem mass spectrometry), loss of circadian rhythm with elevated nighttime salivary cortisol levels, and failure of the serum cortisol to decline to <1.8 μg/dL at 8 AM after ingestion of dexamethasone at 11 PM the previous night.[15] Because approximately 50% of patients with a pituitary adenoma causing Cushing's disease have no visible lesion on MRI, it is occasionally not sufficient to recommend pituitary surgery. The inferior petrosal sinus sampling (IPSS) study is the most precise method to determine if the source of ACTH is the pituitary gland and to exclude ectopic ACTH syndrome. This test involves comparing the central (petrosal sinus, left and right) and peripheral (inferior vena cava) ACTH levels before and after the administration of corticotropin-releasing hormone (CRH). A ratio of the basal central to the peripheral ACTH level of >2 or a CRH-stimulated ratio of >3 indicates a pituitary etiology. Definitive management with surgery remains the first-line therapy.[40] Remission rates from combined microscopic and endoscopic series range from 56% to 86%.[26-28,41-44]

Nonfunctioning Adenomas

Approximately 25% of pituitary adenomas are clinically nonfunctioning. Although their presentation is usually



Figs. 56.3A and B: (A) Sagittal illustration demonstrating the endoscopic, endonasal, extended transsphenoidal surgical corridor with possible transtuberculum/transplanum, transsellar, and transclival approaches. Inset demonstrating the endoscopic view of a sellar/suprasellar tumor (T) after bony removal from the sella, tuberculum sellae, and planum sphenoidale. A1 segment anterior cerebral artery (A1), A2 segment anterior cerebral artery (A2), Anterior communicating artery (Acomm), basilar artery (BA), internal carotid artery (ICA), optic chiasm (OC), Opticocarotid recess (OCR), and optic nerve (ON). (B) Sagittal illustration demonstrating the utility of an angled endoscope for visualization of tumor that extends to the third ventricle.

visual, they may present with panhypopituitarism, headache, or apoplexy. The absence of biochemical criteria for remission requires a radiographic estimate of degree of resection and introduces a degree of subjectivity. Gross total resection (GTR) ranges from 66% to 93 %.[26,28,42]

Craniopharyngiomas

Craniopharyngiomas account for approximately 3%[45] of intracranial tumors and approximately 6–8% of pediatric brain tumors.[46] Craniopharyngiomas can be classified as being sellar in origin, prechiasmatic, or retrochiasmatic. Craniopharyngiomas occur in the basal forebrain region, and the important relevant regional neuroanatomy that must be appreciated and preserved where possible includes the pituitary gland and stalk, the hypothalamus, the intracranial carotid artery, the A1 and A2 segments of the anterior cerebral artery, the M1 branch of the middle cerebral artery, and upper cranial nerves I–III (Figs. 56.3A and B).

A variety of open and minimal-access surgical techniques have been developed to reach these primarily midline tumors. Open skull base techniques use an approach via a lateral or subfrontal route and must traverse cranial nerves and vascular structures before the pathology is encountered.[47] A ventral, midline approach avoids cranial nerves or major vessels, and approaching the tumor from below allows it to fall into the surgical field during dissection, which potentially allows better visualization of the tumor interface with the hypothalamus and undersurface of the optic chiasm. Partly as a result of these reasons, transsphenoidal microscopic resection of intrasellar and subdiaphragmatic lesions has been associated with lower morbidity than open transcranial approaches.[48]

The endoscopic endonasal approach for craniopharyngioma resection was first reported by Locatelli et al.[49] In this study, five pediatric patients with recurrent cystic craniopharyngiomas were successfully treated without recurrence at 48 months of follow-up. The authors found this technique particularly useful in creating a drainage tract into the sphenoid sinus. The primary obstacles to effective endoscopic exploration were later identified to be early descent of the suprasellar cistern, intracavitary bleeding, and a small sella.[50]

Nevertheless, endoscopic exploration was recommended at least as an adjunct to most transsphenoidal surgery. As the primary approach for craniopharyngioma resection, the endonasal endoscopic technique has been found to be safe and effective, particularly for retroinfundibular lesions by allowing transposition of the pituitary gland and stalk[51] to access cystic suprasellar lesions due to its enhanced lighting and visibility. Moreover, this approach has been associated with a significantly shorter hospital stay.[52] This approach requires a steep learning curve with two surgeons adept at endoscopic and skull base techniques[53] and because of the technical difficulty of this

approach and risk of cerebrospinal fluid (CSF) leak, the extended technique has been mainly recommended for small and medium suprasellar lesions located primarily in the midline without encasement of vascular structures.[54-56] Surgical planning must take into account the goal of surgery (gross total vs. subtotal resection) and any proposed adjuvant therapy, as well as a realistic assessment of the capabilities of the operating surgeon. Each case should be considered on an individual basis for surgical planning, although some generalizations on the basis of tumor location may be made.

For a summary of the advantages, disadvantages, and indications for selected surgical approaches for craniopharyngiomas please refer to the paper by Bruce and colleagues.[57] In our meta-analysis of the published literature on endoscopic approaches for the resection of craniopharyngiomas, endonasal approaches had significantly greater rates of GTR, improved visual outcome, and a trend toward fewer recurrences when compared to open and microscopic endonasal routes.[58] In more recent reports of endonasal craniopharyngioma resection, CSF leak rates of 0–4% have been reported.[59,60] Our systematic review indicates that the endoscopic approach is safe and effective for the removal of small, midline craniopharyngiomas. Further prospective studies and further follow-up will help to further characterize the optimal role for a minimally invasive approach in the treatment of these difficult cranial base lesions.

Meningiomas

Skull base meningiomas account for approximately 25% of all meningiomas, of which a subset are in a midline anterior fossa location.[61] They are histologically benign extra-axial tumors that arise from the arachnoid cap cells of the dura, may invade local bone and often abut or sometimes encase local neurovascular structures. The ideal management paradigm for these lesions is GTR with removal of surrounding dura and invaded bone, if this can be done safely. If a subtotal resection only is achieved, adjuvant radiotherapy can be performed to prevent regrowth.[62,63] Open skull base approaches to ventral midline tumors are circuitous, requiring large bone openings, brain retraction, and manipulation of cranial nerves and major vessels. In contrast, a ventral, midline approach may be more logical because it avoids encountering critical neurovascular structures. However, in contrast to pituitary tumors and craniopharyngiomas, the application of endonasal endoscopic approaches for the removal of meningiomas is controversial. Some critics argue that a complete resection of a meningioma, including its dural tail, cannot be achieved through an endonasal approach and that postoperative CSF leak and infection rates are too high.

In our published review there was a significantly higher rate of GTR for tuberculum sellae and planum meningiomas undergoing open versus endoscopic surgery ($P = 0.005$). However, a significantly higher proportion of patients in the endoscopic cohort had improved vision postoperatively (73.5% vs 58.7%, $P = 0.039$).[64] CSF leaks continue to be a major issue with endoscopic meningioma resection; however, rates are decreasing with the use of the vascularized septal mucosal flap technique and the "gasket-seal". Recurrence rates have been reported as < 10% and 5%. [65,66,67-69]

INDICATIONS FOR SURGERY

The need for tissue diagnosis, although seldom the case with functioning pituitary adenomas, is a possible surgical indication in atypical lesions of the sella. This indication may be important in a case with a nonfunctioning sellar mass whose pathologic identity cannot be confirmed with imaging studies alone. The most urgent indication for surgical intervention is related to pituitary apoplexy. Patients may present with hemorrhage into an existing pituitary tumor or with acute necrosis of the tumor and subsequent swelling. The presentation includes sudden headache, precipitous loss of vision, ophthalmoplegia, altered level of consciousness, and collapse from acute adrenal insufficiency. Urgent glucocorticoid replacement and surgical decompression constitute the most reliable and effective form of therapy. Another clear surgical indication is progressive mass effect from a large macroadenoma. Failure of prior therapy represents an indication for surgical intervention for some secreting pituitary adenomas, notably prolactinoma and usually occurs either with intolerability of side effects of medical therapy or from poor or suboptimal response to medical therapy.

Surgical Approaches

Transcranial

The tumor location with respect to the sella, chiasm, carotid artery, and cavernous sinus heavily influences the choice of appropriate surgical approach. It is important to consider each case on an individual basis as the characteristics

of a given tumor and individual anatomical variation strongly influence whether a tumor is amenable to resection via a particular approach. It is crucial that a neurosurgeon embarking on an endoscopic practice be comfortable with the classic approaches to the sellar and parasellar region. These include, but are not limited to (i) the nondominant subfrontal approach, which is most commonly used in children and in patients with a post-fixed optic chiasm (ii) the standard pterional approach, splitting the sylvian fissure, and working through the opticocarotid triangle and/or the lamina terminalis (iii) the cranio-orbital approach where the superior rim of the orbit is resected to provide a lower trajectory of approach (iv) the cranio-orbito-zygomatic variant allows a broader exposure and improved mobilization of the temporal lobe when that is necessary (v) bifrontal interhemispheric approach, which is rarely used currently, although it enjoyed a brief period of popularity[70] (vi) transcallosal approach may be useful for tumors that are primarily intraventricular, and can be combined with additional approaches.[71]

Endoscopic Approaches—Technical Considerations and Contraindications (Figs. 56.4 and 56.5)

The transsphenoidal approaches are variations and extensions of the traditional microscopic transsphenoidal route to the sella. They can be considered "minimally invasive" when compared to craniotomy; however, this is not always the case. The basic approaches are as follows: the sublabial transsphenoidal microscopic approach to the sella, the endonasal transsphenoidal microscopic approach to the sella, endoscope assisted variants of the prior two approaches, and extended transsphenoidal anterior skull base approaches. This can include microscopic, endoscope assisted, and purely endoscopic techniques.

A balanced perspective requires a thorough understanding of the indications and limitations of endonasal endoscopic approaches. Our experience over the past decade has helped us conceptualize not only the appropriate uses but also the confines of this approach. Key factors include tumor location and extent, degree of bony invasion and/or hyperostosis, relative vascularity, and associated brain irritation or invasion as well as encasement of blood vessels.

In general, the endonasal endoscopic approach is not appropriate for patients with malignant tumors who require a gross-total en bloc resection. If this is the oncologic goal, a transcranial or anterior craniofacial approach should be utilized. However, it is possible to achieve

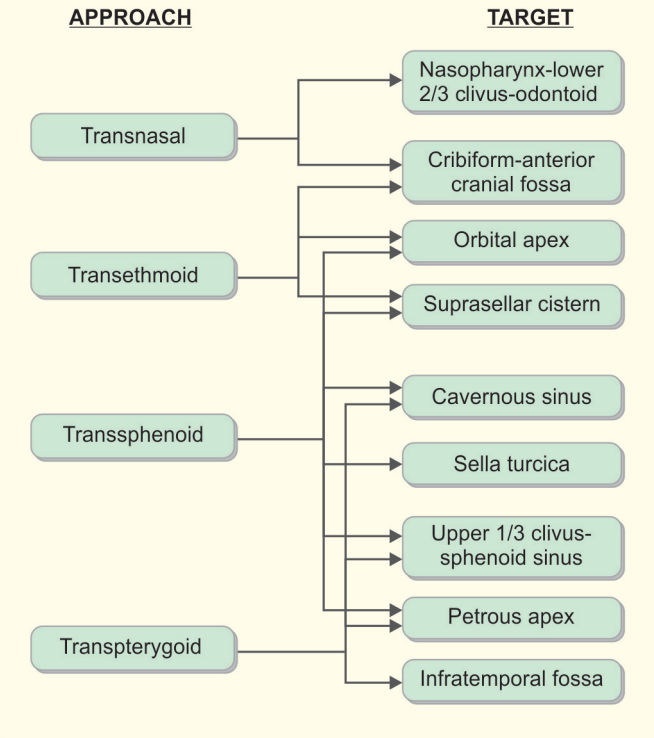


Fig. 56.4: Transnasal or trans-sinus approaches are used to access a variety of intracranial targets. Depicted are the various intracranial targets that can be accessed via a given transnasal or trans-sinus approach. Redrawn with permission from Schwartz et al.[90]

comparable outcomes with an intralesional GTR with negative margins using the endoscopic technique and follow this with fractionated radiation or radiosurgery.[72-76] A highly individualized approach is indicated in patients with skull base malignancy.

Patient comorbidities that preclude prolonged anesthesia are general contraindications to any extended transsphenoidal approach. Next, the lateral extent of the tumor must be carefully assessed. The width of the planum sphenoidale, between the laminae papyracea, has been measured in cadaver studies at 26 ± 4 mm, which narrows to 16 ± 3 mm at the posterior aspect of the tuberculum sellae[77] Tumor just lateral to this area can be mobilized into the surgical field; however, significant lateral extension should be approached via a craniotomy if complete resection is the goal. The extended transsphenoidal approach is the preferred corridor when tumor is medial to these structures and optimally exposes the medial aspect of the optic canal. Encasement of critical neurovascular structures such as the optic nerve, ICA,

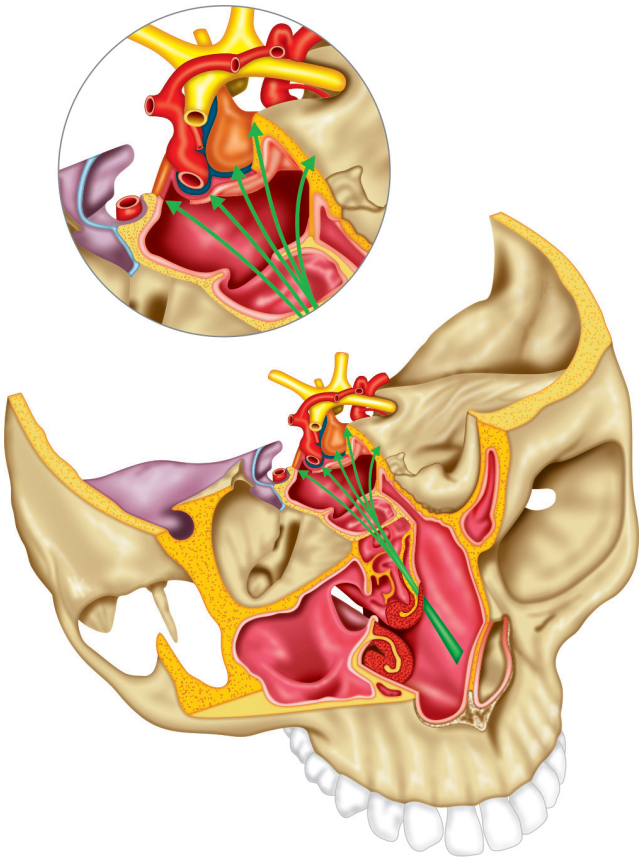


Fig. 56.5: The transsphenoidal corridor provides access to the pituitary, orbital apex, suprasellar cistern, cavernous sinus, upper clivus, and petrous apex. Reprinted with permission from Schwartz et al.[90]

and anterior communicating artery (ACA) complex is not an absolute contraindication to this approach. Much like the transcranial approach, the surgeon must judge his or her ability to safely dissect tumor from these structures and must have a plan to address a surgical emergency such as an ICA injury.

The bony pneumatization (*see* Fig. 56.2) of the sphenoid sinus is another consideration. In patients with a presellar or conchal-type sinus, bony landmarks for the optic nerves and ICAs are not easily identifiable, and the risk of injury is elevated. In addition, if the sella is small or the distance between internal carotid arteries is narrow, the surgeon may not have adequate surgical access with the transsphenoidal approach. Lastly, patients with poor wound healing capabilities may not tolerate successful skull base reconstruction and are at risk for a persistent CSF leak. This includes patients with osteoradionecrosis or who suffer from systemic diseases like poorly controlled diabetes mellitus or immunosuppression.

The transplanum, transtuberculum approach is well suited to address midline suprasellar lesions. More important than the histopathology of the lesion is its location and lateral extension. The transplanum, transtuberculum approach provides a direct route to these lesions that obviates the need for brain retraction. Also, unlike a transcranial approach, it does not place critical neurovascular structures such as the optic nerves and carotid arteries between the surgeon and the tumor. The transplanum, transtuberculum approach facilitates complete, bilateral optic canal decompression without manipulation of a compressed optic nerve. Moreover, approaching these tumors from below enables the surgeon to remove bone at the base of the tumor, which is a common site for meningioma recurrence, and to interrupt the dural vascular supply early in the operation. This enables a relatively bloodless dissection.

Technique

The patient is placed under general anesthesia and given antibiotics, glucocorticoids, and antihistamines. We routinely use cefazolin (1–2 g, intravenous), dexamethasone (10 mg, intravenous), and diphenhydramine (50 milligrams, intravenous). A Foley catheter and an arterial line are placed. A lumbar drain is placed and 0.2 mL of 10% fluorescein (AK-Fluor, Akorn, IL) is injected in 10 mL of the patient's CSF to help visualize and repair CSF leaks.[78,79] This is done for cases where wound healing may be compromised or where a large dural opening is expected. The nasal mucosa is vasoconstricted with cottonoids soaked in 4 mL of 4% topical cocaine. The patient's head is pinned in a Mayfield head-holder and turned slightly to the right and extended almost 30° to facilitate exposure of the subfrontal anterior cranial compartment. The head is elevated above the heart to facilitate venous drainage. The abdomen and/or lateral thigh are prepped for autologous fat and fascia lata grafts. Using a 0°, 18-cm, 4-mm rigid endoscope (Karl Storz, Tuttlingen, Germany), the nasal septum, axilla of middle turbinate, and mucosa adjacent to the sphenopalatine artery (only if a nasoseptal flap is not to be used) are injected with a mixture of 1% lidocaine and epinephrine (1:100 000). If a nasoseptal flap is to be used, care is taken not to inject the region between the sphenoid ostia and choana to avoid damage to the branches of the sphenopalatine artery supplying the nasoseptal mucosa. For tumors where large dural and skull base defects are anticipated, we favor harvesting single or bilateral nasal septal flaps prior to proceeding

with the intranasal exposure. This ensures a maximal size of these mucosal grafts and preservation of the vascular pedicle(s) until rotation and placement at the end of the surgery. The flaps are stored in the nasopharynx during the remainder of the procedure.

The ostium of the sphenoid sinus is then enlarged bilaterally to expose the sphenoid sinus and the posterior third of the nasal septum adjacent to the vomer and maxillary crest is resected with a tissue shaver. At this point, a panoramic view is achieved and bimanual surgery with four separate instruments is possible. The sphenoid sinus rostrum is fully exposed and the floor and lateral wall of the sphenoid sinus are drilled down to facilitate placement of the nasoseptal flap at the end of the operation. If the floor of the sinus is not flattened, the flap will be draped over a large lip of sphenoid sinus and subsequently hang off the posterior wall of the sinus and not adequately cover the defect. It is important to remove the entire anterior wall of the sphenoid sinus to provide enough room for the endoscope and instruments to sit within the sphenoid during the procedure. Care must be taken to avoid fracturing the cribriform plate superiorly, a common site of iatrogenic CSF leak after surgery. All sphenoid septae are removed with a drill and the mucosa of the sphenoid sinus is completely removed so that a mucocele does not form under the nasoseptal flap. Bleeding is stopped either with warm saline irrigation or Gelfoam. At this point a 0-degree, 30-cm rigid 4-mm endoscope (Karl Storz) is introduced through the left nostril and held in place with an endoscope holder. The carotid protuberance, optic protuberance, and medial and lateral opticocarotid recesses are identified.

The anterior and lateral extent of the sphenoidotomy are verified using intraoperative neuronavigation ensuring that optimal exposure is obtained in all dimensions before proceeding with progressively deeper exposure. In some cases, bilateral posterior ethmoidectomies must be performed to adequately visualize the most anterior portion of the planum sphenoidale. Care must be taken to avoid injuring the posterior ethmoidal arteries or to identify and coagulate them upfront. The extent of bony removal depends on tumor location.

The location of the carotid and ophthalmic arteries are verified using a Doppler ultrasound probe. The dura above and below the superior intercavernous sinus is opened and the sinus is coagulated and cut just medial to the cavernous sinus bilaterally. The diaphragma sella is then incised and removed with microscissors.

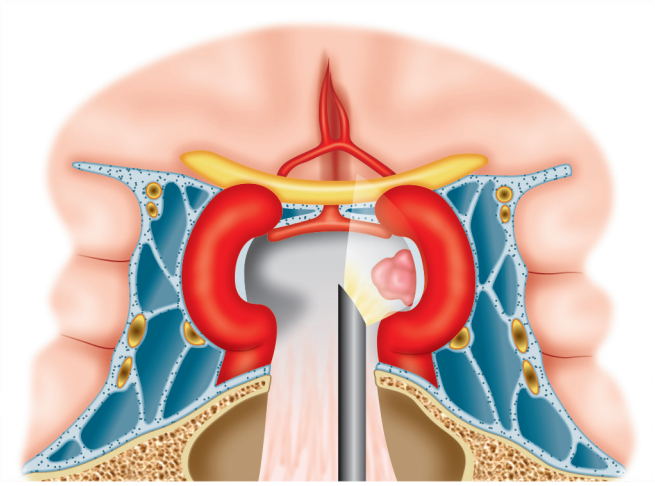


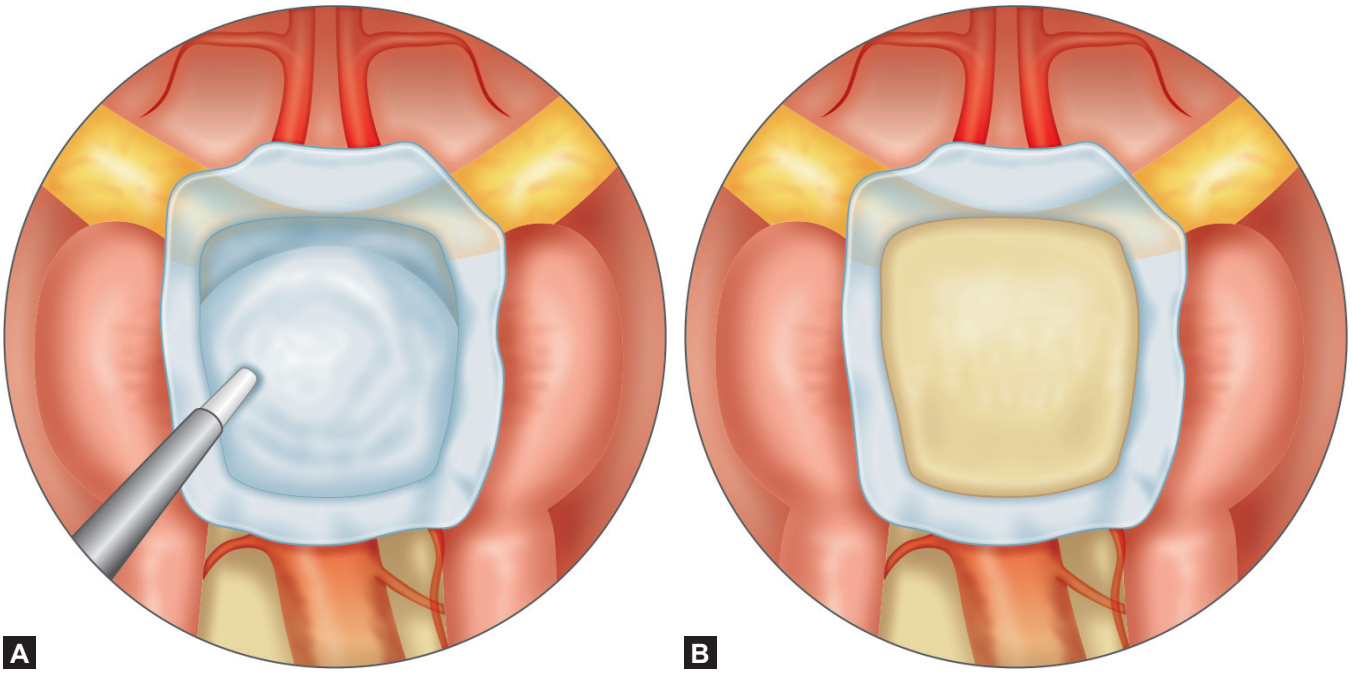
Fig. 56.6: Illustration showing the use of an angled nasal endoscope to visualize tumor behind the carotid artery within the cavernous sinus. Redrawn with permission from Schwartz and Anand.[91]

Internal decompression is performed either with two upwardly curved suctions or, if the tumor is firm, with a Cavitron ultrasonic surgical aspirator (Valleylab, Boulder, CO), Elliquence monopolar or ring cautery (Elliquence, Oceanside, NY) or Myriad (NICO, Indianapolis, IN), as well as with microscissors.

Visualization is enhanced with a 30-degree, 30-cm rigid 4-mm endoscope (Karl Storz). Once decompressed, the tumor capsule can be mobilized, and any artery complex and perforators are dissected sharply off the tumor capsule. For tumors in the vicinity of the anterior circulation, care must be taken to preserve the recurrent artery of Heubner and the subchiasmatic perforating vessels. The optic nerves and pituitary stalk are identified and dissected off the tumor capsule with preservation of the arachnoid membrane when possible. The resection bed is examined with a 45-degree, 18-cm rigid 4-mm endoscope (Karl Storz) to ensure the absence of any residual tumor. Curved suctions, angled micropituitary rongeurs, and dissectors can be used to reach residual pieces of tumor (Fig. 56.6).

Skull Base Repair

The defect in the skull base may be quite large, as can be the dead space under the brain. Although fat can be used to fill this space, Gelfoam is also a reasonable option. Filling this dead space to avoid hematoma or brain sag must be balanced with the need for close radiographic follow-up. Avoiding any intradural implants can improve the resolution of the postoperative imaging.



Figs. 56.7A and B: Endoscopic view of the "gasket seal" skull base closure. (A) A fat graft is first placed intracranially to eliminate dead space. However, this step is skipped if there is a wide communication with the third ventricle after tumor resection. Next, a piece of autologous fascia lata, larger than the bony defect, is centered over the defect. (B) The fascia lata is countersunk into the defect with a piece of vomer or Medpore that is similar in size to the defect. Last, a vascularized nasoseptal flap and DuraSeal is laid over the "gasket seal" to complete the closure.

Our preferred closure is the "gasket-seal closure"[68] (Figs. 56.7A and B). A fascia lata graft that is larger than the opening in the skull base is laid over the defect. A piece of vomeric bone or Medpore (Porex, Fairburn, GA) that is cut to fit the defect is countersunk over the graft and wedged in place so the edges of the graft emerge circumferentially around this rigid buttress. If fascia lata is not available, we recommend Dura-Guard (Synovis, MN). Finally, a water-tight closure is achieved with the use of either fibrin matrix (Tisseel; Baxter, IL) or polymerized hydrogel (DuraSeal; Confluent Surgical, MA); the latter product is preferable. When combining the gasket-seal closure with a nasoseptal flap, the DuraSeal is placed on top of the flap rather than below to facilitate neovascularization between the flap and the gasket seal. The sphenoid sinus, ethmoid sinuses, and roof of the nose are filled with thrombin-infused gelatin matrix (FloSeal; Baxter, IL) to facilitate hemostasis. A small thin piece of Telfa is placed in each nostril overnight to absorb any drainage and is removed on postoperative day 1. A dry gauze dressing is placed under the nostrils to catch any additional fluid.

POSTOPERATIVE MANAGEMENT CONSIDERATIONS

Patients are extubated atraumatically to avoid a sudden increase in intracranial pressure and are brought to the recovery room with the head elevated to 30°. We leave the lumbar drain open on extubation to avoid a rapid increase in intracranial pressure when the endotracheal tube is removed. The patient is closely observed in the intensive care unit overnight for frequent neurological examination and monitoring of blood pressure. If a lumbar drain is in place, we drain no more than 5 mL/h for the first 24 hours and generally remove it the night of the second postoperative day. Heparin is administered subcutaneously until the patient is ambulatory, and patients are encouraged to get out of bed on the second postoperative day. Care is taken to avoid significant Valsalva maneuvers or nose blowing, which can increase intracranial pressure, disrupt the closure and induce a CSF leak. A postoperative MRI scan is obtained on the second postoperative day and 3 months after surgery. A fat-suppressed MRI scan may be helpful

in differentiating residual tumor from fat graft, although the latter does not enhance with intravenous contrast. Patients can be discharged home on the second or third postoperative day or as soon as they are ambulating and eating comfortably.

Investigation of postoperative CSF leaks should begin with a physical examination of the patient to confirm leakage and to rule out meningitis. Repeat imaging should be performed to ensure no obvious skull base defect or flap failure. Placement or reinsertion of a lumbar drain (5–10 cc/h) with bed rest is often sufficient in patients with a postoperative CSF leak. Some surgeons recommend repeat endonasal surgery to repair the leak. We agree with this philosophy, and emphasize that the location of the leak is critical. Leaks that are very anterior, just behind the frontal recess or in the back wall of the frontal sinus, are difficult to reach endonasally and more easily managed through a craniotomy. In addition, we have successfully managed leaks with placement of a lumbar drain. However, care must be taken not to introduce pneumocephalus and lumbar drainage is only viable if there is a small volume leak and a meticulous multilayer closure has been achieved. Based on the success of lumbar drainage in this situation, we have increased our placement of lumbar drains prophylactically at the time of surgery, assuming there is no large intracranial mass causing increased intracranial pressure. We have also routinely adopted the use of Medpore as part of our gasket-seal closure to buttress the fascia lata before placing a nasoseptal flap. Medpore is a porous composite material that allows vessel ingrowth and promotes early vascularization. Although CSF leak may increase the length of stay, the greater risk is meningitis or abscess. Infectious complications are often raised as an argument against using an endonasal approach that traverses a microbe-rich cavity as opposed to the relatively sterile transcranial route. We have not encountered intracranial infectious complications in our experience, further justifying the safety of this approach. While sinusitis may be troubling in the early postoperative period, frequent nasal rinsing and appropriate antibiotic therapy as well as frequent rhinologic follow-up can reduce this complication dramatically.

Bleeding

Bleeding can entail nasal mucosal bleeding from a traumatic opening, troublesome slow oozing at the tumor bed, brisk venous bleeding from the cavernous sinus, pulsatile arterial bleeding from a small intracranial perforator, or arterial bleeding within the nose from branches of the sphenopalatine artery. Heavy bleeding that occurs postoperatively is most commonly related to arterial injury. During the course of transsphenoidal surgery, the posterior septal branch of the sphenopalatine artery or anterior and/or posterior ethmoidal arteries may be injured. Arterial nasal bleeding can be managed with nasal packing, surgical exploration and control with bipolar cautery, or, for posterior bleeding, angiography and embolization.

Injury to the carotid artery is rare but can have serious immediate and long-term consequences. Patients typically present with profuse bleeding. Direct surgical repair is generally not feasible, and the best chance for control is by way of angiography and endovascular treatment. Confirmed or suspected abrasion of the carotid should be followed with serial imaging to rule out pseudoaneurysm formation. When patients present with profuse bleeding, it is important to control the bleeding and stabilize the patient by applying direct pressure at the bleeding site. A large Foley catheter or other form of nasal packing can help stabilize the bleeding to allow for angiography.

ROLE OF ADJUVANT THERAPY

Radiation therapy has played an important role in sellar pathology for over a century. In 1909, Gramegna reported his experience with the use of transoral X-ray therapy to treat acromegaly.[80] Hirsch, in 1910, had used a radium "bomb" placed transnasally to treat a pituitary tumor.[81,82] External beam radiation therapy (EBRT) was demonstrated to be a viable alternative to surgery when Béclère reported a case of 16 years old with acromegaly who had 5-year symptom-free follow-up of headaches and visual improvement in 1913.[83] To discuss the details of modalities, dosages, and treatment specifics is beyond the scope of this chapter. In brief, conventional fractionated EBRT and stereotactic radiosurgery (SRS) are the two common modes of delivery. The third is proton therapy, which is most commonly prescribed for clival chordomas, and due to its expense, its use is not widespread.

Radiation can play a role in tumors not completely resected that recur after surgery, or in patients considered high risk for recurrence despite surgical resection based on anatomic and/or biological factors. In rare situations, it can be used in patients who are poor surgical candidates. Technology in radiation oncology is continuously evolving to improve the delivery of therapeutic doses to involved regions while minimizing dose to normal tissues. The

optimal timing of radiation therapy is often difficult to ascertain and should be determined in a multidisciplinary setting.

As in most disease sites, the risk of second malignancy after radiation therapy is difficult to measure because it is heavily dependent on dose, treatment volume, length of follow-up, and underlying host genetics. Radiation-induced tumors are most commonly meningiomas, gliomas, and sarcomas. Based on data from the literature for pituitary adenomas, the long-term risk for a second malignancy after standard fractionated EBRT is 1–3% at 20 years.[84-86] In a large review of 1621 patients who received SRS, there were no reported radiation-induced malignancies.[87]

The goal of pituitary adenoma radiosurgery is to permanently control tumor growth, to maintain pituitary function, to normalize hormonal secretion in case of functional adenomas, and to preserve neurological function, especially vision.[87] Sheehan recently published the largest current series of SRS for pituitary adenomas with 418 patients.[88] Tumor control via Gamma Knife radiosurgery was achieved in 90.3% of patients. Biochemical remission was achieved in 53% of patients with acromegaly and 54% of patients with Cushing's disease and median time to remission overall was 48.9 months. Tumor control was related to margin dose, which was frequently limited by risk of radiation to nearby structures. New pituitary hormone deficiency was present in 24.4% of patients. Thirteen patients experienced new cranial neuropathies including eight with visual acuity or field deficits. This study has helped to better characterize the effectiveness of SRS for pituitary tumors as well as its risks. Tumor control was reported as 83% over an 80.5-month median follow-up.

Typically acromegaly patients respond best with normalization of GH hypersecretion in over 70% of patients and in approximately half of those with Cushing's disease.[89] It was found that all patients with microadenomas and 97% of patients with macroadenomas had tumor control after radiosurgery. Gamma knife radiosurgery was essentially equally effective for control of adenomas with cavernous sinus invasion and suprasellar extension. Endocrine deficits are less common after radiosurgery, although some recent reports with detailed testing show some hormone deficiencies over time.

CONCLUSION

Sellar and parasellar tumors have a variety of clinical presentations. Endoscopic surgical resection represents an important part of the treatment paradigm for these patients. Radiographic and endocrine results after surgery are favorable. Long-term follow-up of these patients is required to detect recurrence. Radiosurgery is proving to be a viable option for selected cases where reoperation is not ideal. A team-based approach for optimum diagnosis and medical/surgical management is crucial in order to obtain the best outcomes in these complex pathologies.

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CHAPTER

57 Endoscopic Surgery of the Anterior Skull Base

Carl H Snyderman, Paul A Gardner, Juan C Fernandez-Miranda, Eric W Wang

INTRODUCTION

There has been a revolution in all of the surgical disciplines over the last few decades since the introduction of the endoscope. Just like prior innovations, the endoscope has challenged the status quo and led to further innovations. Within otolaryngology, endoscopic techniques became the new standard for the treatment of inflammatory disease. The application of endoscopic techniques to the treatment of sinonasal neoplasms has been just as controversial, especially for neoplasms that involve the skull base. Traditionally, sinonasal neoplasms were treated by oncological head and neck surgeons. The endoscope fostered a greater division between the subspecialties of rhinology and head and neck surgery as rhinologists began applying endoscopic techniques to benign and then malignant sinonasal tumors. Controversy arose over the preservation of oncological principles.

The oncological principles of head and neck surgery arose in a pre-endoscopic era that lacked the high resolution of modern imaging modalities. In the absence of precise definition of tumor margins, wide margins were excised in an en bloc fashion to ensure complete removal. In reality, this concept has been dispelled by our experience with other head and neck neoplasms. For example, equivalent or superior results have been achieved with the endoscopic resection of inverting papillomas of the nasal cavity, microscopically controlled excision of skin cancers (Mohs surgery), and transoral laser resection of pharyngeal and laryngeal cancers. Even with external approaches, en bloc excision of sinonasal neoplasms is often not possible due to fracturing of the specimen and proximity of tumor to critical neural and vascular structures.

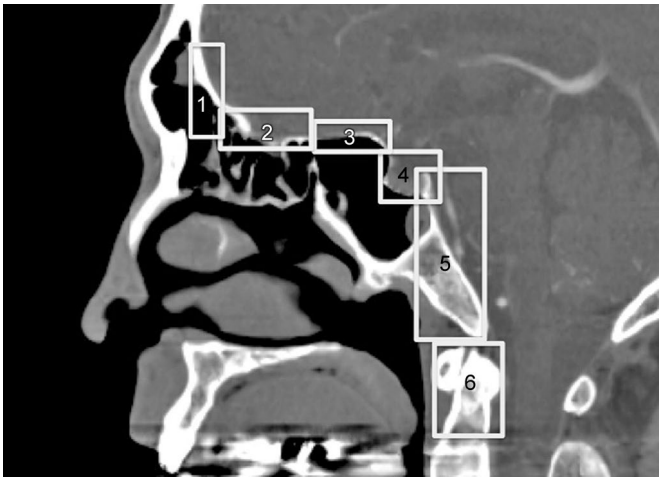


Fig. 57.1: Endoscopic endonasal approaches to the anterior cranial base in the sagittal plane include modules 1–4. 1: Transfrontal approach; 2: Transcribriform approach; 3: Transplanum approach; 4: Transsellar approach; 5: Transclival approach; 6: Transodontoid approach.

Skull base surgery has been similarly transformed by endoscopic technology. Endoscopic endonasal surgery (EES) is becoming the new standard for pituitary surgery. The entire ventral skull base is now accessible using an endonasal approach with the description of surgical modules oriented in sagittal and coronal planes.[1] The sagittal plane encompasses the midline corridor from the frontal sinus to the upper cervical spine (Fig. 57.1). Coronal plane modules correspond to the cranial fossae and extend from the midline across the orbital roof (anterior coronal plane), from the parasellar region to Meckel's cave and the floor of the middle cranial fossa (middle coronal

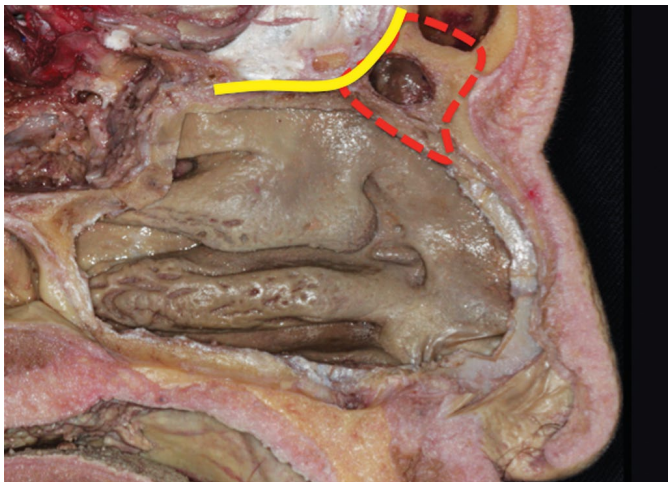
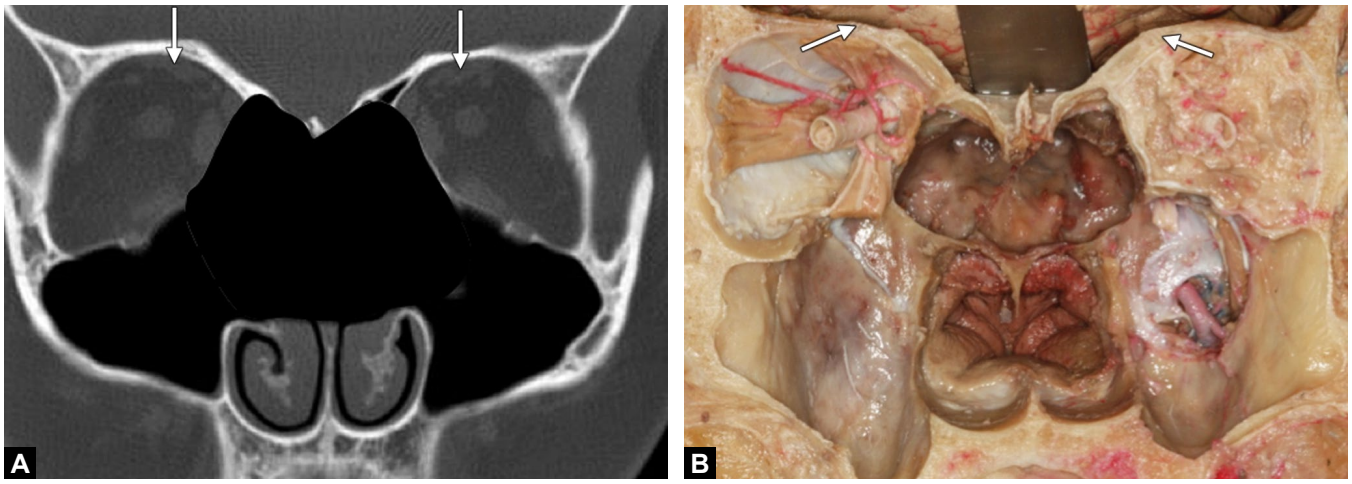


Fig. 57.2: In the sagittal plane, the anterior cranial base includes the floor of the frontal sinus (dotted line) and its posterior wall, the roof of the ethmoid and sphenoid sinuses (solid line) to the optic canals and sella posteriorly.



Figs. 57.3A and B: In the coronal plane, the anterior cranial base includes the roof of the ethmoid sinuses, cribriform plates, crista galli, and planum sphenoidale. The exposure can be extended by removing the medial walls of the orbit and retracting the orbital contents to gain access to the roof of the orbits. The lateral limit is the midplane of the orbit (arrows).

plane), and from the foramen magnum across the occipital condyle to the jugular foramen (posterior coronal plane). The anterior cranial base extends from the frontal sinus to the sella in the sagittal plane (Fig. 57.2) and can be extended in the coronal plane to include the orbital roofs (Figs. 57.3A and B).

The principles of oncological surgery can be preserved with endoscopic techniques.[2] The goal of surgery is complete oncological resection with the least morbidity for the patient. An endonasal approach is selected since it provides the most direct access to the tumor with the least manipulation of normal tissues. For most tumors, the area of tumor invasion (dura) is excised in an en bloc fashion with pathological confirmation of clear resection margins by frozen section. The extent of resection should be the same as an open craniofacial resection until similar oncological outcomes have been collectively demonstrated in the medical literature. For a classical skull base tumor such as an esthesioneuroblastoma (olfactory neuroblastoma), this means bilateral excision of involved bone, dura, olfactory bulbs, and tracts.[3] The endoscope is not an excuse to perform incomplete surgery.

DIAGNOSIS

Sinonasal tumors are varied in their presentation depending on location and biological behavior. Significant delay in diagnosis is a consequence of patient delay in presentation and misdiagnosis by physicians. Symptoms are nonspecific and are often misinterpreted as allergies or

sinusitis. Common symptoms include unilateral nasal obstruction, mild epistaxis or serosanguinous drainage, epiphora secondary to nasolacrimal duct obstruction, headache or sinus pressure, hyposmia or altered taste, and hearing loss or "popping" in the ear secondary to Eustachian tube obstruction. Late symptoms are proptosis, diplopia, and visual loss due to orbital invasion, trismus due to extension into the masticator space, facial hypesthesia or decreased strength of mastication due to involvement of the trigeminal nerve, and neurocognitive changes (personality change, decreased mental status) due to intracranial invasion.

Physical examination includes a complete examination of the head and neck region supplemented with nasal endoscopy. Nasal endoscopy provides information regarding the site of origin, extent, and areas of invasion of the tumor. Coexistent pathology may include rhinosinusitis, nasal polyposis, or mucocele formation. Clues to the diagnosis are provided by the location and appearance of the tumor. A tumor arising medial to the middle turbinate is more likely to be an olfactory neuroblastoma. A papillary tumor arising from the lateral nasal wall is more likely to be an inverting papilloma. A smooth highly vascular tumor of the posterolateral nasal cavity in an adolescent male is indicative of an angiofibroma.

Tumor invasion of the maxilla may result in loose teeth or submucosal swelling of the palate. Palpation of the anterior maxilla may reveal tumor erosion of the anterior maxilla with soft tissue invasion. Tumor extension to the orbit can displace the orbital contents resulting in proptosis and diplopia. Obstruction of the nasolacrimal duct or tumor growth along the duct may result in swelling of the lacrimal sac. Examination of the ears may demonstrate a retracted tympanic membrane or serous effusion from Eustachian tube obstruction. Trismus implies invasion of the masticator space (pterygoid muscles). The neck should be examined for the presence of lymphadenopathy. A neck mass secondary to metastatic lymphadenopathy is uncommon with sinonasal cancers and implies a highly aggressive neoplasm such as squamous cell carcinoma or sinonasal undifferentiated carcinoma. All of the cranial nerves should be assessed. Olfactory function can be measured objectively using "scratch and sniff" tests (Sensonics, Inc, Haddon Heights, NJ). Extraocular movements should be assessed along with visual acuity. Hypesthesia of the 2nd division (V2) of the trigeminal nerve (cheek and palate) is usually due to tumor extension to the maxilla. Sensory and motor involvement of the 3rd division (V3) of the trigeminal nerve implies direct tumor extension to the pterygopalatine space or perineural invasion to Meckel's cave. Loss of motor function is manifested as decreased muscle bulk and contraction with palpation, malocclusion, and jaw drift to the side of the lesion. The lower cranial nerves are unlikely to be involved.

Table 57.1: Classification of neoplasms of anterior cranial base

Benign neoplasms		
Intracranial	*Cranial*	*Extracranial*
Meningioma	Osteoma	Inverted papilloma
Craniopharyngioma	Ossifying fibroma	
Pituitary adenoma	Fibrous dysplasia	
Malignant neoplasms		
Intracranial	*Cranial*	*Extracranial*
	Metastatic	Squamous cell carcinoma
		Adenocarcinoma
		Adenoid cystic carcinoma
		Esthesioneuroblastoma
		Neuroendocrine carcinoma
		Sinonasal undifferentiated carcinoma
		Ewing sarcoma
		Melanoma

The differential diagnosis of a sinonasal neoplasm is diverse and includes both benign and malignant tumors (Table 57.1). The differential diagnosis is greatly aided by radiologic studies. Computed tomography (CT) and magnetic resonance imaging (MRI) provide complementary information and both are usually obtained. CT is best for demonstrating the bony architecture of the sinuses and skull base. Benign and slow-growing malignancies may cause remodeling of bone, whereas bone destruction is more characteristic of a high-grade malignancy. MRI is superior for demonstrating soft tissue changes and detecting invasion of the orbit, dura, or masticator space. Perineural invasion is suggested by enlargement of neural foramina on CT or enhancement of perineural tissue on MRI. MRI can help differentiate between tumor and secretions in an obstructed sinus; secretions are typically bright on T2-weighted sequences. Positron emission tomography in combination with a CT (PET-CT) is useful for

staging of malignancy and can help differentiate inflammatory from malignant disease, especially in someone who has had prior radiation therapy.

Whenever possible, a biopsy of a tumor should be performed prior to surgical or medical treatment. This can usually be accomplished in an office setting but is relatively contraindicated if the tumor appears to be highly vascular or the patient is on anticoagulant or antiplatelet medication. A negative biopsy may not be representative of the tumor and should be repeated if clinical suspicion remains high. If there are concerns about bleeding or the patient is symptomatic from bulky tumor, endoscopic biopsy and debulking of the tumor in the operating theater may be considered without compromising further therapy.

INDICATIONS

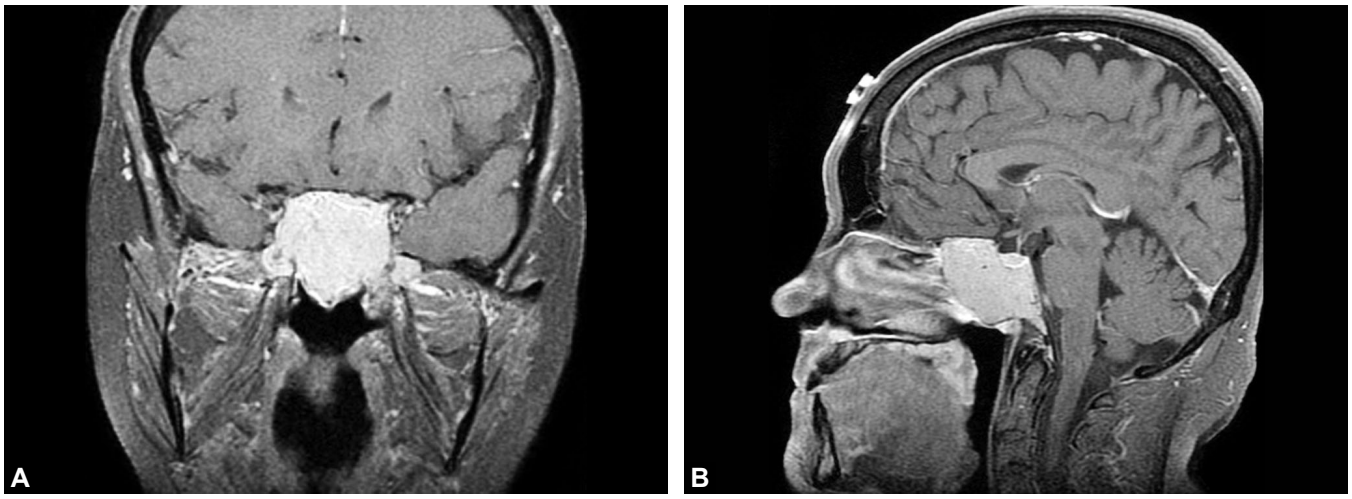
Sinonasal malignancies can be categorized into four groups based on biological behavior and treatment recommendations. The first group includes those tumors that are best treated with radiation therapy: lymphoma, plasmacytoma (Figs. 57.4A and B), and metastasis. Remaining tumors can be categorized as "good," "intermediate," or "poor" depending on their biological behavior and prognosis (Table 57.2). The treatment strategy varies accordingly. Good and intermediate tumors may be treated surgically for cure, whereas poor tumors may be best treated by radiochemotherapy or immunotherapy with surgical salvage of residual tumor. Operability is determined by the biological behavior and extent of the tumor. Tumor involvement of critical neural and vascular structures does not make the tumor inoperable but changes the goal of surgery: cure versus palliation. Extensive tumors with involvement of superficial tissues (frontal bone, orbit) are best managed with an open approach. Brain invasion by itself is not a contraindication to EES; rather, involvement of cerebral vessels limits the goals of surgery.

Treatment options for operable tumors include a standard craniofacial resection, completely transcranial resection, endoscopic-assisted craniofacial resection, and completely endoscopic endonasal resection. In our experience, EES provides the same degree of resection with

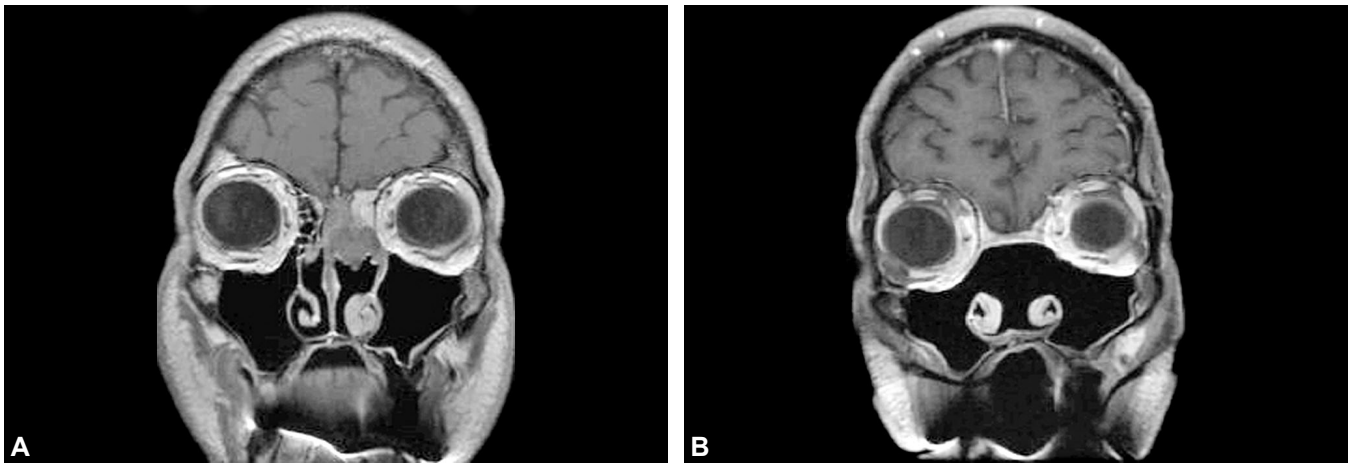
Table 57.2: Prognostic classification of sinonasal malignancy

Prognostic group	*Diagnosis*	*Primary treatment*
Good	Esthesioneuroblastoma Low-grade adenocarcinoma	Surgery (+RT)
Intermediate	High-grade adenocarcinoma	Surgery + RT
	Squamous cell carcinoma	Surgery + RT
	High-grade adenocarcinoma	Surgery + RT
	Adenoid cystic carcinoma	Surgery + RT
Poor	Sinonasal undifferentiated carcinoma	RT/Ch (+ surgery)
	Melanoma	Ch/Im (+ surgery)

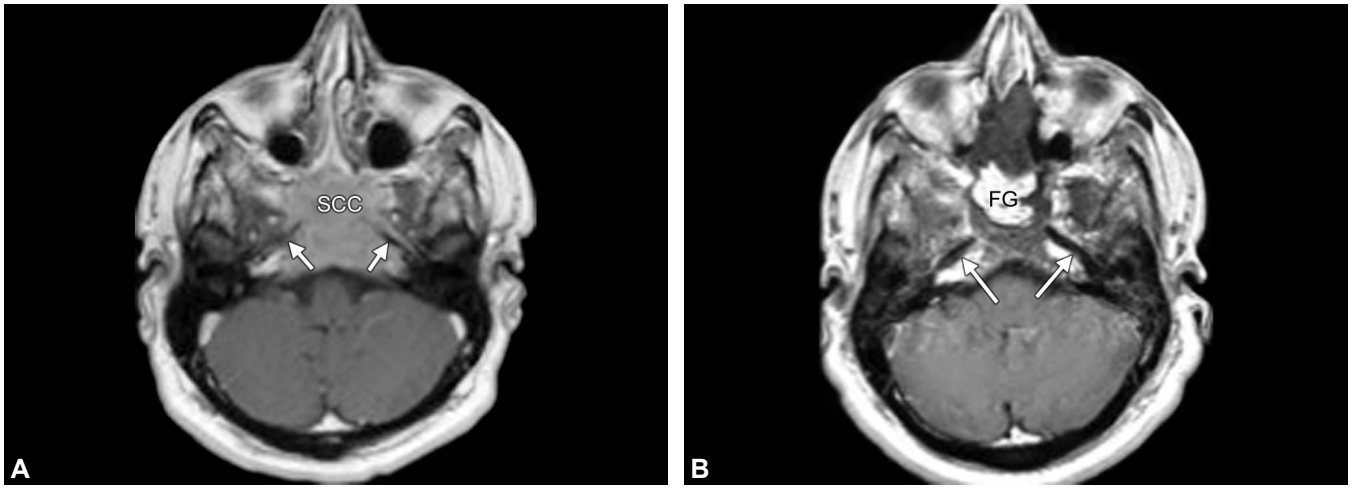
(RT: Radiation therapy; Ch: chemotherapy; Im: immunotherapy).



Figs. 57.4A and B: A plasmacytoma should always be included in the differential diagnosis when an intraoperative biopsy shows small blue cells. Complete resection should not be performed without a definitive diagnosis.



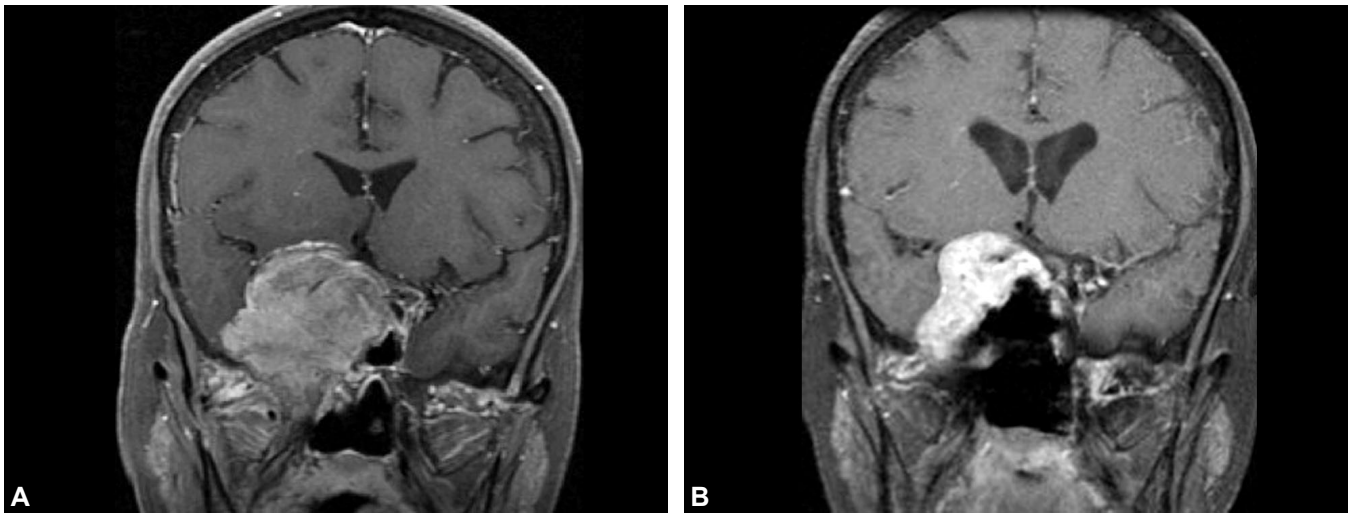
Figs. 57.5A and B: Preoperative (A) and postoperative (B) magnetic resonance imaging (MRI) of a complete oncological resection of an adenocarcinoma of the left olfactory cleft with cranial base involvement.



Figs. 57.6A and B: Preoperative (A) and postoperative (B) magnetic resonance imaging (MRI) of a squamous cell carcinoma (SCC) with encasement of the internal carotid arteries (arrows) that underwent endoscopic debulking prior to definitive radiochemotherapy. (FG: Fat graft).

improved visualization and less potential morbidity. The surgical team should be skilled in both open (transcranial) and endoscopic (endonasal) approaches and should choose an approach or combination of approaches that provides a complete oncological resection with the least morbidity for the patient (Figs. 57.5A and B).

The endoscope provides treatment options other than complete surgical excision for cure. Debulking of large tumors prior to radiation therapy may be considered to provide immediate relief of symptoms (nasal obstruction, bleeding, sinus obstruction, compression of adjacent tissues or nerves) (Figs. 57.6A and B). This also provides valuable information regarding the extent of the tumor and areas of invasion. Radiographic images risk over-predicting the areas of invasion; much of the tumor may be intranasal and simply compressing adjacent tissues. Such information may allow redesign of the radiation ports and relative sparing of critical tissues (optic nerves, brain). Finally, there is a theoretical benefit of debulking surgery. Decreased tumor volume may enhance the ability of radiation therapy to achieve a complete response. If debulking surgery is performed, it should be done without violating the dura with the attendant risk of delaying the institution of radiotherapy. The endoscope also increases the possibilities for palliation of patients with incurable disease (Figs. 57.7A and B). The endonasal corridor provides easy access for repeated palliative surgeries without the need for more invasive approaches with greater morbidity.



Figs. 57.7A and B: (A) Unresectable olfactory neuroblastoma with complete encasement of the right orbital apex and cavernous sinus. (B) Palliative endoscopic endonasal surgery (EES) with limited resection of residual tumor was performed to limit spread of tumor to the uninvolved eye and preserve vision (MRI is 2 years following radiochemotherapy and 1 year following surgery).

SURGICAL PLANNING

Much of the surgical planning is completed as part of the initial evaluation. If malignancy is suspected or confirmed, a metastatic workup consisting of a CT scan of the chest and abdomen or whole body PET should be obtained. Initial CT and MRI scans should be performed using a navigation protocol so that they can be used for intraoperative navigation.

At the time of surgery, the patient is positioned supine with the head fixed by a Mayfield head holder. This allows precise positioning of the head and prevents movement of the patient during surgery. The neck is hyperextended to increase access to the frontal sinuses anteriorly. The Mayfield pins are placed posterior to the plane of a coronal scalp incision in case a pericranial flap is needed for reconstruction. The patient is placed in reverse Trendelenburg position to increase venous return and decrease bleeding during surgery. Registration of the navigation system is performed and electrodes for monitoring of neurophysiological function are placed. Somatosensory-evoked potentials provide a measure of cortical function and are sensitive to global ischemia due to blood loss or hypotension.

Cottonoids soaked in 0.05% oxymetazoline are placed intranasally to decongest the nasal mucosa. Antibiotic prophylaxis consists of a 3rd-generation cephalosporin with moderate cerebrospinal fluid (CSF) penetration (ceftriaxone or cefepime). Temporary tarsorrhaphy sutures are placed to protect the eyes and the skin and nasal vestibule are prepped with Betadine solution. Antiseptic solutions are not used intranasally except for the nasal vestibule due to risk of mucosal injury and olfactory loss. The abdomen is prepped in case a fat graft is needed.

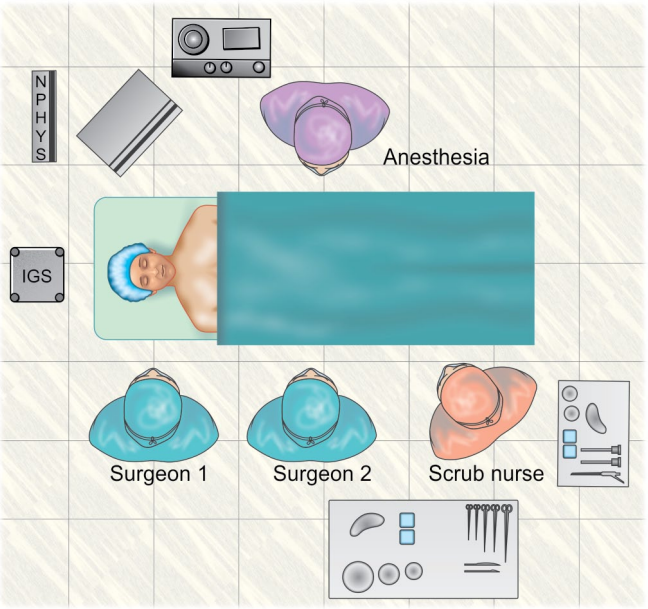


Fig. 57.8: Configuration of operating room setup for two right-handed surgeons. (IGS: Image-guidance system; M: Monitor; NPhys: Neurophysiology).

The operating room setup is designed to provide optimal access to the patient with ergonomic comfort for the surgeons (Fig. 57.8). The patient is turned at right

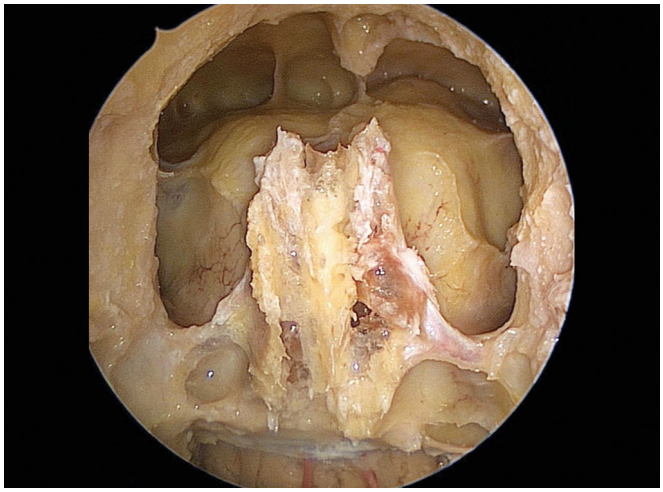


Fig. 57.9: A complete sphenoethmoidectomy and Draf 3 frontal sinusotomy is performed to expose the margins of the tumor and limits of resection. This often requires debulking of large tumors.

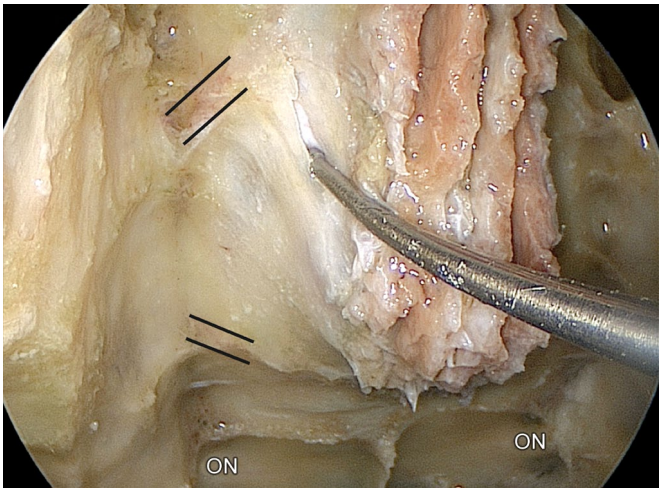


Fig. 57.10: Bony landmarks are identified and the bone of the anterior cranial base is thinned with a drill around the periphery of the tumor. The anterior and posterior ethmoid arteries (parallel lines) are cauterized. Bone removal posteriorly is limited by the optic nerves (ON).

angles to the anesthesia team and separate viewing monitors are placed around the head for each surgeon. The navigation screen is at the head of the bed for simultaneous viewing. Right-handed surgeons typically stand on the right side of the patient.

EES is team surgery consisting of an otolaryngologist and a neurosurgeon working side by side to provide the optimal view and maximal access. There are multiple advantages to team surgery. Each specialty brings a unique fund of knowledge and skill set to surgery that contributes to the preoperative evaluation and postoperative care of patients in addition to surgery. Although a mechanical scope holder can be used to allow a single surgeon to operate, this greatly compromises visualization. Endoscopy is a dynamic process where there is constant jockeying for position to provide better visualization and greater access for instrumentation. Dynamic endoscopy also enhances three-dimensional visual cues. A skilled endoscopist is essential in the event of a major vascular injury when good visualization is critical. Perhaps the greatest benefit of team surgery is problem solving during surgery; the surgeons function as co-pilots by evaluating the situation, providing feedback, and developing solutions.

INTRAOPERATIVE CARE

The first goal of surgery is to define the margins of the tumor and visualize the landmarks of the cranial base. Large bulky tumors need to be debulked to establish the areas of tumor invasion and provide access to the skull base. Hemostasis can be achieved through ligation of feeding vessels (anterior and posterior ethmoidal arteries) and direct tumor cautery (bipolar electrocautery). Some surgeons prefer a fiberoptic laser or coblation for their hemostatic properties. Bilateral sphenoethmoidectomies are performed to provide visualization of the medial orbital walls, frontal recess, roof of the ethmoid sinus, and planum sphenoidale. A Draf 3 frontal sinusotomy is performed to provide wide access to the frontal sinuses (Fig. 57.9); the posterior table of the frontal sinus is the anterior limit of resection. The nasal septum is transected inferior to the tumor from the nasion to the posterior-free edge to establish an adequate resection margin.

Reconstructive needs should be considered at the beginning of the operation. If the septum is not involved by tumor, a contralateral nasoseptal flap provides ample coverage of large anterior cranial base defects.[4] If there is invasion of the superior septum, a septal flap is still a consideration but may not be large enough. Frozen sections of the septal margin are obtained before elevation of a septal flap for reconstruction. Generally, an extracranial pericranial flap is preferred for reconstruction if there is septal involvement.[5]

The bone around the periphery of the tumor is drilled to expose the dural margins (Fig. 57.10). A 4-mm coarse diamond bit provides the right blend of bone removal and hemostasis. Anteriorly, the crista galli is drilled in the midline and the posterior table of the frontal sinuses

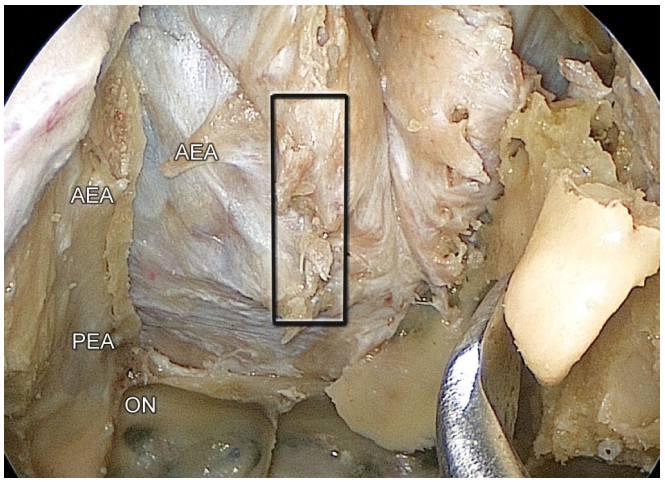


Fig. 57.11: The thinned bone is carefully elevated from the underlying dura to allow wide en bloc resection of the area of dural invasion. The crista galli is removed. Olfactory fibers are enclosed by rectangle.
(AEA: Cut ends of anterior ethmoid arteries; PEA: Cut end of posterior ethmoid artery).

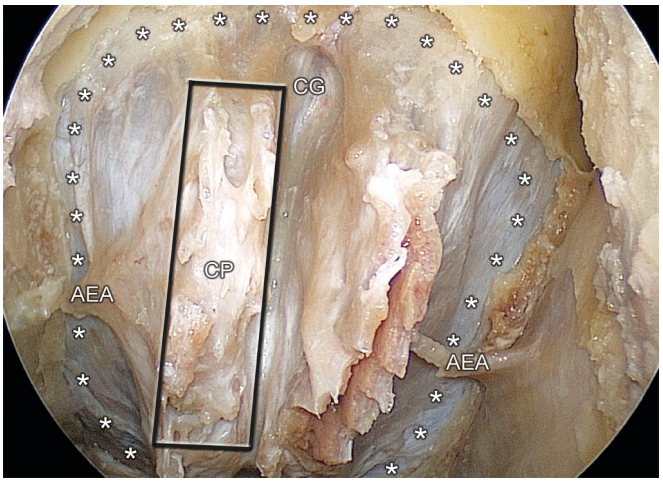


Fig. 57.12: The dura is incised laterally and then continued across the falx anteriorly and planum posteriorly. The margins of dural resection are shown (asterisks). (Rectangle, area of cribriform plate [CP]; AEA: Anterior ethmoid artery; CG: Site of crista galli).

is thinned. Laterally, the medial walls of the orbit (lamina papyracea) are fractured and removed to the level of the skull base. The periorbita is elevated from the bone to identify the anterior and posterior ethmoidal arteries where they exit the orbit to cross the skull base. The anterior ethmoid artery (AEA) is located between the 2nd and 3rd lamellae of the ethmoid sinus posterior to the nasofrontal recess. Intraoperative navigation localizes the AEA in a coronal plane that is tangential to the posterior surface of the globe. The vessel is cauterized with bipolar electrocautery and transected on the orbital side of the skull base, leaving a small stump to avoid retraction into the orbit with consequent risk of a retrobulbar hematoma. The posterior ethmoid artery (PEA) is smaller in size and is situated near the junction of the ethmoid and sphenoid sinuses, approximately 4–7 mm anterior to the optic canal. The AEA and PEA diverge from each other as they traverse the skull base. The bone is drilled at the junction of the medial orbit and ethmoid roof. The bone of the posterior planum is thinned with the drill, establishing a bone margin anterior and medial to the optic canals. The bone is then elevated to expose the underlying dura (Fig. 57.11). The bone of the cribriform plates is thin and fractures easily. The base of the tumor and olfactory filia are cauterized with bipolar electrocautery. At this point, it is helpful to undermine the dura extending laterally over the orbit. This is more difficult to do once the dural cuts have been made.

If more lateral access is necessary due to bone involvement or intracranial extension, a supraorbital approach can be performed in the anterior coronal plane (Fig. 57.3). The medial orbit is decompressed by removal of the lamina papyracea and the AEA and PEA are cauterized and transected. This allows dissection of the periorbita from the roof of the orbit. By displacing the orbital contents, the orbital roof can be exposed to the midline of the orbit.

The dura is initially incised laterally on both sides of the skull base (Fig. 57.12). An initial stab incision is made with a retractable knife and the incision is extended anteriorly and posteriorly with endoscopic micro-scissors. The dural edges are carefully retracted to visualize the cortical vessels and avoid injury to the frontopolar vessels near the midline anteriorly. The residual of the crista galli is dissected free from the dura and removed. If the crista is very tall, it is not necessary to remove the entire crista. The venous channels within the falx cerebri are then cauterized and the falx is transected with scissors to release the dural specimen anteriorly. The dura is carefully dissected from the underlying frontal lobes with blunt and sharp dissection of the arachnoid membrane. The olfactory bulbs and tracts are identified and a plane of dissection is developed between the olfactory bulbs and the brain (Fig. 57.13). Manipulation of the brain tissue and cauterization of surface vessels is minimized. The dural specimen is hinged on the posterior dural attachment and olfactory tracts. The remaining posterior dural cut is

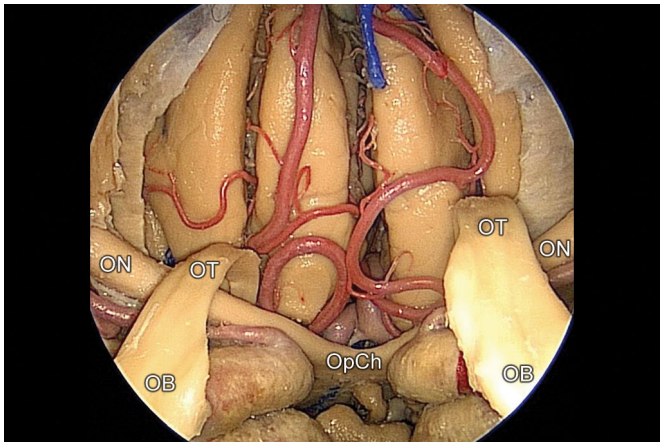


Fig. 57.13: The olfactory bulbs (OB) are dissected from the surface of the brain and elevated with the dural specimen. (OpCh: Optic chiasm; OT: Olfactory tract).

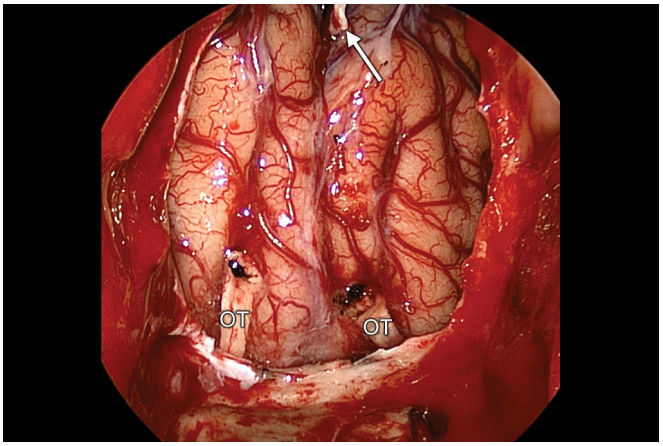
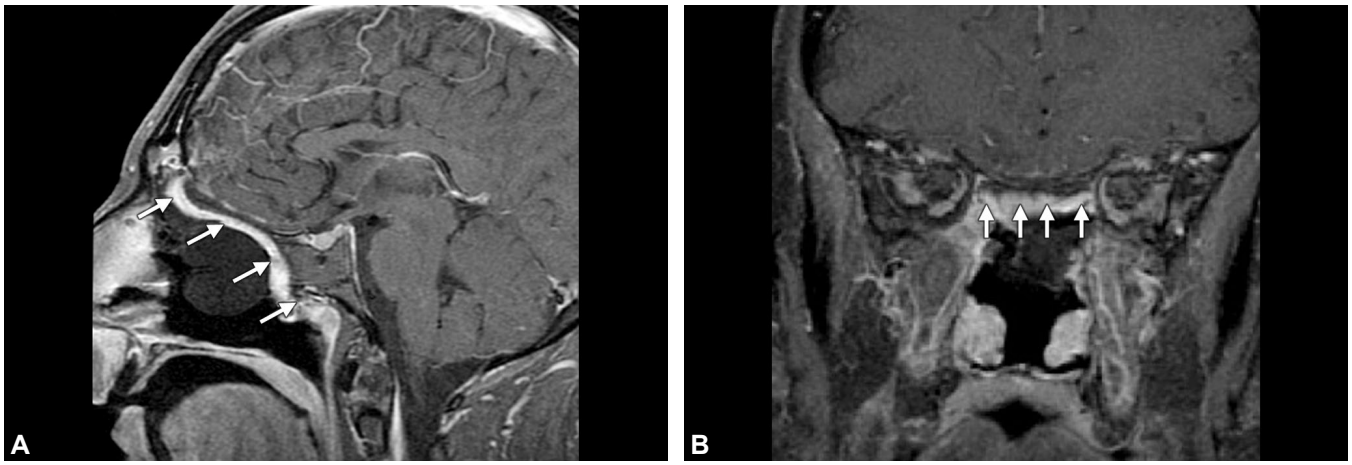


Fig. 57.14: Final dural defect with transected ends of olfactory tracts (OT). (Arrow: Transected falx cerebri).



Figs. 57.15A and B: Postoperative magnetic resonance imaging (MRI) demonstrates a well-vascularized nasoseptal flap reconstruction (arrows) that extends from the frontal sinus to sella (A) and from orbit to orbit (B).

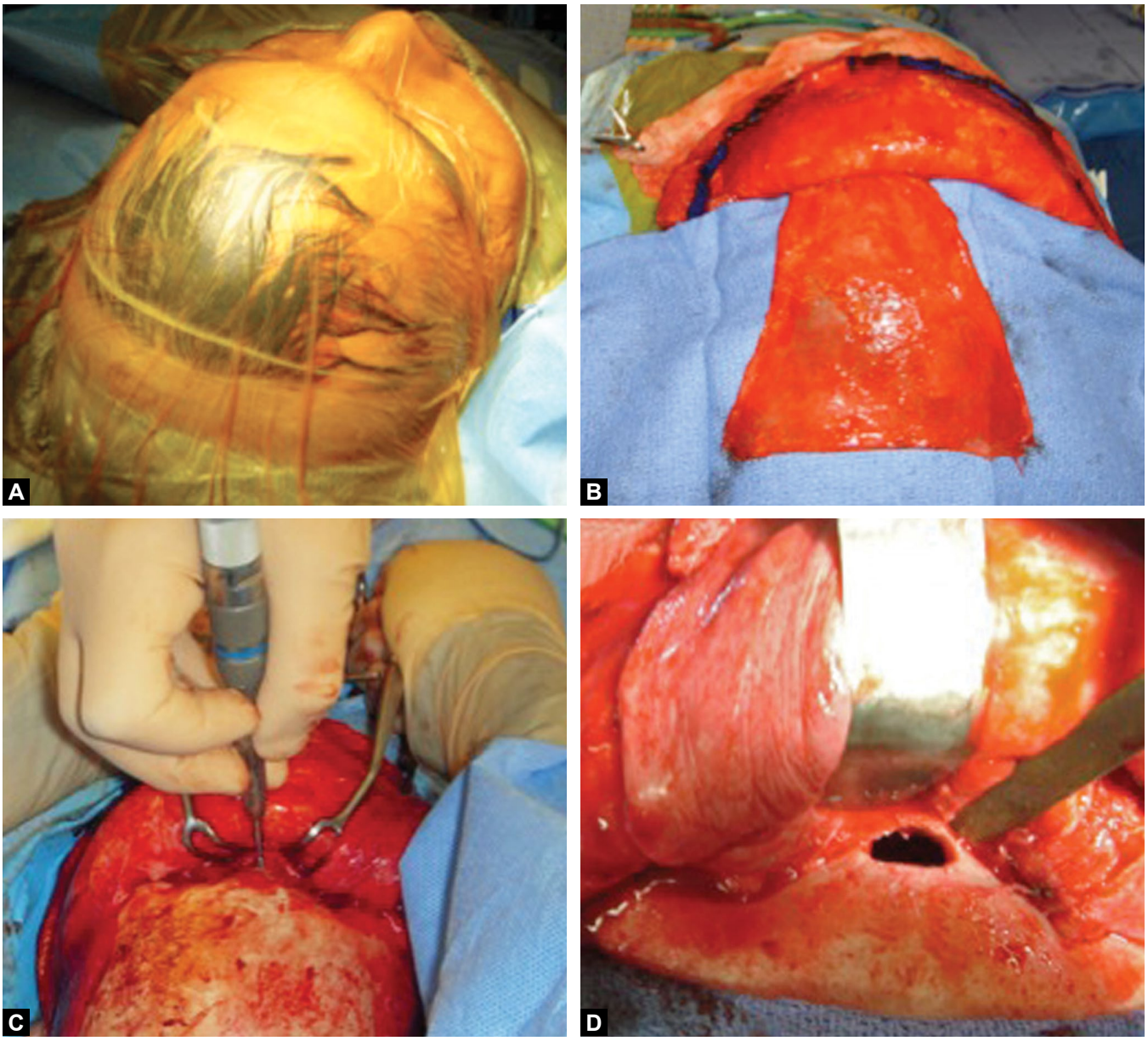
made with scissors and the olfactory tracts are transected (Fig. 57.14). The olfactory tracts course posterolaterally superior to the optic nerves. The entire dural specimen is removed and oriented with sutures.

Additional dural margins are resected circumferentially for frozen section confirmation of clear resection margins. Additional bone removal may be necessary if initial frozen sections are positive. Hemostasis is achieved using a combination of techniques. Dural edges are cauterized with bipolar electrocautery. Minimal oozing from the surface of the brain can be effectively controlled with gentle irrigation with warm saline (40°C) through an irrigation catheter.[6]

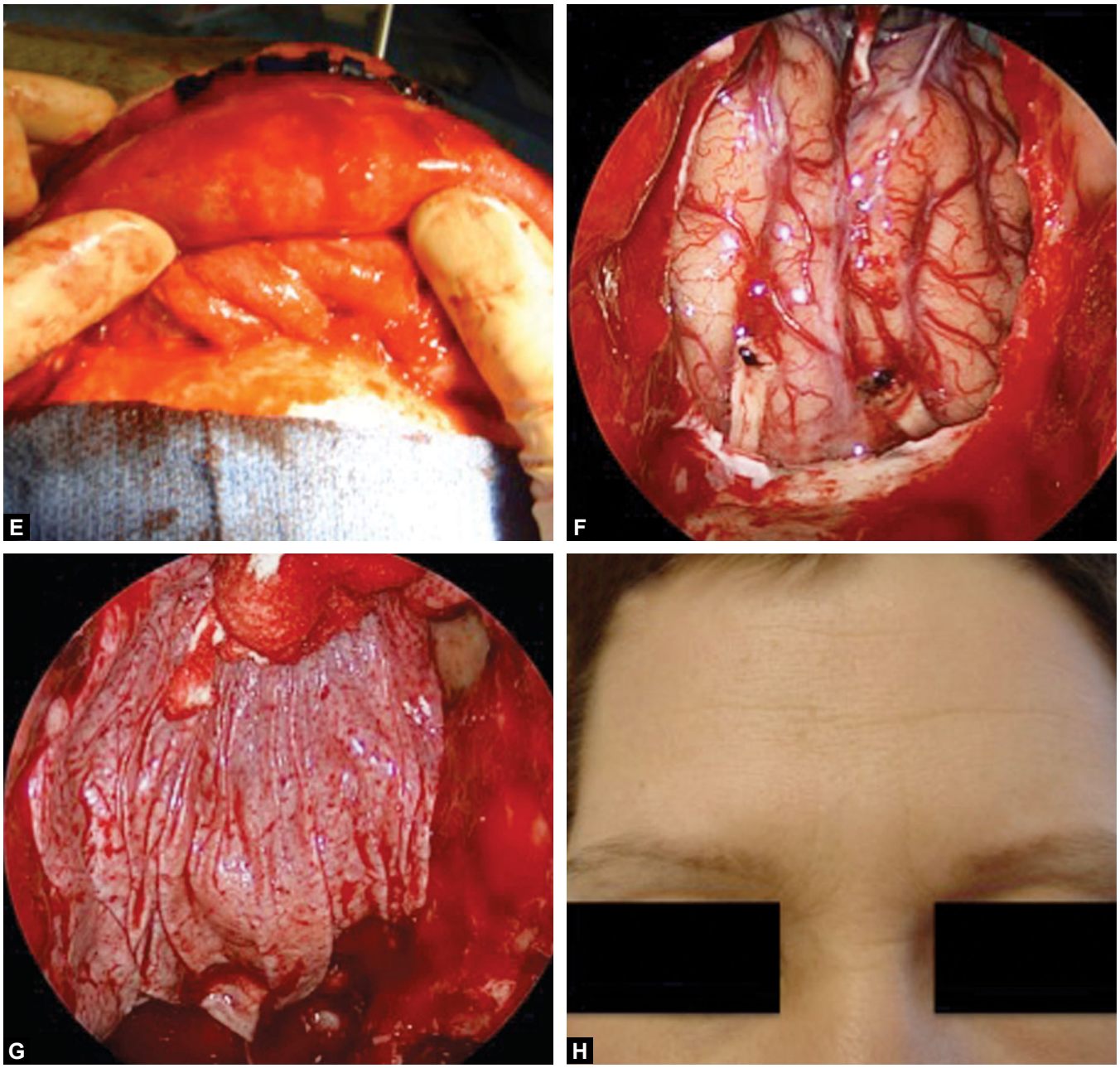
Reconstruction is performed using multiple layers of tissue. An intradural collagen graft (Duragen, Durasis, or autologous fascia) is placed between the brain and the dura. The edges of the graft are tucked above the dural edge to minimize egress of CSF. A second extradural layer of fascia is optional. If a septal flap is used (*see* Chapter 61), it is rotated to cover the entire defect (Figs. 57.15A and B). It is important that the flap be in contact with bone or dura throughout its length, and overlaps the edge of the dural defect. If the flap does not reach the anterior edge, the reach of the flap can often be extended by mobilizing the flap pedicle, removing bone from the floor of the sphenoid sinus, or filling the sphenoid defect with a fat graft deep to the flap pedicle. Sometimes, the flap is easier to orient if it is brought up the side of the orbit at an oblique angle. If the flap is not large enough to cover the entire defect, it can be augmented with an extracranial fascial graft

(Durasis, Alloderm, or autologous fascia) deep to the flap or with fat grafts placed around the periphery of the flap.

An extracranial pericranial flap[5] is preferred for most reconstructions due to the possibility of a positive tumor margin with a septal flap and the larger size of the pericranial flap (Figs. 57.16A to H). A bicoronal scalp incision is made and the scalp is elevated in a subperiosteal plane to the orbital rims. The supraorbital neurovascular bundles are identified and preserved. The periosteum is elevated to the nasal bones to provide full access at the level of the nasion. A bony channel is then drilled at the level of the nasion from orbit to orbit and measuring approximately 2 cm in width and 0.5 cm in height. Drilling of bone continues until communication with the nasal cavity is achieved, inferior to the frontal sinuses. The opening can be enlarged with Kerrison rongeurs. The pericranial flap is dissected from the galeal layer using tenotomy scissors. Dissection continues to the base of the flap where the pericranial



Figs. 57.16A to D: Extracranial pericranial scalp flap reconstruction following endoscopic endonasal resection of a sinonasal malignancy. (A) Bicoronal scalp incision. (B) Pericranial scalp flap. (C) Drilling a subcranial window at the nasion. (D) Completed subcranial window measuring approximately 1 x 2.5 cm.



Figs. 57.16E to H: Extracranial pericranial scalp flap reconstruction following endoscopic endonasal resection of a sinonasal malignancy. (E) Insertion of pericranial flap through bony window. (F) Endonasal view of dural defect. (G) Endonasal view of pericranial flap covering defect. (H) Postoperative view of patient without visible cosmetic defect.

and galeal layers merge. Mobility of the flap is enhanced by sacrificing the neurovascular pedicle on one side. The flap is rotated and passed through the bony window into the nasal cavity. Under endoscopic visualization, the flap is spread over the defect with the edges of the flap in direct contact with bone or dura. It is important to displace the flap pedicle to one side to maintain a drainage pathway for the frontal sinuses. Also, the flap pedicle must be in contact with the posterior table of the frontal sinus anteriorly to seal a potential route for CSF leakage.

The reconstruction is supported with a layer of oxidized cellulose (Surgicel) followed by tissue glue (fibrin glue or Duraseal), absorbable gelatin sponge (Gelfoam), and packing with Merocel nasal tampons. Silastic splints are

sutured to the nasal septum. A lumbar spinal drain is not routinely used unless the patient is considered to be at increased risk of a postoperative CSF leak.

CASE EXAMPLE: OLFACTORY NEUROBLASTOMA

A 46-year-old man presented with a 6-month history of left nasal obstruction and intermittent mild epistaxis. Examination with nasal endoscopy demonstrated a large polypoid mass originating from the left olfactory sulcus (Fig. 57.17A). Biopsy confirmed an olfactory neuroblastoma. Preoperative imaging demonstrated erosion of the left cribriform plate with intracranial extension but no brain invasion (Fig. 57.17B). The medial wall of the orbit was intact and orbital tissues were not involved. The tumor extended across the midline with invasion of the superior nasal septum.

The full extent of the tumor was accessible via an endonasal approach (Figs. 15.17C to F). The medial wall of the left orbit was resected to achieve a clear resection margin and to provide access to the orbital roof for a lateral dural margin if needed. At the time of surgery, there was gross tumor involvement of the left olfactory bulb and subpial dissection of tumor from the left frontal lobe was necessary with preservation of cortical vessels. Final margins included the posterior table of the frontal sinus, left orbital roof, right roof of ethmoid sinus, planum, and superior nasal septum.

Due to septal involvement, the defect was reconstructed with an extracranial pericranial flap pedicled on both supraorbital vessels. An inlay collagen substitute and onlay dural substitute were placed before the pericranial flap. Supportive packing was maintained for 7 days.

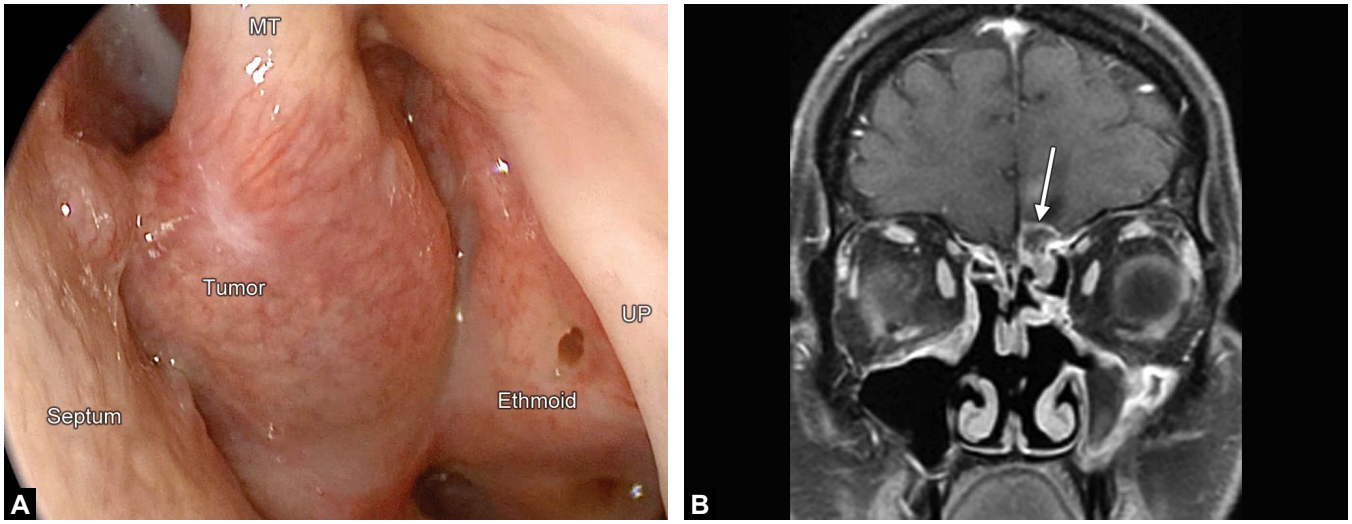
The postoperative course was uncomplicated and final pathology confirmed esthesioneuroblastoma with clear resection margins. Due to the extent of the tumor, postoperative intensity modulated radiation therapy (IMRT) was administered.

POSTOPERATIVE CARE

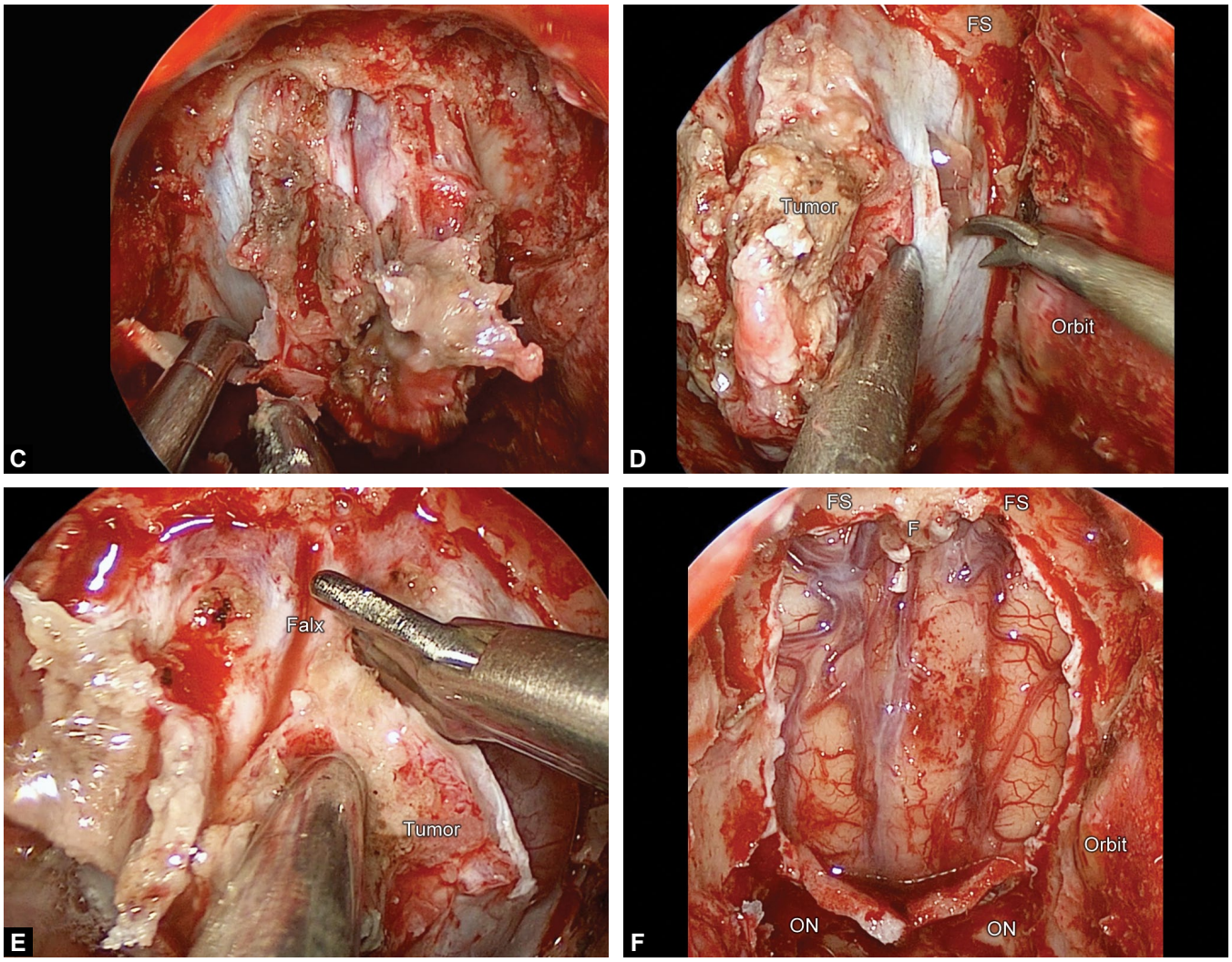
Patients are initially observed in an intensive care unit setting. A CT scan of the head is obtained within 8 hours to look for evidence of intracranial hemorrhage or tension pneumocephalus. Antibiotic prophylaxis is continued for the duration of nasal packing. Patients can usually be discharged within several days. They are instructed to use a saline nasal spray liberally and avoid activities that may increase intracranial pressure. Packing and septal splints are typically removed at 1 week. Saline irrigations of the nasal cavity are instituted at 3 weeks postoperatively, and endoscopic debridement of the nasal cavity is performed periodically as needed.

COMPLICATIONS

Intraoperative complications are unusual. Direct injury to orbital or brain tissues is rare. Loss of cortical vessels (arterial or venous) can result in a frontal lobe infarct with subtle changes in personality, memory impairment, and loss of executive brain functions. Retraction of a transected AEA into the orbital tissues can result in a retro-orbital



Figs. 57.17A and B: Olfactory neuroblastoma. (A) Endoscopic view of tumor left olfactory sulcus and middle turbinate. (B) Preoperative MRI demonstrates intracranial extension of tumor (arrow) without brain invasion.



Figs. 57.17C to F: Olfactory neuroblastoma. (C) Dissection of bone from dura. (D) Incision of dura lateral to tumor. (E) Transection of falx to release anterior dural margin. (F) Final dural defect with clear resection margins.
(MT: Middle turbinate; UP: Uncinate process).

hematoma with risk of visual loss. Preservation of olfactory function is difficult even in patients undergoing a unilateral resection due to minimal separation of the olfactory bulbs.

Postoperatively, the most common complication is a CSF leak. This may not become apparent until nasal packing is removed and can occur as late as a month following surgery. After the introduction of the nasoseptal flap, the rate of postoperative CSF leaks decreased to 4%, a rate comparable to open series.[7] A follow-up study of 70 consecutive CSF leaks reconstructed with a nasoseptal flap demonstrated that the postoperative CSF leak rate was 5.7%.[8] The etiology is multifactorial; factors include the patient, technique, materials, and perioperative care (Table 57.3). Obesity appears to be a major risk factor, and the reconstructive algorithm may need to be altered in such patients. The use of vascularized tissue for reconstruction of skull base defects has been associated with a decreased risk of CSF leak. In a systematic review of the literature, the CSF leak rate was 15.6% for free grafts and 6.7% for vascularized reconstruction ($p = 0.001$).[9] The routine use of a lumbar drain for CSF diversion has not been demonstrated to decrease the risk of postoperative CSF leak in randomized clinical trials and exposes the patient to other risks. Its use is reserved for "high-risk" patients.

Patients who develop a postoperative CSF leak are treated as an emergency with return to the operating room within 24 hours. If there is uncertainty, the diagnosis is

Table 57.3: Potential risk factors for cerebrospinal fluid leak

Patient factors	*Material*	*Technique*	*Perioperative care*
Prior therapy	Allograft	Flap harvest	Lumbar drain
High flow leak	Nonvascularized autograft	Inlay graft	Debridement
Recipient bed	Vascularized flap	Flap placement	Patient activity
Increased cerebrospinal fluid pressure		Packing	Packing
Tumor type			

confirmed with beta-2-transferrin testing of nasal drainage. The majority of CSF leaks are effectively managed with a single endoscopic repair: repositioning of the reconstructive flap or augmentation with fascial or fat grafts. A lumbar drain is often placed for 3–5 days.

OUTCOMES

Potential advantages of EES include decreased morbidity, decreased economic cost, and improved oncological outcomes. Oncological outcomes of EES appear to be comparable to those achieved with traditional open approaches. Unfortunately, there is insufficient data for most tumor types at this time. An evidence-based review of the medical literature is complicated by small series of patients collected over a long time span, lack of prognostic factors, and limited follow-up following therapy. Changes in histological criteria for diagnosis and advances in diagnostic and treatment modalities limit comparison of series. In the absence of randomized trials, there is an inherent bias for endoscopic series with the inclusion of earlier stage tumors.

Olfactory neuroblastoma is appealing to study due to its site of origin and clear benefits of skull base resection. Prior reviews established the craniofacial resection as the gold standard for surgical treatment and confirmed the benefits of combined treatment with surgery and radiation therapy.[10] A large multi-institutional collaborative study demonstrated a 5-year survival rate of 78%.[11] Excellent results (5-year survival 87%) have also been achieved with radiation therapy followed by surgical salvage of incomplete responses and recurrent tumors.[12] In a meta-analysis of 361 patients from 21 studies, there was a greater published survival rate for endoscopic surgery compared to open surgery, even when stratifying for year of publication (p = 0.0018).[13] Although patients from endoscopic series had similar follow-up, they had earlier Kadish stage disease. Longer follow-up from larger series are needed before making any conclusions.

Squamous cell carcinomas of the nasal cavity often present with an advanced stage and consequently have a poor prognosis. Studies have shown a 5-year overall survival ranging from 43% to 59%.[14] A European Position Paper on EES for the treatment of sinonasal cancers had limited data for squamous cell carcinomas and the majority of reported patients were early stage.[15] A limited comparison of open and endoscopic series suggests superior results for EES.

Undifferentiated carcinomas are difficult to treat due to their aggressive biological behavior with intracranial extension and cervical metastases. Intensive multimodality therapy is recommended. The role of surgery is not well defined; it has been employed as a primary therapy as well as salvage following radiochemotherapy. For patients undergoing surgical resection, limited data suggests similar outcomes for open and endoscopic series.

Another important outcome is the impact of surgery on quality of life. Studies of anterior cranial base surgery demonstrate significant morbidity of craniofacial resection for sinonasal malignancy. The anterior skull base questionnaire developed by Gil et al. measures morbidity within seven domains.[16] Studies comparing endonasal approaches to transcranial approaches have found clinically and statistically better results with endoscopic approaches in physical function and emotional domains. However, these studies tend not to compare homogeneous populations, and more controlled, larger scale prospective trials are needed. Quality of life instruments that are suitable for all surgical approaches to the anterior cranial base are currently being validated at multiple institutions.[17] The greatest morbidity of EES is sinonasal morbidity with loss of olfaction and chronic rhinitis with nasal crusting. Overall, subjective ratings of sinonasal morbidity are low, and patient symptoms stabilize by 4–6 months.[18] As expected, greater sinonasal morbidity is noted in patients undergoing surgery of the anterior cranial base compared to the sella (pituitary tumors). Neurocognitive morbidity

of transcranial surgery due to brain retraction may be decreased with EES, but data are lacking at this time.

CONCLUSION

EES is an effective alternative to transcranial and transfacial approaches to the anterior cranial base for the treatment of both benign and malignant conditions. Oncological principles can be preserved with endoscopic techniques. A growing body of literature suggests that oncological outcomes are equivalent if not superior to traditional techniques with lesser morbidity. EES should be performed by a multidisciplinary team of surgeons with adequate experience in both open and endoscopic techniques.

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CHAPTER

Endoscopic Surgery of the Pterygopalatine and Infratemporal Fossae

58

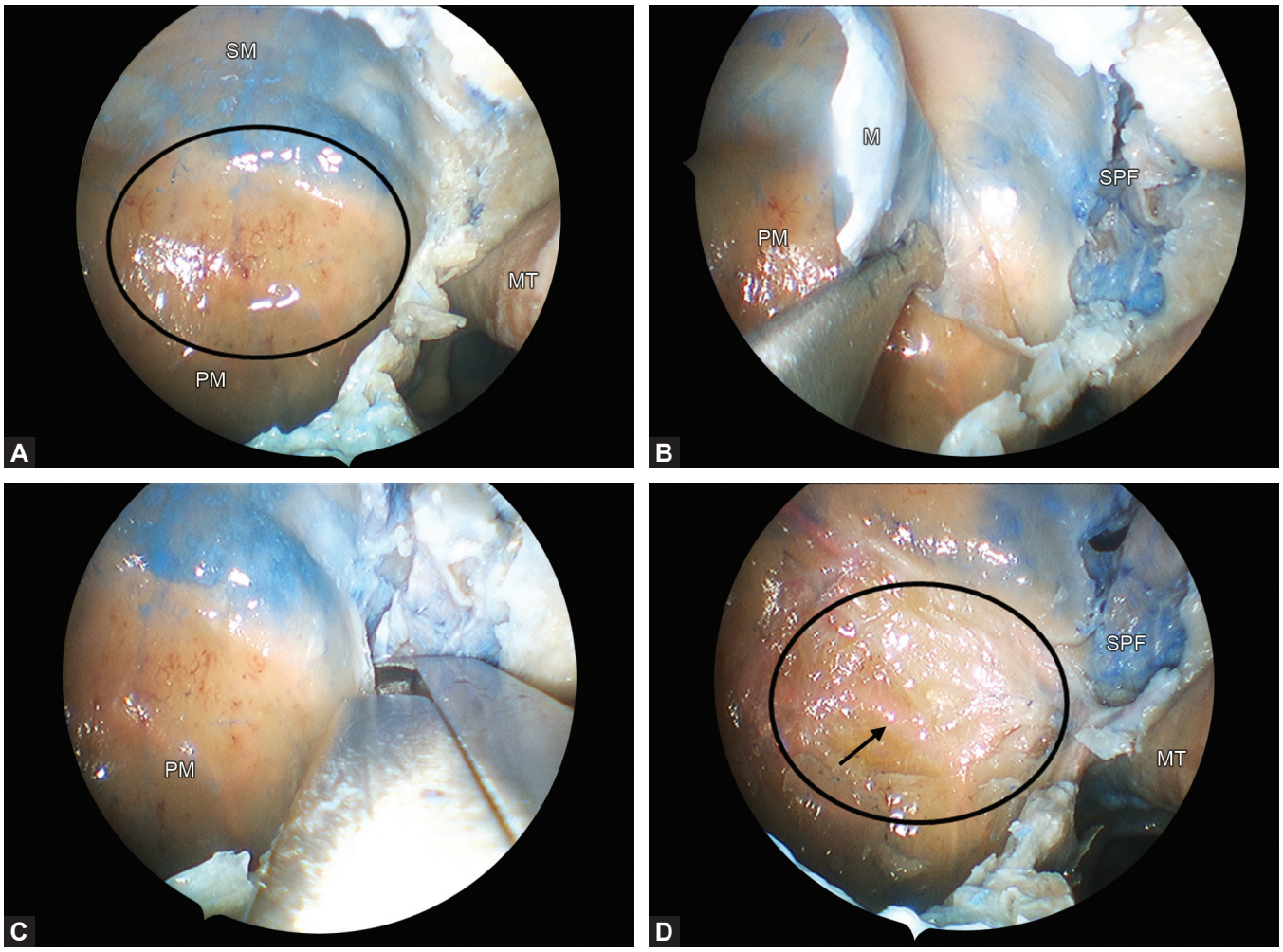
Mark E Friedel, Marc R Rosen, Gurston G Nyquist

INTRODUCTION

Endoscopic surgery has gained acceptance as an excellent surgical method in the treatment of sinonasal disease. Increasing familiarity with endoscopic techniques and advancements in technology and instrumentation has led to a natural extension of these techniques to include treatment of disease processes involving the pterygopalatine (PPF) and infratemporal (ITF) fossae. The PPF and ITF are difficult-to-access anatomic areas that are positioned between the posterior maxillary sinus wall anteriorly and the base of the pterygoid plates posteriorly (Figs. 58.1A to D). Standard approaches to the PPF and ITF typically have required transmaxillary or transfacial techniques that violate the skin and carry the risks of cosmetic deformity, facial edema, pain, infraorbital nerve injury, facial nerve injury, oroantral fistula, chronic maxillary sinusitis, and vascular injury. However, with an endoscopic approach to the PPF and ITF, potential avoidance and reduction in these risks are possible. These extended endoscopic approaches allow excellent visualization of these difficult-to-access locations with the potential for decreased morbidity and shorter recovery periods. In the following chapter, endoscopic approaches and techniques to access the PPF and ITF will be reviewed and discussed.

INDICATIONS

The endoscopic approach to the PPF and ITF allows for precise, magnified, angled, and superior visualization while avoiding the potential morbidity of an open procedure. Additional advantages include avoidance of external facial incisions and scarring, potential avoidance of unnecessary nerve injury and dysfunction, elimination of the need to transect structures associated with chewing and speech, ability to perform four-handed dual-surgeon technique, and often a shorter hospital course. A significant number of lesions involving the ITF and PPF can be approached using endoscopic techniques. One common indication for endoscopic PPF and ITF approaches includes intractable epistaxis requiring internal maxillary artery ligation (Fig. 58.2). Neoplasms are also commonly encountered emanating from or extending to the PPF and ITF. Multiple foramina and adjacent spaces allow for easy spread into the ITF and PPF including, but not limited to, the inferior orbital fissure, descending palatine canal, sphenopalatine foramen, foramen ovale, foramen spinosum, and pterygoid space (Figs. 58.3A and B). Benign neoplastic processes such as juvenile nasopharyngeal angiofibroma (JNA) and inverted papilloma are often accessible endoscopically (Figs. 58.4A and B). Trigeminal schwannoma is another neoplasm that may be encountered in this region. Meningoceles or meningoencephaloceles may be identified extending into the ITF from the temporal lobe and may be amenable to endoscopic resection and repair. Malignant lesions such as low-grade minor salivary gland malignancies or neuroendocrine tumors may extend into these fossae and occasionally will be amenable to endoscopic or combined open and endoscopic resection. Tumor size, anatomic location, and histology will dictate the ability to utilize endoscopic techniques to obtain negative margins of resection. Although not frequently performed, vidian neurectomy may be executed via an endoscopic approach for intractable vasomotor rhinitis.



Figs. 58.1A to D: Endoscopic cadaveric view of the pterygopalatine fossa approach. (A) Wide maxillary antrostomy and posterior maxillary sinus wall. (B) Maxillary sinus mucosa elevated off bony wall. (C) Bony maxillary sinus wall removed. (D) Exposure of pterygopalatine fossa with internal maxillary artery (black arrow) visualized through periosteal layer. Oval line demarcates pterygopalatine fossa. (M: Maxillary sinus mucosa; MT: Middle turbinate; PM: Posterior maxillary sinus wall; SM: Superior maxillary sinus wall; SPF: Sphenopalatine foramen).

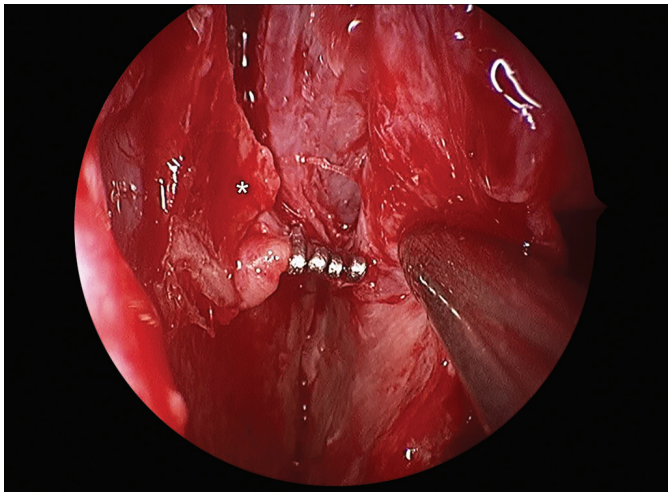
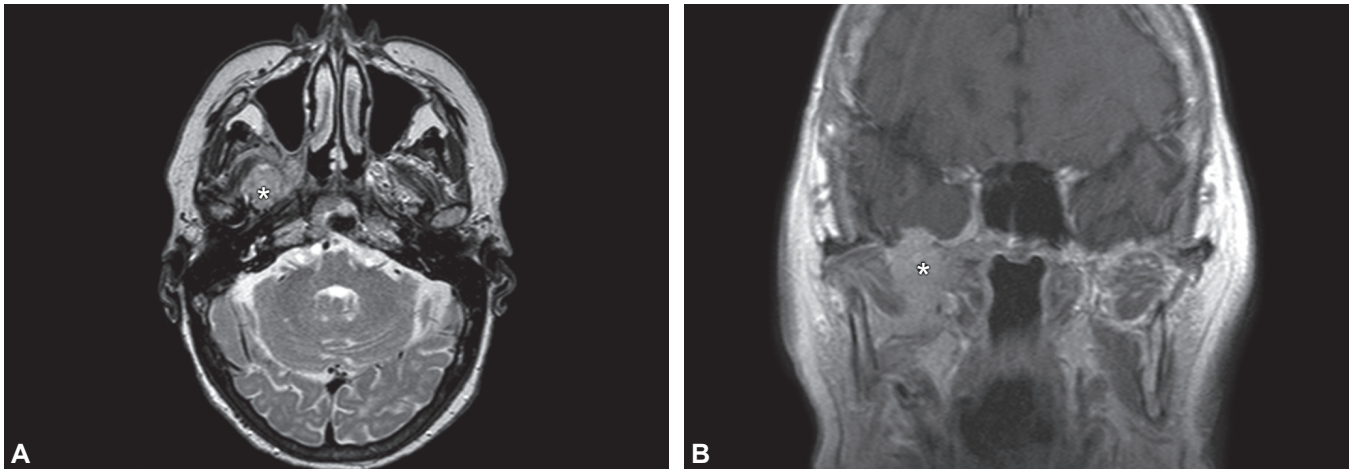
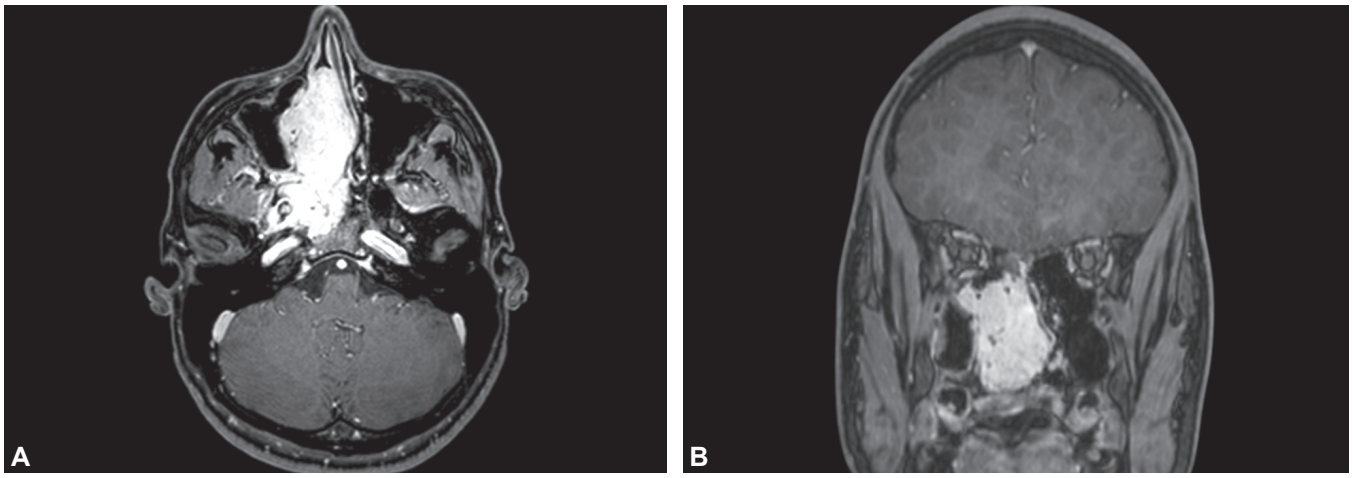


Fig. 58.2: Endoscopic view of a right sphenopalatine artery (SPA) during ligation procedure. The probe seen at the right of image is retracting a mucosal flap off of the crista ethmoidalis (asterisk). Titanium clips have been applied to the SPA.



Figs. 58.3A and B: Magnetic resonance imaging (MRI) of the cranial base and paranasal sinuses demonstrating a right infratemporal fossa adenocarcinoma of a minor salivary gland (asterisks). (A) T2-weighted fat-saturated axial cut image. (B) Post-gadolinium T1-weighted coronal cut image.



Figs. 58.4A and B: T1-weighted magnetic resonance imaging (MRI) of the paranasal sinuses with gadolinium enhancement axial-cut (A) and coronal-cut (B), demonstrating a juvenile nasopharyngeal angiofibroma extending from the pterygopalatine fossa into the nasal cavity.

CONTRAINDICATIONS

The contraindications for endoscopic approaches to the PPF and ITF are constantly evolving as technology and surgical skill improve. Tumors that have significant intracranial or intraorbital extension, such as extension to the cavernous sinus or orbital apex, may be less amenable to a purely endoscopic approach. Additionally, lesions extending to the parasellar region, cavernous sinus, or middle cranial fossa may limit endoscopic resection. Far extension to the gingivobuccal sulcus, masseteric space or maxillary soft tissues may be difficult to access via a purely endoscopic approach as well.

Many centers still consider malignant neoplasms to be a contraindication for endoscopic resection. Most research into this area is limited and primarily retrospective in nature. However, there is active and continued interest in measuring outcomes for endoscopic versus open approaches to these challenging tumors, and at least one case study has suggested excellent, if not equivalent, outcomes in select patients undergoing endoscopic resection of ITF and PPF malignancies.[1]

Critical to successful endoscopic outcomes is appropriate patient selection. Preoperative imaging, planning, and judgment are crucial in identifying the right surgical approach for the pathology at hand. Concern for

sound oncologic surgical principles is paramount, and compromise of complete oncologic resection is a contraindication for an endoscopic approach to the PPF and ITF for malignant neoplasms. The surgical team should always be prepared to perform an open approach if oncologic margins cannot be obtained endoscopically.

DIAGNOSTICS

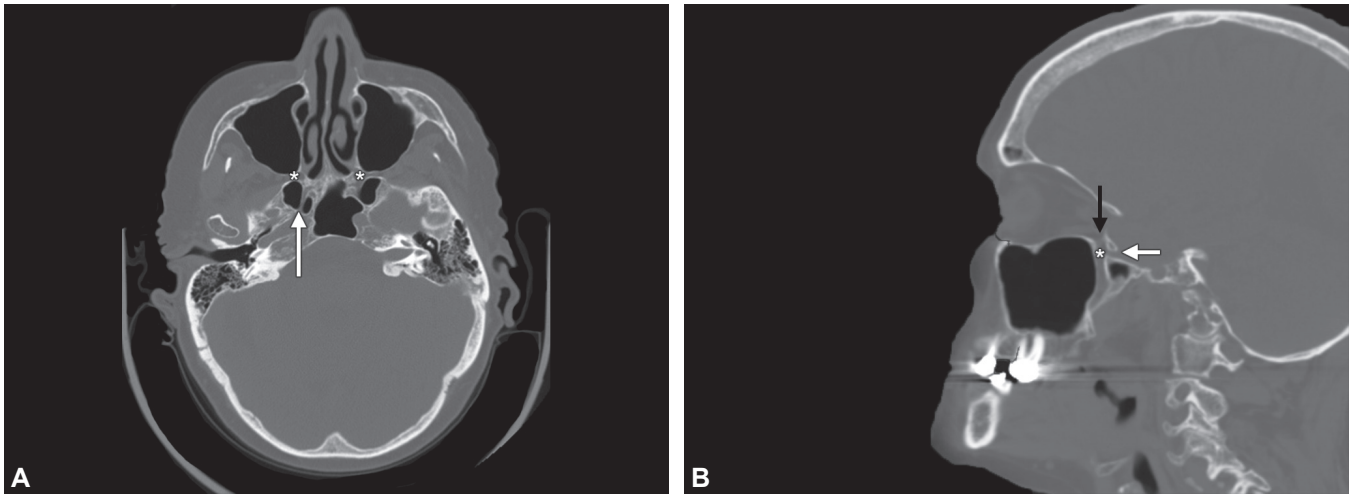
Imaging Studies

Given the deep-seated location of the PPF and ITF, imaging is often crucial for diagnosis and management planning. High-resolution computed tomography (CT) is often performed initially and provides excellent delineation of pathology with particularly accurate demonstration of bony anatomy (Figs. 58.5A and B). CT is useful for the establishment of tumor involvement of bony structures, such as the paranasal sinuses, clivus or bony foramina, and to determine the integrity of the skull base and orbital walls. Additionally, CT imaging with intravenous contrast administration may be extended to include the neck or chest to assess for regional or pulmonary metastatic disease in suspected malignant cases. Magnetic resonance imaging (MRI) is often helpful in determining the extent of soft tissue involvement, including intraorbital, dural, and intracranial invasion. High-resolution MRI may identify extension of pathology along critical neurovascular structures such as cranial nerves (Figs. 58.6A and B). Of particular relevance to ITF and PPF pathology is tumor extension into the inferior orbital fissure, vidian canal, foramen rotundum or ovale, cavernous sinus, and orbital apex. Localization of the carotid artery relative to tumor pathology is important in surgical planning. CT and MRI can be utilized with current stereotactic intraoperative navigation systems and is a useful adjunct for endoscopic ITF and PPF approaches.

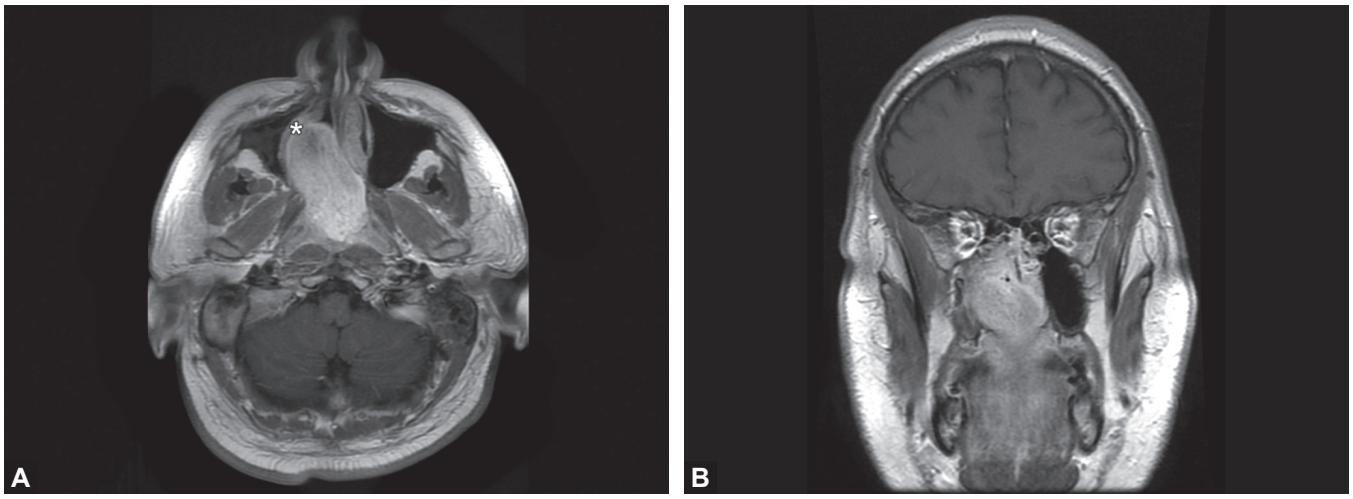
In certain cases, angiography may be necessary to assess vascular supply to a PPF or ITF tumor. Often angiography can be performed in conjunction with therapeutic embolization in preparation for surgical extirpation. JNAs are highly amenable to preoperative embolization 24–48 hours prior to endoscopic surgical resection in order to diminish vascular supply and minimize intraoperative blood loss. Arteriography will also help to demonstrate the major blood supplies to the targeted pathology including both external and internal carotid artery feeder vessels. This is critical to surgical planning, particularly for large and extensive disease, to determine their appropriateness for endoscopic resection.

Clinical Evaluation

A thorough history and physical examination that includes a careful cranial nerve examination is required of any patient presenting with ITF or PPF pathology, and is crucial for accurate diagnosis. Flexible or rigid nasal endoscopy is frequently utilized to assess the extent of disease as well as to obtain biopsy for histopathologic diagnosis. Select lesions may be amendable to an endoscopic, endonasal in-office biopsy. However, this should only be performed



Figs. 58.5A and B: High-resolution computed tomography (CT) scan of paranasal sinuses. (A) Axial cut and (B) parasagittal cut through the pterygopalatine fossa (PPF; asterisks), demonstrating the foramen rotundum (white arrows) and the inferior orbital fissure (black arrow).



Figs. 58.6A and B: T1-weighted magnetic resonance imaging (MRI) of the paranasal sinuses with gadolinium enhancement, axial-cut (A) and coronal-cut (B), demonstrating a juvenile nasopharyngeal angiofibroma extending from the pterygopalatine fossa into the nasal cavity. Asterisk demonstrates anterior displacement of the posterior maxillary sinus wall.

after imaging studies to assess the tumor vascularity and relationship to critical neurovascular structures. Vascular neoplasms are encountered in this location and are associated with the potential for catastrophic hemorrhage. A diagnostic endoscopy with biopsy under local or general anesthesia in the operating room may be more appropriate. Physicians should also avoid tumor debulking during a diagnostic biopsy as this complicates identifying the tumor origin and often translates into a compromised surgical resection.[2] In a study published by Hanna et al. in 2009, patient survival was significantly greater for those who presented with previously untreated malignant disease than for patients who presented with persistent disease after incomplete surgical debulking.[2]

SURGICAL TECHNIQUES AND APPROACHES

Operative Setup

The patient is placed supine on the operative table with gel or foam head support. Depending on the institution, general inhaled or total intravenous anesthesia may be used intraoperatively.[3] Standard intraoperative antibiotics are administered prior to the start of surgery at the time of anesthesia induction. A third-generation cephalosporin with good cerebrospinal fluid (CSF) penetration is advocated if a concomitant skull base resection is planned. Once positioned, the operative table is lowered to its base and then the head of the bed is elevated to approximately 30° with some additional reverse-Trendelenburg elevation depending on surgeon height and comfort. These maneuvers help to minimize blood-loss during the procedure.

At this time, local anesthetic agents may be injected. If a septoplasty is necessary for access, injection in the submucoperichondrial and submucoperiosteal plane can be useful. Additional injection along the lateral nasal wall near the sphenopalatine foramen and the inferior turbinates will aid in vasoconstriction. Particularly for ITF/PPF approaches, some surgeons will inject transorally through the greater palatine foramen for additional hemostasis intraoperatively. This can be done by bending a needle at approximately 22–25 mm from its tip at an angle of 45° and inserting at the greater palatine foramen near the posterior hard and soft palate junction. It is important to withdraw on the plunger prior to injection to assure that the anesthetic is not infiltrated directly into an artery.

Instrumentation

Endoscopic approaches to the PPF and ITF typically require additional instrumentation beyond the standard equipment used for endoscopic sinus surgery. Operating room staff should be alerted to additional needs early so that equipment is on-hand and readily available when challenges arise intraoperatively. Standard high-quality Hopkins-rod 4-mm endoscopes of varying degrees (0°, 30° or 45°, and 70°) are often necessary for adequate visualization of these lateral regions. Newer rotatable endoscopes are now available that allow visualization from 0° to 110° as well. Endoscope scrubbing devices are also particularly useful during extended endonasal approaches. These

systems typically utilize a thin sheath that fits over a standard endoscope and uses saline to irrigate over the distal lens of the scope when soiled.

As discussed in previous chapters, standard sinus instruments are helpful in dissection and bone removal. In addition to some of these standard instruments, powered tools are often necessary as well. A microdebrider is often very useful for soft tissue or tumor removal. Powered drills and ultrasonic aspirators may be necessary for bony removal along the pterygoid plates, medial maxilla, or hard palate. These may be particularly useful when tumors extend along the infraorbital fissure and the medial pterygoid plates. Additionally, strong flexible cutting instruments like the SerpENT (ENTrigue, San Antonio, Texas) are useful for reaching lateral regions of the maxillary sinus, PPF and ITF. In case of difficult access laterally, a Caldwell-Luc gingivobuccal sulcus incision may be needed for access. A standard dental or head and neck instrument tray may be useful for retractors and ratcheting mouth gags.

At many institutions, stereotactic navigation is available and often helpful for dissection into the PPF and ITF. Navigation instrumentation and suctions should be part of the OR setup and CT and MRIs uploaded appropriately prior to the start of the surgery.

Surgical Preparation

Operative preparedness is critical to any endoscopic procedure. When approaching the ITF or PPF, the surgeon must consider and anticipate the possibility of a dural defect that will need repair. The need for grafting material or vascularized flap coverage at the end of resection should be taken into account prior to the operation. In cases with obvious extension of tumor intracranially toward the middle cranial or temporal fossa, a nasoseptal flap based on branches of the sphenopalatine artery may be required. If this is the case, the mucoperichondrial and mucoperiosteal flap is often elevated at the onset of the procedure from the contralateral nasal septum to allow for the vascular pedicle to swing toward the defect site without kinking. If necessary, the flap can be elevated from the ipsilateral septum, but may be more difficult to position secondary to tethering of the pedicle. Additionally, tumor extension to the nasal septum or sacrifice of the internal maxillary artery may preclude use of an ipsilateral nasoseptal flap. The flap may have a slightly increased risk of injury during the resection if raised from the ipsilateral side.

Once the necessary local vascularized tissue flaps are harvested and protected, the surgical approach to the PPF or ITF may commence. The first step is to perform a routine uncinectomy and large maxillary antrostomy using standard techniques. An anterior and posterior ethmoidectomy may also be performed on the ipsilateral side for additional visualization and access to the target region. Often a large sphenoidotomy will be needed to identify the skull base posteriorly and address any pathology that may extend into the sinus or toward the foramen rotundum, vidian canal or orbital apex. The frontal sinus does not routinely need to be addressed unless tumor pathology extends to this region or postresection reconstruction will obstruct the natural outflow tract.

Depending on the extent of the pathology, limited or wide exposure of the PPF and ITF may be required. If only limited access to the PPF is required or if there is minimal involvement of the medial ITF, a tissue sparing approach can be utilized. A wide maxillary antrostomy may provide enough access to these regions in this setting (*see* Fig. 58.1A). Often the inferior and middle turbinates can be spared if there is no tumor involvement and are simply repositioned with lateralization and medialization respectively. At this point the posterior wall of the maxillary sinus can be removed. Typically, the mucosa from the posterior maxillary antrum is incised and reflected laterally along the posterior wall using a Cottle elevator (*see* Fig. 58.1B). An initial osteotomy is than performed using through-cut forceps or a Kerrison punch, at the junction of the medial and posterior maxillary walls (*see* Fig. 58.1C). Often the bony wall thins as you progress laterally from this junction. As the bone thins, a Cottle elevator, Lusk seeker, or other instrument can be used to flake off the bony fragments. If more exposure is required, a mucosal flap can be elevated from this junction point posteriorly along the palatine bone of the lateral nasal wall until the crista ethmoidalis is identified (*see* Fig. 58.2). This serves as a landmark for the sphenopalatine foramen and artery. If necessary, the artery can be clipped and divided or cauterized at this point. Once the foramen is encountered, Kerrison punches can be used to remove bone from the foramen medially to the PPF laterally. This maneuver will also create exposure to the sphenopalatine ganglion and branches of the trigeminal nerve including the descending palatine and infraorbital nerves.

If significant tumor involvement of the ITF exists, a wider exposure is typically needed and an endoscopic medial maxillectomy can be performed. In this case, the

medial wall of the maxillary sinus is removed using a powered microdebrider, drill, osteotome, or cutting forceps. Occasionally, the inferior turbinate can be spared, but most often the inferior turbinate is removed during this portion of the dissection. It is important to take the bony wall down to its junction with the floor of the nose to allow for unrestricted passage of instrumentation into the maxillary sinus. To perform the medial maxillectomy and turbinate removal, a heavy turbinate scissors or through-cut instrument is first used to cut across the turbinate along its anterior attachment to the lateral nasal wall. A mucosal incision is then made from the maxillary antrostomy anteriorly to the nasal floor and then extended posteriorly to the posterior attachment of the inferior turbinate. An osteotome, heavy cutting instrument, or punch can be used to create the osteotomies. Alternatively, a powered drill with a cutting or diamond burr can be used to take the bone down to the level of the nasal floor. In some cases, the nasolacrimal duct will be encountered anteriorly and division of the duct may be necessary for access. An endoscopic dacryocystorhinostomy can be performed by making an incision along the nasolacrimal sac at the end of the procedure and splaying the mucosal flaps out on the lateral nasal wall to prevent postoperative stenosis. A stent may be placed to ensure patency of the lacrimal sac.

Excellent endoscopic access to the PPF and ITF is achieved after the medial maxillectomy. However, if pathology dictates the need for far lateral or superior access, additional maneuvers exist to achieve a wider range of instrumentation and visualization. A sublabial, gingivobuccal incision can be used to access the anterior wall of the maxillary sinus in the Caldwell-Luc fashion. Once the incision is made down and through the periosteum of the maxilla, a Freer elevator can be used to elevate the periosteum up to the level of the infraorbital nerve. An anterior maxillary window is then created using small osteotomies or a powered drill and access into the maxillary sinus can be achieved. Often a small anterior window will allow passage of instruments or the endoscope for visualization of lateral lesions in the ITF. These approaches often do not have any significant cosmetic alterations for the patient, but do potentially place the infraorbital nerve at risk of injury. It is important when elevating the periosteum that the infraorbital nerve is not directly injured or placed under too much tension. Additional care should be taken when creating the osteotomies to avoid injury to roots of the maxillary teeth.

Some surgeons prefer to avoid sublabial incisions during these approaches and alternative endoscopic techniques can be utilized to extend lateral visualization and instrumentation. A transseptal window can be created to provide greater angulation of endoscopic instruments with a binostril technique. To accomplish this, a vertical hemitransfixion incision of the septum is made on the contralateral to the side of pathology. If a septal deviation exists, this can be addressed in the standard fashion at this time. Otherwise, a strip of posterior septal cartilage is removed using cutting instruments. Once the cartilage is removed a horizontal incision is made along the ipsilateral septal flap that enables passage of instruments to the surgical field from the contralateral side. This technique facilitates a four-handed technique and provides a better angle for far lateral lesions.[4] Potential complications from this septotomy approach include permanent septal perforation that, if placed too anteriorly, can lead to loss of tip support and/or saddle nose deformity, particularly if a septotomy is required at <1.5 cm from the columella.[5] A similar but alternative transseptal approach has been described that attempts dislocation or transposition of the septal cartilage from the maxillary crest instead of removing a cartilaginous strip. The cartilage is then repositioned at the end of the procedure. This allows for potential preservation of the nasal tip support and avoidance of long-term septal perforation.[6]

Another option for lateral ITF access is the creation of an anteromedial maxillotomy, also known as the Denker's approach. Denker's approach has been demonstrated to add an additional 30° of access to anterolateral maxillary sinus and ITF.[5] In this technique, the medial maxillectomy can be extended anteriorly to include the bone of the piriform aperture. This typically requires powered drills or heavy bone rongeur4s for removal. This approach is useful but can increase the risk of postoperative loss of alar support from disruption of the maxillary buttress, leading to functional or cosmetic deformity, or superior alveolar nerve or canine root injury.[5]

When tumor extends deep into the ITF or if the origin of the pathology is at the foramen ovale, dissection can be carried into this region. Although visualization and reach can be obtained via an endonasal or sublabial approach, certain aspects of this deep region may be inaccessible. Cadaver studies have demonstrated the feasibility of an endoscopic-assisted transtemporal (Gilles) approach to this region as well.[7] This is essentially a posterosuperior approach that is utilized in combination with the endoscopic approaches described above. A standard Gilles

incision is made approximately 1 cm posterior to the temporal hairline and carried down through the subcutaneous tissues. Elevation of the soft tissues can then be done in a subdeep temporalis fascia, subtemporalis muscle, or subperiosteal plane. Blunt dissection is continued inferiorly through the temporal space, leading to the ITF following the slope of the sphenoid bone as a guide. Care must be taken not to injure the critical neurovascular structures as they exit the skull base foramina during this elevation. The Gilles port can be used for an additional endoscopic view or as a corridor for instrumentation, although the authors acknowledge this is a significantly limited corridor.[7]

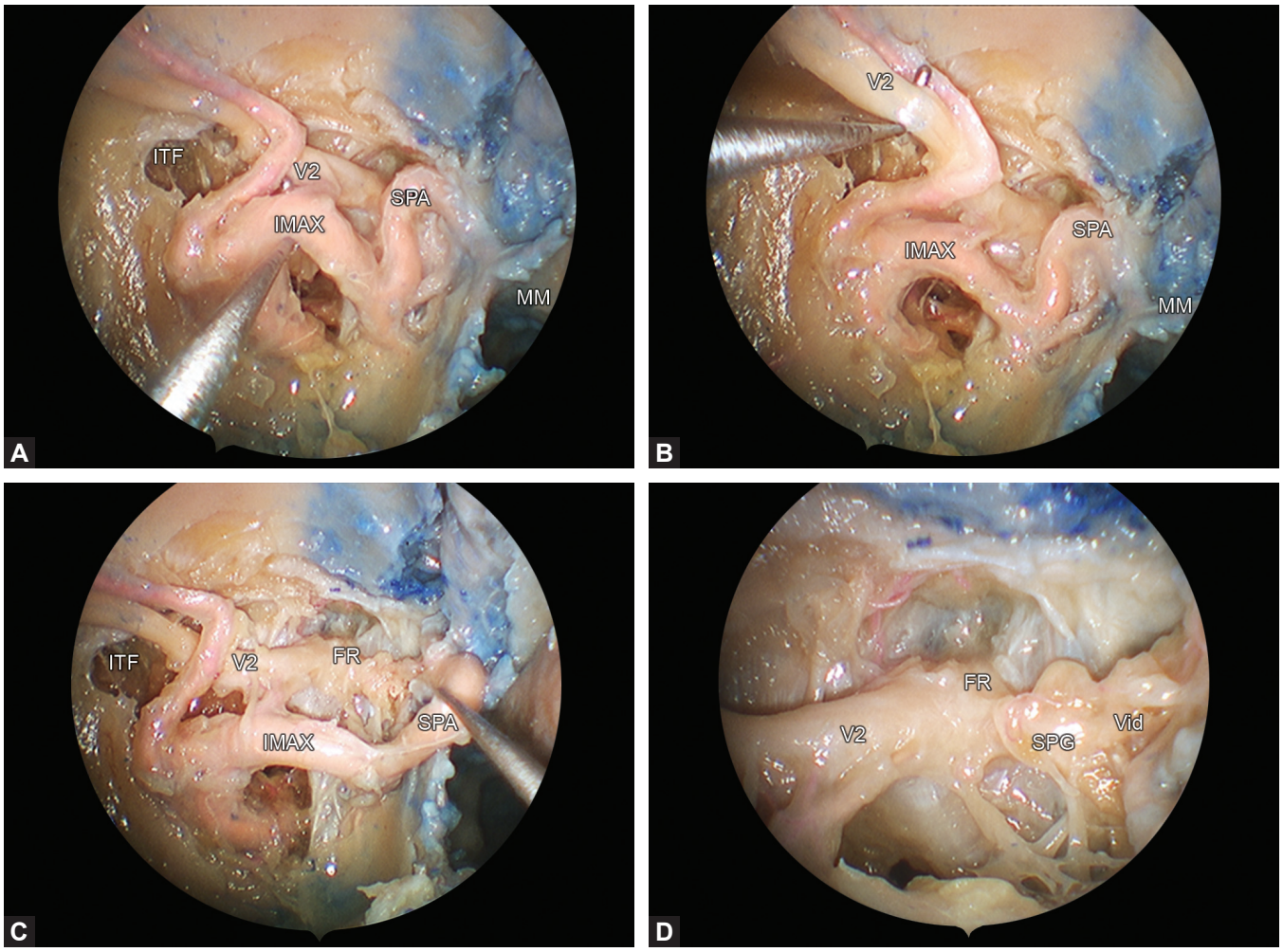
NUANCES OF THE PPF AND ITF APPROACH

Most commonly, tumors involving the PPF and ITF will extend into the sinonasal cavity. In order to access this region endoscopically, tumor debulking is usually required. The nasal component of the tumor is typically removed with the assistance of a microdebrider. It is often necessary to remove a portion of the tumor for frozen section histological analysis at the onset of the procedure. Once specimen has been obtained, the microdebrider can be used to debulk and shave the tumor back toward its origin, typically near the sphenopalatine foramen and lateral nasal wall, depending on underlying pathology. Disease that extends toward the sphenoid sinus is resected early to visualize the posterior margin of the tumor. This is helpful in defining the extent of resection and need for additional exposure. A wide sphenoidotomy can be created if tumor extends to the sphenoid floor or superiorly toward the planum sphenoidale. Tumor can be mobilized from the sinus and resected once a larger opening is created. Inspection of the septum and the choana should be performed to exclude tumor involvement as well.

The main vessels found in the PPF and ITF include the internal maxillary artery, a branch of the external carotid system, and terminal branches including the sphenopalatine artery and descending palatine artery. Critical neurologic structures include the maxillary branch of the trigeminal nerve (V2), and the sphenopalatine ganglion with branches including the vidian nerve. From an endoscopic endonasal perspective, the order of structures identified from anterior to posterior on dissection would include fat, followed by blood vessels, and then by neural structures (Figs. 58.7A to D). The vidian canal can be identified at the posteromedial border of the PPF and courses posteriorly along the inferolateral sphenoid sinus toward the petrous carotid artery and lateral edge of the cavernous segment of the carotid artery. If bleeding is encountered during debulking, cautery is often sufficient for control. Some surgeons advocate the use of coblation for tissue debulking that may aid in minimizing bleeding. Depending on the underlying pathology, tumor embolization may be advisable prior to surgery to aid in tumor devascularization. This is particularly important in cases of vascular tumors like JNAs. Most often this is performed within 24–48 hours prior to a planned surgical resection. Despite these techniques, bleeding is often encountered and a strategy of slow concentrated dissection toward the primary tumor origin and vascular supply will often avoid persistent uncontrolled hemorrhage.

Once the obstructing nasal component of the tumor is debulked and mobilized, the extended approaches to the PPF and ITF are possible. Typically the intranasal portion of the tumor can be delivered from the nose through the nostrils or, if too large, from the oral cavity. At this point, uninvolved mucosa of the posterior maxillary antrum can be elevated and reflected laterally off of the posterolateral maxillary wall. This flap also allows access to the perpendicular plate of the palatine bone and identification of the crista ethmoidalis and nearby sphenopalatine foramen as described previously. The sphenopalatine artery and branches can be cauterized or clipped for devascularization of the tumor. Using Kerrison punches or a diamond drill, the posterior maxillary wall can be removed from the sphenopalatine foramen to as far lateral as instrumentation will allow. If tumor pathology dictates, the bone can be removed from the floor of the maxillary sinus all the way to the roof with exposure of the infraorbital nerve. The nerve can be traced along the orbital floor and exposed posteromedially toward the PPF. Typically, the nerve can be spared during dissection, but in cases where tumor invades or encompasses the nerve it may be sacrificed. Preoperative discussion with the patient is important to highlight the possibility of infraorbital nerve sacrifice.

Once the PPF and ITF are completely exposed, the tumor is identified and can be resected. Gentle traction on the tumor is possible, but may require a two-surgeon technique. As the assistant places traction on the tumor, the primary surgeon can work with the endoscope and another dissecting instrument to continue the resection. Occasionally, the extended techniques described above including the Caldwell-Luc sublabial approach, Denker's anterior maxillotomy, or transseptal approach can provide extra extension and exposure for lateral access and/or



Figs. 58.7A to D: Endoscopic cadaveric view of pterygopalatine fossa and infratemporal fossa. (A) Probe identifying the internal maxillary artery. (B) Probe identifying infraorbital nerve. (C) Probe retracting sphenopalatine artery with visualization of the sphenopalatine ganglion. (D) Magnified view of the sphenopalatine ganglion and foramen rotundum.
(IMAX: Internal maxillary artery; ITF: Infratemporal fossa; FR: Foramen rotundum; MM: Middle meatus; SPA: Sphenopalatine artery; SPG: Sphenopalatine ganglion; V2: Infraorbital nerve; Vid: Vidian nerve).

additional instrumentation. Whichever technique is applied, the primary surgeon will typically work to separate the tumor along its capsule from the contents of the ITF and PPF in a lateral to medial direction. This provides controlled resection and avoidance of injury to critical neurovascular structures. When tumor vessels are encountered, suction bipolar cauterization or clipping should be performed allowing for further mobilization.

As tumor is mobilized from the lateral ITF, the surgeon will encounter the lateral and medial pterygoid muscles and pterygoid plates. Tumor may extend deep into the pterygoid space inferiorly or along the inferior orbital fissure superomedially. In the case of pterygoid space involvement, a powered drill can be used to remove a portion of the medial pterygoid plate to allow for access. If tumor extends toward or involves the mandibular division of the trigeminal nerve near foramen ovale, then dissection can continue along the medial pterygoid plate elevating the lateral pterygoid muscle posteriorly. This will allow for visualization of the disease near foramen ovale, although instrumentation may be limited in this region. When extension into the inferior orbital fissure or toward the foramen rotundum or vidian canal is identified, a wide sphenoidotomy will allow for excellent visualization of the skull base and recognition of the underlying internal carotid artery and optic nerve. The vidian nerve serves as an important anatomic landmark of dissection. Following the nerve/artery in its canal posteriorly will lead to

the lateral aspect of the cavernous portion of the internal carotid artery.[8] This junction is typically located 1.5–2 cm posteriorly along the sphenoid floor from the opening of the canal, but may vary.[4] It is critical to review CT and/or MR imaging for variation in anatomy on an individual basis to avoid vascular injury. Tumor extension toward these areas often involves dissection into a concentrated venous plexus or near the cavernous sinus that may lead to significant venous bleeding. This can be controlled in a variety of ways including warm saline irrigation, packing with gentle pressure, or use of hemostatic agents such as Floseal (Baxter Healthcare Corporation, Deerfield, IL) or thrombin-soaked Neuro Patties. Monopolar cautery should be avoided as thermal injury can occur to critical neurovascular structures including the trigeminal branches and the carotid artery. Benign tumors often create a resection plane that can be dissected without extensive resection of normal tissue. Tumors, like JNAs, can often be reduced by cauterizing the capsule allowing dissection back toward its vascular origin at the sphenopalatine artery allowing for early disruption of tumor blood supply. After disruption of the vascular supply, the capsule can be further dissected and the tumor removed transorally without sacrifice of normal anatomy including the turbinates.

In advanced PPF or ITF pathology, intracranial extension is not uncommon. Most benign tumors, however, will not directly invade dura, but will cause bony erosion and remodeling of the skull base. These tumors will commonly have a capsule that can be used as a plane of dissection between tumor and the middle cranial fossa dura. In cases where dura is directly involved, dural incisions can be made sharply and a margin of normal dura should be taken with the tumor. Dural incisions are made with retractable neurosurgical blades, most commonly a #11 scalpel. A multidisciplinary team approach, consisting of both an otolaryngologist and neurosurgeon, is important to ensure the best outcomes for these patients. When tumor extends intradurally, the neurosurgeon should assist in neurosurgical dissection as indicated.

Once the tumor has been completely resected, it can be delivered through the nostrils or pushed down through the nasopharynx into the oral cavity for removal. Frozen-section histologic analysis can be utilized at this time to ensure clear tumor margins, particularly in cases of malignancy. Critical areas of inspection include the posterior margin near the choanae, sphenoid sinus floor and clivus, as well as anterolateral maxillary sinus and infratemporal regions. If extension toward the inferior orbital fissure, foramen rotundum, or vidian canal was identified intraoperatively, nerve margins may be sent for analysis as well.

REPAIR AND RECONSTRUCTION

Most cases involving the PPF and ITF do not require dural repair or repair of a CSF leak. In the majority of cases, no extended reconstruction is required and repositioning of elevated mucosa or mucosal flaps over the resection site will suffice. Typically, the sinonasal cavity does not requiring postoperative packing. Use of absorbable hemostatic agents can aid in postoperative hemostasis if needed. If a septoplasty or transseptal approach has been utilized, a standard quilting mattress suture should be used to reapproximate the mucoperichondrial flaps and minimize risk of a septal hematoma. The hemitransfixion incision can be closed with 4-0 chromic or plain-gut in a simple interrupted fashion.

If a dural defect is acquired or a CSF leak has occurred intraoperatively, a direct dural repair is necessary. For a small dural injury, a simple inlay or onlay dural graft may suffice. This can be performed utilizing a dural substitute or from harvesting a section of fascia lata. This may be bolstered with a free mucosal or vascularized mucosal graft, typically harvested from septal mucosa or inferior turbinate. In cases of a large dural defect, a multilayered dural repair is required. There are many techniques to accomplish this task. At our institution, we typically use a fascia lata bilayered “button” graft that consists of an inlay–onlay construct of fascia lata.[9] The inlay portion of the graft is approximately 25% larger than the measured dural defect. The onlay graft is roughly the size of the dural defect. These two grafts are then sutured together in a simple mattress fashion using two to four 4-0 Neurolon sutures (Ethicon, Johnson & Johnson, Somerville, NJ).[9] Once constructed, the button graft is placed intranasally with endoscopic visualization. The inlay portion is tucked intradurally and the onlay portion is then positioned over the defect extradurally between the dura and bony margin when possible. If there is inadequate space or lack of bony margin, the onlay can be draped over the defect. This allows for a secure dural repair that should not migrate postoperatively. After the dura is repaired, the nasoseptal flap or other vascularized flap that had been harvested at the onset of the procedure is mobilized and positioned to cover the fascia lata repair. It is important to place the mucosal surface of the flap intranasally. It is also critical

that any mucosa around the defect site is removed to avoid mucocele formation deep to the flap and to allow for adherence of the flap to the bony skull base. Often biologic glue is applied around the edges of the flap for additional support. Additional support with absorbable nasal packing or nonabsorbable Vaseline gauze or other nasal packs can be placed against the flap site. If nonabsorbable packs are used, they will often remain in place for 5–10 days depending on surgeon preference. Most surgeons will maintain patients on antibiotics while packing is in place.

POSTOPERATIVE CARE

Patient cooperation and routine follow-up is critical to successful healing and remucosalization of the resection cavity. Most centers will have patients return in the immediate postoperative period, typically 5–14 days, for visual inspection and debridement of crusting and necrotic debris. Debridement will assist in more rapid healing and potentially avoid scarring and adhesions that may lead to sinusitis or nasal obstruction. Debridements are repeated until crusting is minimal and the cavity has remucosalized. Most patients require two to three postoperative debridements usually scheduled in 2-week intervals. Patients are instructed to use nasal saline irrigations starting 24-hours from surgery and continuing for several weeks to months. Patients are also instructed to avoid straining or heavy lifting for 2 weeks postoperatively and advised against nose blowing to prevent epistaxis.

In tumor cases, close follow-up and surveillance are required both endoscopically and radiographically. Postoperative MRI or CT imaging is routinely performed in 3–6 months intervals depending on underlying pathology to identify early recurrence or residual tumor. If there is obvious tumor enhancement, growth, or residuum, repeat biopsy and/or surgical exploration may be warranted for additional resection. Adjuvant therapy may be warranted including radiation and chemotherapy depending on tumor histology and high-risk pathologic features as well as extent of tumor and status of resection margins.

COMPLICATIONS

Surgical complications can occur in any of the described approaches to the PPF and ITF. It is important to recognize the risk of bleeding or infection postoperatively and discuss this with your patient prior to surgery. Neural injuries can occur in these approaches as well. Branches of the maxillary nerve or even the mandibular division of the trigeminal nerve can be injured from direct harm or from traction. When a sublabial approach is used, care must be taken to avoid excessive traction on V2 or injury to maxillary dentition and nerve roots. These injuries can lead to transient or permanent facial paresthesias or atypical facial pain. Injury to the vidian nerve or pterygopalatine ganglion can result in dry eye syndrome. If the maxillectomy is extended anteriorly, the nasolacrimal system may be injured resulting in scarring and stenosis of the duct and epiphora. Often an endoscopic DCR is performed at the time of resection to avoid long-term sequelae. Given the close proximity to the orbit, intraorbital injury is a possibility as well, including damage to the extraocular muscles leading to restricted motion or diplopia, injury to the optic nerve or vascular supply resulting in visual impairment or blindness, or orbital hematoma. An iatrogenic CSF leak is possible with risk of intracranial bleeding or injury that may not be identified intraoperatively. This may potentially increase the risk of meningitis if a delay in diagnosis occurs. Additionally if a septoplasty or transseptal approach has been performed, the risk of septal perforation increases in addition to the risk of a saddle nose deformity or disruption in nasal tip support. Tumor recurrence is always a potential risk and patients must be monitored closely in the postoperative period.

OUTCOMES

These endoscopic approaches to the PPF and ITF are relatively new advancements in surgical technique to address pathology found in these regions. Over the past few years, an increase in the number of studies analyzing the success and outcomes of these approaches has been published. However, overall, there is limited clinical data, particularly randomized control trials, that compare endoscopic approaches to the more traditional open techniques to access the PPF and ITF.

Most research into clinical outcomes has been targeted at the treatment of JNA via an endoscopic approach. A study by Fyrmpas et al.[10] analyzed 10 patients undergoing endoscopic resection of a JNA. Their endoscopic treatment involved total ethmoidectomy, middle meatal antrostomy, sphenoidotomy, clipping of the sphenopalatine artery and its branches, and drilling of the pterygoid basis. The mean follow-up period was 23.7 months (range 3–70) and all but one patient was free of macroscopic disease. They found that intraoperative blood loss was not excessive and no

patient required a blood transfusion. Patients were discharged in an average of 5 days postoperatively and with minimal complications. Their results demonstrated that endoscopic treatment of early to mid-staged JNAs is a valid alternative to external approaches.[10] In another study by Pryor et al.,[11] the authors compared traditional open approaches to purely endoscopic approaches for resection of JNA. The authors found that endoscopic approaches were safe and effective with comparable outcomes and rates of complications as the open techniques. In the 65 patients treated for JNA during their study interval, 6 patients underwent successful resection of JNA by way of an endoscopic approach. In comparison to the conventional surgery group, the endoscopic group had less intraoperative blood loss (225 vs. 1,250 mL), a lower occurrence of complications (1 patient vs. ≥30 patients), shorter length of hospital stay (2 vs. 5 days), and lower rate of recurrence (0% vs. 24%).[11] Of course with any retrospective study, the conclusions are limited by the fact that the two treatment groups were not randomized or compared prospectively. Retrospective data have been published for other diseases affecting the PPF and ITF as well. A recent study looking at endoscopic treatment for nonmalignant neurogenic tumors found success in terms of complete tumor extirpation without recurrence at 12–78 months in all five patients analyzed.[12]

The need for additional research and formalized analysis, particularly randomized controlled trials, will be necessary to further our understanding of outcomes and success for endoscopic approaches to the ITF and PPF. As the familiarity of these techniques grows, more data will be available to determine true outcomes and the appropriate indications for their utilization.

CONCLUSION

Transnasal endoscopic surgery is an overall excellent option for patients harboring PPF and ITF disease. The endoscopic approach is a safe and effective procedure, in the appropriately selected patient, with the potential to minimize postoperative morbidity. These techniques can be used for clinical indications ranging from diagnostic biopsy, to control of epistaxis to definitive tumor resection, where appropriate. The endoscopic methods described in this chapter highlight the need for keen clinical acumen and intraoperative preparedness that will aid in appropriate patient selection, improving patient outcomes, and minimizing complications.

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CHAPTER

Endoscopic Surgery of the Clivus, Craniocervical Junction, and Posterior Fossa

59

Aldo Cassol Stamm, Diego Rodrigo Hermann, Leonardo Balsalobre, Eduardo de Arnaldo Silva Vellutini

INTRODUCTION

Before the modern endoscopic era, lesions in the central skull base were managed using extensive craniotomies, often resulting in significant morbidity to patients.[1] In contrast to the traditional transcranial or transfacial cranial base surgical approaches, the endoscopic endonasal techniques offer a direct and minimally invasive approach that allows excellent midline access to the sphenoid sinus walls, clivus region, and retroclival spaces, while obviating brain retraction.[2] However, even with several endoscopic proposed approaches, effective and safe treatment of lesions involving these regions is still a challenge.[3]

Malignant tumors and benign lesions involving the clivus, posterior fossa, and craniocervical junction (CCJ) are not commonly seen in the routine of the skull base surgeons. Lesions involving these structures are rare, and are not limited to clivus chordomas and chondrosarcomas. Other malignant and benign tumors and inflammatory and infectious diseases can be found arising from this region.

There have been several critical advances, considering malignant tumors that have allowed endoscopy to achieve comparable rates of resection with conventional open approaches, including understanding of anatomy, endoscopic instrumentation, image guidance, and modern reconstructive techniques.[4]

There has been a misperception that the endoscopic approach is a minimal surgery, which it actually is in some cases. But endoscopic-assisted surgery can remove and can be as ablative as open approaches. The resection cavities, whether performed endoscopically or open, are equivalent in most cases,[4] depending on the lesion that will be treated, not the approach.

BRIEF ANATOMY

The anatomy of the clivus, posterior fossa, and CCJ is described in detail elsewhere in this book. Thus, our intention is only to review some important landmarks in this region. Anatomical alterations are often seen with tumors in this region, because they usually displace structures, such as major arteries and cranial nerves (CN), in all directions. It is important to relate the anatomy, the endoscopic surgical anatomy, and its relation with the tumor observed on imaging studies.

The clivus is actually a bony region formed by the posterior portion of the sphenoid body (basisphenoid) and the basilar part of the occipital bone (basiocciput). The clivus is related posteriorly to the posterior cranial fossa, anteriorly to the sphenoid sinus and nasopharynx, superiorly to the sella turcica, and inferiorly to the foramen magnum. It is subdivided into upper, middle, and lower thirds. The upper third (Fig. 59.1) is at the level of the sphenoid sinus and is formed by the basisphenoid bone, including the dorsum sellae. The middle clivus corresponds to the rostral part of the basiocciput and is located above a line connecting the caudal ends of the petroclival fissure, and the lower third is formed by the caudal part of the basiocciput. The intracranial surface of the upper two-thirds faces the pons; the lower clivus is related to the nasopharynx and extends below the sphenoid sinus, and, at this level, the intracranial surface faces the medulla oblongata. The internal carotid arteries (ICAs), in the lower third (Fig. 59.2), are further lateral, and a lateral dissection is limited by the jugular foramen, occipital condyles, and

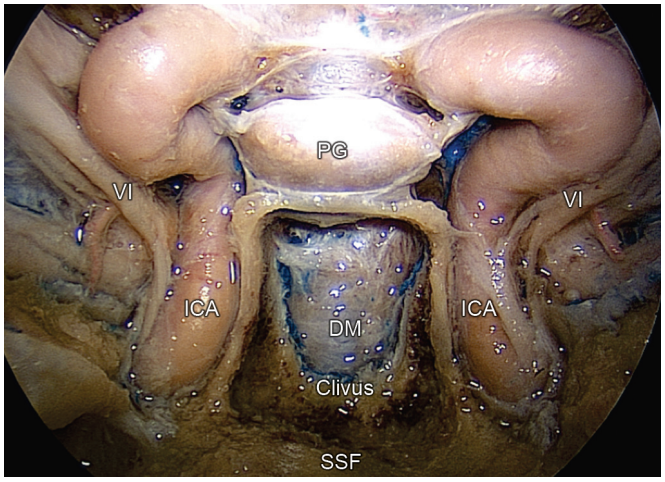


Fig. 59.1: Cadaver dissection demonstrating the upper and middle clivus and structures that border it.
(PG: Pituitary gland; DM: Dura mater; ICA: Internal carotid artery; SSF: Sphenoid sinus floor; VI: Cranial nerve VI).
Courtesy: T. Scopel.

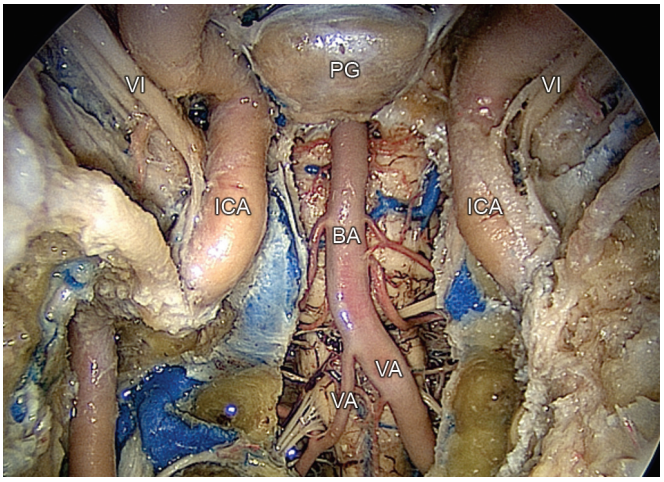


Fig. 59.2: Cadaver dissection demonstrating the upper, middle, and lower clivus, as well as the craniocervical junction.
(PG: Pituitary gland; VI: Cranial nerve VI; ICA: Internal carotid artery; BA: Basilar artery; VA: Vertebral artery).
Courtesy: T. Scopel.

hypoglossal canal. Two layers cover the intracranial surface of the clivus, the periosteal outer layer, and the meningeal inner layer; the basilar venous plexus and abducens nerve run between them. The abducens nerve (CN VI) arises at the vertebrobasilar junction; it runs between dura layers obliquely, from prepontine cistern to Dorello's canal and then to the cavernous sinus, laterally to the ICAs. When the inner layer of the clival dura and the arachnoid are opened, the vertebral arteries, the basilar artery, and its branches (superior cerebellar arteries, anterior inferior cerebellar arteries), posterior cerebral arteries, the brainstem, mammillary bodies, and the intradural way of CN III, IV, V, and VI are exposed. CN III runs between the posterior cerebral and superior cerebellar arteries. CN V is located laterally to the superior part of the pons. Beneath and deeper to the CN V, the cerebellopontine angle and CN VII/VIII and lower CN are seen using the 45° and 70° endoscopes.

The CCJ is a complex region between the skull base and the upper cervical spine. It is located behind the nasopharynx, and can be accessed through the nose. It is important to understand the bony configuration, ligamentous attachments, and vascular supply to reach this unique region through endoscopic transnasal approach. After lateral displacement of the nasopharynx mucosa and the longus capitis muscle, the anterior arch of C1 and C2 and odontoid process can be assessed. The neural structures situated at this level are caudal part of the brainstem, cerebellum, fourth ventricle, the rostral part of the spinal cord, and the lower cranial and upper cervical nerves. The major arteries related to CCJ are the vertebral arteries, the posteroinferior cerebellar artery, and the anterior spinal artery. The vertebral arteries runs behind the lateral masses of the axis and enter the dura behind the occipital condyles, ascending through the foramen magnum to the front of medulla, and join to form the basilar artery at the pontomedullary junction.[5-7]

Tumor Types

The endoscopic transnasal transsphenoidal approach may be used for lesions involving the clivus, retroclival region, and CCJ. The most common lesions treated through the endoscopic approach are clival chordomas and chondrosarcomas. Other rare lesions can also be found in this region and can be malignant, benign, inflammatory, or infectious diseases (Table 59.1).

Chordomas are thought to originate from the notochord.[8] Chondrosarcomas are believed to originate from primitive mesenchymal cells or from embryonal rest of the cartilaginous matrix of the cranium.[9,10] Chordomas and chondrosarcomas are rare tumors, each comprising approximately 0.1% of all brain tumors. The vast majority of skull base chordomas are midline tumors, whereas chondrosarcomas are paramedian with a predilection for the sphenopetroclival area. Their location, propensity to infiltrate bone, and notorious ability to recur make them difficult tumors to be treated.[9,11] Other lesions found in

Table 59.1: Clivus, posterior fossa, and CCJ lesions

Cases	*Number*
Chordomas	31
Chondrosarcomas	3
Mucoceles	10
Primary CSF leaks	6
Myoepithelioma	1
Meningioma	1
Angiosarcoma	1
Plasmacytoma	1
Breast cancer metastasis	2
Fibrous dysplasia	1
Lymphoma	1
Prostate cancer metastasis	1
Adenoid cystic carcinoma	1
Tuberculosis	1
Invasive aspergilloma	1
Epidermoid cyst	1
Teratoma	1
Foramen magnum meningioma	1
In the CCJ	2
Total	67

(CCJ: Craniocervical junction; CSF: Cerebrospinal fluid).

these regions do not have accurate epidemiologic data in literature, due to their rarity.

DIAGNOSTIC TESTING

Coronal, axial, and parasagittal computed tomography (CT) images of the paranasal sinuses and skull base are essential in preoperative assessment. It is also necessary to evaluate the size of the sphenoid sinus, the position of the ICAs, especially the paraclival portion, and the thickness of the clivus in the sagittal plane.

Magnetic resonance imaging (MRI) is important to demonstrate the morphology of the soft tissues. Additionally, MRI should be used to evaluate for involvement of the carotid arteries, vertebrobasilar system, the dura in this area, the relationship between the tumor and brainstem, and cavernous sinus.

Magnetic resonance angiography (MRA) or CT angiography (CTA) can also be helpful to look at the relationship between the basilar and ICAs and the pathology. Particular attention should be given to the cavernous sinus, the inferior end of the superior intercavernous sinuses, and the basilar venous plexus. Angiography can also be important to verify the functional integrity of the circle of Willis and the extent of any carotid artery compromise, and to differentiate an aneurysm from a tumor.[5]

In clival chordomas, the CT scan is preferable for demonstration of bone erosion, osteolysis, and intralesional calcifications; typically, there is no surrounding sclerosis,[12] and MRI demonstrates a characteristic bright T2-weighted signal. Midline locations are also typical. Chondrosarcomas may appear very similar to chordomas on MRI, but they are typically off of the midline, as they tend to invade the skull base through the foramen lacerum and petroclival fissure.[13] Special consideration should be given regarding the paraclival and petroclival portions of the ICA. It is important to make sure that the "mass" that should be resected or biopsied is not an aneurysm. A giant aneurysm in this area can mimic mass lesions due to the slow flow and partial thrombosis. In these cases, MRA usually allows identification of such aneurysms. CTA has superior spatial resolution, but sometimes it may be difficult to differentiate the enhancing vessel lumen from other structures.[13] A carotid artery occlusion test may be performed whenever the ICAs are encased and narrowed or just encased in a patient with a history of surgery or radiotherapy.[8]

EQUIPMENT AND INSTRUMENTS

Skull base surgery requires precise and gentle maneuvers and in order to achieve good results with low morbidity rates, the use of proper instruments is indispensable. High-definition cameras (Karl Storz, Tuttlingen, Germany) help in a more accurate view of the operative field. The instruments are longer than those designed for surgery within the paranasal sinuses, and they are essential for accurate surgical techniques, such as delicate scissors and bipolars (Stamm Skull Base Set—Medtronic, MN, USA, Fig. 59.3). New technology should be incorporated in the surgical armamentarium if possible: image guidance system, monitoring of CN [especially the abducens nerve (VI), the oculomotor nerve (III) and lower CN], micro-Doppler to identify the course of major vessels, and intraoperative MRI to assess the degree of resection.

Endoscopic Surgical Technique

Surgery is usually carried out under hypotensive general anesthesia. The patient is positioned supine with the head

Fig. 59.3: Delicate bipolar used to provide accurate hemostasis with low risk of injury.

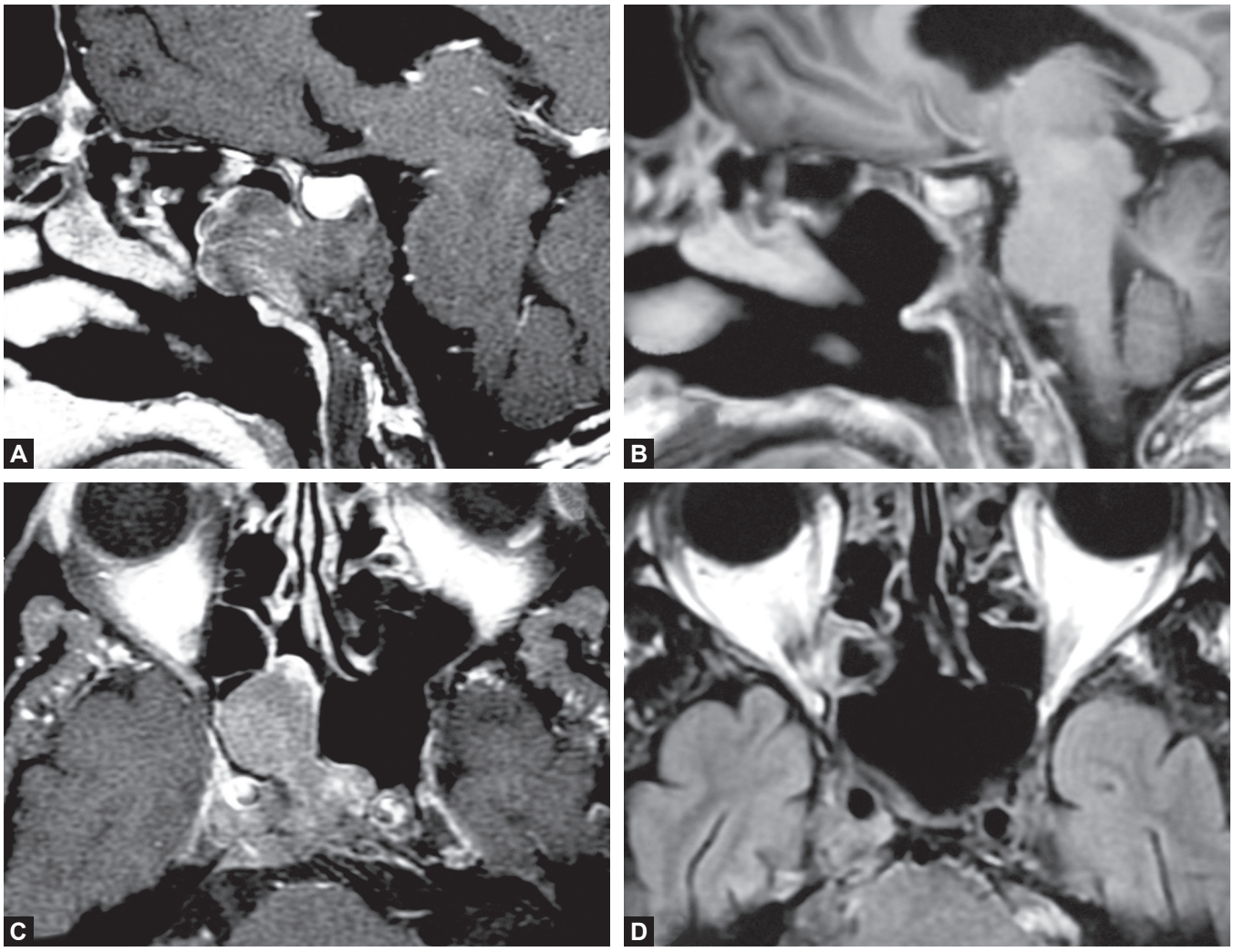
up at about 30° to reduce venous bleeding. The routine use of lumbar drains or shunts is not necessary. The first step in the surgery is the nasal corridor preparation. It allows an adequate exposure of the deep surgical field and enables the use of pedicled flaps for final reconstruction of the skull base. The access is performed using the combined binostril approach through the transnasal and transseptal route,[14] allowing for a 3- or 4-handed surgical technique. A 5 mm 0^0 Hopkins endoscope allows better visualization than the standard 4 mm scope (Karl Storz, Tuttlingen, Germany). Topical decongestants are used to maximize hemostasis and nasal patency. High-concentration epinephrine-soaked cottonoids (1:2000) are placed in the nasal cavity for 10 minutes before the beginning of the surgical procedure. Local infiltration is performed to aid the flap elevation thus decongesting the nose. The septum is infiltrated with a combination of lidocaine with epinephrine (1:100,000).

A hemitransfixion septal incision is performed and the mucoperichondrium/mucoperiosteum is elevated. A pedicled flap is harvested to use in the reconstruction. It should be a generous size, larger than the defect that will be produced. To reduce bleeding from the free edges of the mucosal flap and remaining in situ mucosa, the incision is made with the use of a monopolar diathermy needle. In primary cases, when the septum is intact, the flap should be performed as anterior as possible, and it may be started in the mucocutaneous transition; the nasal floor mucosa can be used to enlarge the flap, all pedicled on the posterior nasal septal branch of the sphenopalatine artery. Most of the septal cartilage and bone are removed, leaving a sheet of contralateral mucosa as the remaining septum and an "L"-shaped cartilage strut to support the nasal dorsum and tip. The inferior turbinate is usually left in situ, but may be resected if it precludes surgical access. In revision cases or when there is a pre-existing septal defect, the flap is harvested from the lateral wall and nasal floor. In this case, an incision is performed under the middle turbinate and the mucosa is dissected off the lateral wall of the nose, around the inferior turbinate and the nasal cavity floor. A mucosal island is left around the opening of the nasolacrimal duct. The bone of the inferior turbinate could then be removed if the lateral flap is harvested. Again, this flap is pedicled around the sphenopalatine vessels and can be left inside the maxillary sinus during the surgery.

The next step is the exposure of the tumor, which is performed according to its extension. There are basically three different variations in the endoscopic transnasal transclival approach: (1) tumors located in the upper clivus midline are removed through an endoscopic transnasal transsphenoidal approach, (2) tumors extending laterally to the carotid artery are accessed through both a transnasal transsphenoidal and a transnasal transpterygoid approach, and (3) tumors located in the lower clivus are removed through a transnasal retropharyngeal approach. Due to the infiltrative nature of clivus tumors, the surgical approach may be a combination of these corridors, in most cases.

Tumors Located in the Upper Clivus Midline

Initially, the anterior sphenoid sinus wall is removed using a micro-Kerrison punch and then it is drilled out using a cutting burr, as low as possible, in order to expose the whole clivus, and to allow better flap position in the skull base reconstruction at the end of surgery. Key anatomical structures of the sphenoid sinus may be identified, such as the sella floor, ICA prominences, optic nerve canals, and the upper clivus. The clivus mucosa is removed. Clival bone removal is necessary not only to achieve access to the tumor access but also to remove the infiltrated bone. This is a requirement for complete tumor removal, and it is performed carefully, using a 5 mm or 6 mm diamond drill. Caution is key to ensure complete hemostasis at this point of the procedure. The surgical field should be completely dry before proceeding to the next step of the procedure. The surgical boundaries of the bone removal, in this approach, are the sella floor superiorly, the ICAs laterally, and the sphenoid sinus floor inferiorly (Figs. 59.4A to D).



Figs. 59.4A to D: Clivus chordoma in the upper and middle clivus midline. (A) Preoperative T1-weighted sagittal cut magnetic resonance imaging (MRI) demonstrating a clivus chordoma invading the sphenoid sinus, the clivus, and the posterior fossa. (B) Postoperative T1-weighted sagittal cut MRI after tumor removal. (C) Preoperative T1-weighted axial cut MRI. (D) Postoperative T1-weighted axial cut MRI after near total tumor removal; there is a residual tumor behind the right internal carotid artery.

Extradural lesions can be resected, usually, with the use of regular or ultrasonic suction. In cases of chordomas, it is very important to make certain that the bone margins are tumor free.

For intradural exposure, if not invaded by the tumor, the dura needs to be incised. In extradural tumors with intradural extension, bleeding from the basilar plexus may not be vigorous if the plexus is partially occluded by the tumor and may define the infiltration limits. However, in purely intradural tumors, bleeding from the basilar venous plexus can be problematic and its control is performed using Surgicel and/or Surgiflo (Ethicon, New Jersey, USA). Judicious packing, time, patience, head-up position, and hypotension are mandatory requirements to control bleeding. Meticulousness is needed to avoid damaging of the CN VI, located at the two-thirds of the way down the clivus between the two dural layers. The internal (meningeal) dural layer is opened in the midline, superiorly, avoiding the basilar artery. Once the dura is opened, bipolar diathermy can be used to control dural bleeding. Tumors extending to the posterior fossa (Fig. 59.5) may involve important neurovascular structures at this region. Surgical dissection in order to separate the tumor from vascular structures, such as the vertebral arteries, basilar, and its branches, especially the perforating arteries, should be performed with extreme precision

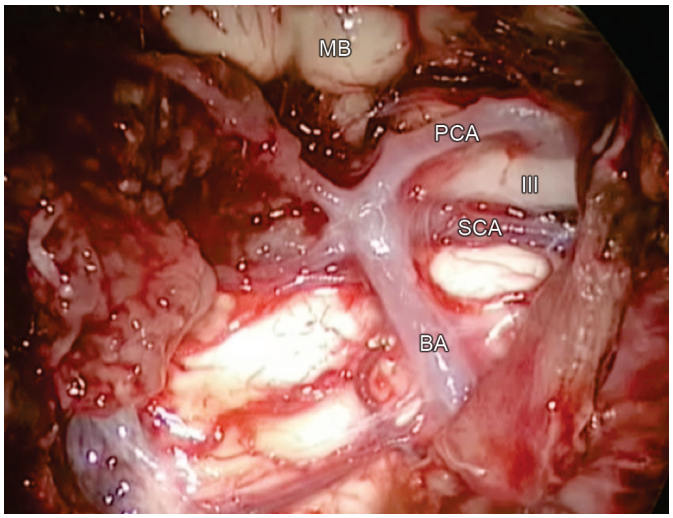
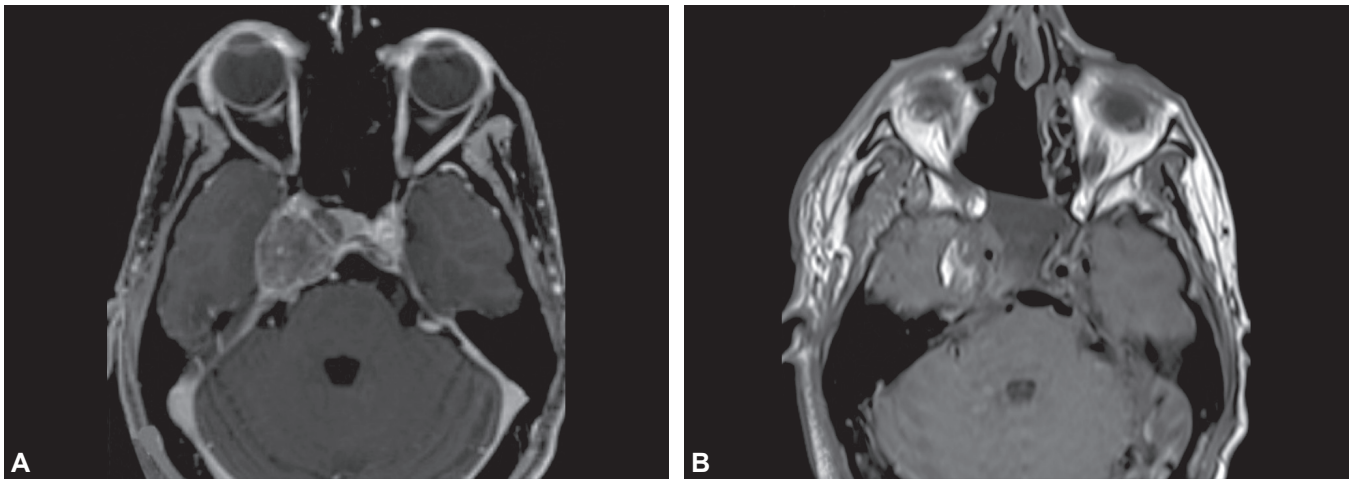


Fig. 59.5: Intraoperative endoscopic view of the posterior fossa dissection.
(BA: Basilar artery; PCA: Posterior cerebral artery; MB: Mammillary bodies; III: Cranial nerve III; SCA: Superior cerebellar artery).



Figs. 59.6A and B: Clivus chordoma. (A) Preoperative T1-weighted axial cut magnetic resonance imaging (MRI) demonstrating a clivus chordoma with lateral extension to the carotid artery and cavernous sinus. (B) Intraoperative axial cut MRI, after the tumor removal.

since lesions of these small vessels—the perforating arteries —may cause ischemia at the level of the brainstem and surrounding areas, with serious neurological sequelae. Another important aspect of the posterior fossa dissection is the identification and careful dissection of CN III, IV, V, VI, VII, and VIII and other lower CN. After careful tumor removal and perfect hemostasis, the reconstruction can begin.

Tumors Located Laterally to the Internal Carotid Artery (Figs. 59.6A and B)

For lesions extending laterally to the sphenoid sinus and to the ICA, the transnasal transpterygoid approach complements the transnasal transsphenoidal approach. The key is centralizing the vertical portion of the carotid artery (Fig. 59.7). It is usually combined with the removal of the medial and posterior walls of the maxillary sinus. In most cases, the removal of the ethmoid sinus cells and the middle turbinate is required. In these cases, the nasal septal flap needs to be prepared on the contralateral side due to the sphenopalatine artery, which is located on the same side of the lesion and needs to be coagulated. In those cases where the contralateral flap cannot be harvested, the flap is made on the same side. In those cases, in order to not cause injury to the sphenopalatine artery branches, the posterior wall of the maxillary sinus should be removed, and the flap can be left in the maxillary antrum until the end of surgery. The medial wall of the maxillary sinus is removed to create an opening that extends inferiorly up

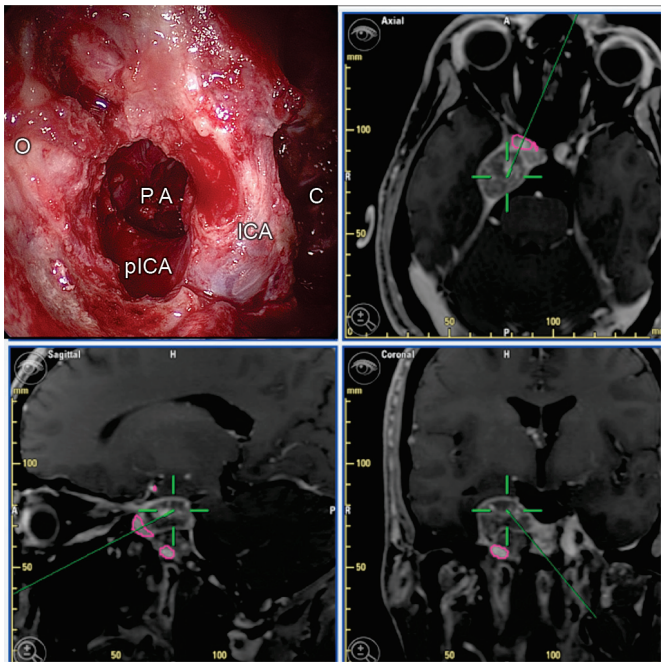


Fig. 59.7: Intraoperative magnetic resonance imaging (MRI)-based image-guided tracking of the lesion (chordoma). The transpterygoid approach allows the tumor resection laterally to the internal carotid artery.
(O: Orbit; C: Clivus; ICA: Internal carotid artery; pICA: Petrous portion of the ICA; PA: Petrous apex).

to the nasal floor, up to the nasolacrimal duct anteriorly, and up to the pterygoid plate posteriorly. The posterior wall of the maxillary sinus is opened to enlarge the sphenopalatine foramen and to expose the pterygopalatine and infratemporal fossa periosteum. The pterygoid plates are removed with the use of a drill or a Kerrison punch, in order to expose the lateral portion of the sphenoid sinus and the cavernous sinus. Anatomical landmarks include the lamina papyracea, the vidian nerve running toward the vertical ascendant portion of the carotid artery, the maxillary artery in the sphenopalatine fossae, and the maxillary portion of the trigeminal nerve, running on the maxillary sinus roof. The CN related to this approach are the abducens, the oculomotor, and the trigeminal nerves. In tumors arising medially to the carotid artery, nerves should be displaced laterally.

Tumors Located in the Lower Clivus and Craniocervical Junction (Fig. 59.8)

The transnasal–retropharyngeal is the best approach to manage tumors originating or secondarily extending to the lower clivus, inferior to the floor of the sphenoid sinus.

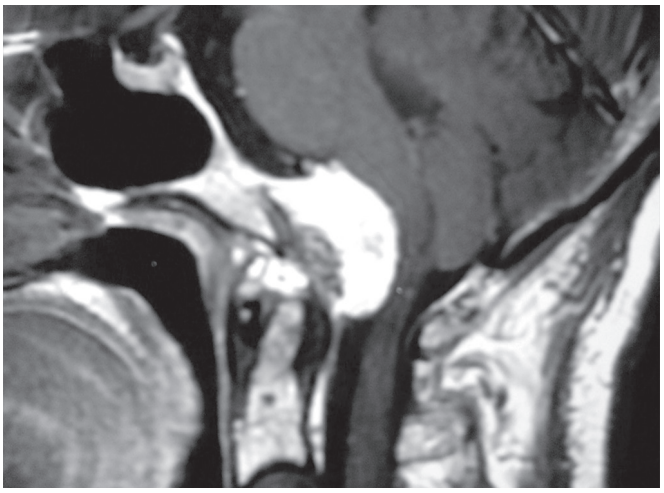


Fig. 59.8: Sagittal T1-weighted magnetic resonance imaging (MRI) image showing a foramen magnum meningioma.

After performing the nasal septal flap, the sphenoid sinus is opened and its entire floor is drilled out. The lateral dissection limits are the vertical portion of the carotid artery, which can be identified by the vidian nerve canal. Below the sphenoid sinus, the nasopharynx mucosa is opened and the longus capitis muscle is exposed; its lateral retraction allows the exposure of the inferior clivus, the atlantoaxial membrane, and the anterior arch of cervical vertebrae C1 and C2. Dissection limits are the pharyngeal portion of the carotid artery and the occipital condyle laterally and the soft palate inferiorly. Removal of more than one-third of the occipital condyles can create occipitocervical instability, which needs to be repaired. The CN related to this approach are the lower CN, especially the hypoglossal nerve, which runs more anteriorly at the occipital condyle level. Caution with the vertebral artery in the lower portion of C2 is highly recommended, where most of its course takes place medially.

RECONSTRUCTION

Successful repair of the skull base is the key to avoid cerebrospinal fluid (CSF) leaks and infectious complications. Dural defects in the clivus region are submitted to more pressure hence are prone to more problems than the other regions. The “triple F” technique (fat, fascia and flap) is used. The free fat grafts are used to fill dead space and to form a buttress for a fascia lata inlay graft. More than one layer of fascia may be used. Synthetic material such as Duragen (Integra Life Sciences Corp.; Plainsboro, NJ) or Duraform (Codman; Raynham, MA) may be used

instead of the fascia. Finally, all these structures are covered with the nasoseptal or lateral nasal wall flap pedicled in the sphenopalatine artery. The use of pedicled flaps reduces CSF leaks significantly.[5] Fibrin glue is not used routinely. The Spongostan (Ethicon, New Jersey, USA) and the Gelfoam (Pfizer, New York, USA) are used in layers underneath the flap, and followed by a ribbon gauze packing soaked in antibiotic ointment. A Rapid Rhino 900 Epistaxis Device (ArthroCare ENT, Austin, Texas) or a Foley catheter balloon is inflated to support the repair and to avoid displacement of the nasal packing into the nasopharynx. The balloon must be positioned under direct vision, and it is left in this position for about 5 days. Then anterior packing supports these structures.

AUTHORS' EXPERIENCE

From 1995 to 2013, the authors have treated 67 lesions of the clivus region, posterior fossa, and CCJ through the endoscopic transnasal transsphenoidal approaches (*see* Table 59.1).

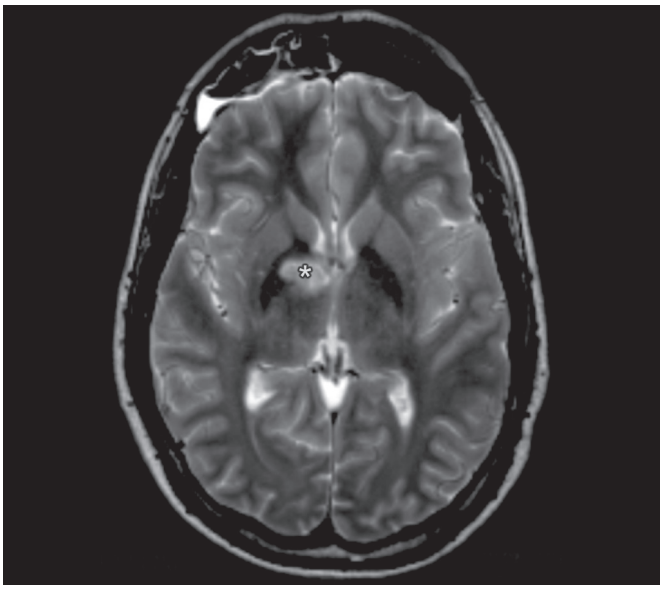


Fig. 59.9: Axial T1-weighted magnetic resonance imaging (MRI) image showing an ischemic thalamic stroke, after perforating arteries injury during a posterior fossa surgery for clivus chordoma.

COMPLICATIONS

Although endoscopic transnasal approaches often have a lower morbidity rate, the risk of complications is similar to that of conventional open transcranial techniques.[15] The prompt and precise identification of complications, which may occur with patients harboring lesions in these skull base regions, are paramount for correct complication management. Complications may include CSF leakage (the incidence in our experience, after the use of the pedicle flap, is about 5%), nasal bleeding, bleeding from ICA, intracranial bleeding, basilar plexus bleeding, cavernous sinus bleeding, CN injuries, stroke (Fig. 59.9), intracranial infections such as meningitis and ventriculitis, orbital hematoma due to the nasal approach, nasal synechia, and nasal/paranasal infection,[5] endocrine and electrolyte disorders.

Prevention and Management of Complications

Complications of skull base surgeries may occur as in every surgical procedure. Prevention of these complications begins with adequate preoperative evaluation of the patient, including a history of current disease, the use of medications, previous surgeries, allergies, and other medical conditions that may worsen during prolonged general anesthesia. The teamwork between the otolaryngologist and the neurosurgeon is indispensable. In cases of lesions involving the pituitary gland, an endocrinologist evaluation helps in prevention and treatment of hormonal complications. Likewise, an evaluation by an ophthalmologist helps in identification of visual and eye movement alterations that may be occur. Because of the presence of major and delicate structures located in this region, a meticulous CT scan and MRI evaluation are essential. Preoperative analysis of arteries and veins, venous sinuses, and CN located near or involved by the lesion is critical. Major structures that must be identified and their relationship with the region to be operated are the orbits, bony septa within the sphenoid sinus, the optic chiasm, CN II, III, IV, V and VI; both carotid and vertebral arteries and the basilar artery.

The use of high-definition cameras helps in more accurate identification of surgical structures. Surgical technique must be as aseptic as possible; precise and gentle maneuvering with the use of delicate instruments appropriate for endoscopic skull base surgery, with meticulous hemostasis using delicate bipolar coagulation, and all this preferably with the use of image-guided system. The correct and precise identification of venous, arterial, and venous sinuses during the surgery also aid. For extradural lesions, beware small CSF leaks that may occur. Also for dural or intradural tumors, the correct defect management at the end of surgery is critical, as described previously.

The use of prophylactic antibiotics may help to reduce crust formation, improve healing, and decrease the chance of infectious complications. Usually a third-generation cephalosporin is used for 10 days.[5] The patient needs to be educated for signs of infectious complications. Some tragic complications may occur, such as ICA injury, meningitis, ventriculitis, and compressive pneumoencephalus.

Advantages

Endoscopic-assisted approaches allow improved visualization, illumination, and an up-close panoramic view of the operative field. The possibility of using different angled scopes improves removal of lesions located in lateral and posterolateral positions. The "four hand technique" offers the possibility of using up to three instruments in addition to the endoscope.[14] This technique can be minimally invasive for the surgical treatment of benign lesions, preserving the structures of the nose and paranasal sinuses. It can also be expanded to resect involved structures in patients with malignant lesions. In contrast, microscope-based transcranial approaches require large bone openings in all cases to allow the passage of sufficient light to the lateral extensions of the tumors.[15] Finally, endoscopic techniques avoid significant sequelae produced by transfacial approaches, including esthetic facial scars and deformities, vestibular stenosis, and facial hypoesthesia. The incidence of injury to the lower CN may be lower with endoscopic techniques.

Limitations

A deep surgical field surrounded by complex anatomy, with important neurovascular structures in conjunction with the infiltrative nature of most tumors located in this area, are all challenging factors. Other limitations include patient comorbidities that might preclude prolonged general anesthesia; tumor location; unfavorable anatomy, such as small sphenoid sinus or diminished space between the ICAs, which makes drilling the clival bone more difficult and riskier; lack of multidisciplinary team cooperation and interaction: and lack of specialized equipment/instruments.

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CHAPTER

Endoscopic Surgery of the Cavernous Sinus and Petrous Apex

60

Seth M Lieberman, Mohammad Al Bar, Roy R Casiano

INTRODUCTION

Classic surgical approaches to the cavernous sinus and petrous apex have included transcranial and transtemporal approaches. With advancements in endoscopic instrumentation and technique, these complex areas have become accessible through transnasal approaches. Disadvantages of the traditional open approaches include the potential risk to hearing, balance, facial nerve function, and brain retraction. Potential advantages of the endoscopic approach include decreased perioperative morbidity including avoidance of a craniotomy, a faster recovery time, and shorter hospital stay, fewer postoperative symptoms, and improved maintenance of a drainage pathway that is accessible in the office.[1,2] However, it is the improved ability to visualize and effectively manage lesions within the cavernous sinus and petrous apex that represents the primary benefit of endoscopic surgery. Ultimately, the endoscopic approach is just another tool in the armamentarium of the skull base surgeon. It is up to the surgeon and the clinical situation to determine when it is appropriate.

ANATOMY

Prior to embarking on an endoscopic approach to the cavernous sinus or petrous apex, the surgeon must have a firm understanding of the critical structures at risk and the anatomical landmarks that will guide them to a safe surgical exposure of the area.

Cavernous Sinus

The cavernous sinuses are paired structures on both sides of the sella turcica extending on each side from the superior orbital fissure (SOF) to the dorsum sellae. Each cavernous sinus is composed of four walls of dura mater: lateral, medial, superior, and posterior. In coronal section, each appears trapezoidal in shape that is larger posteriorly and narrower anteriorly. Within these dural walls is venous blood, the internal carotid artery (ICA) with its branches, the sympathetic plexus, and cranial nerves (CN) III, IV, V1, and VI.

Though there has been some debate, it has been found that the lateral, superior, and inferior walls are composed of two dural layers, an outer meningeal and an inner periosteal layer, while the medial wall is composed of only a single layer.[3] Both layers of the lateral wall of the cavernous sinus continue laterally with the dura covering the middle cranial fossa, medially with the dura of the superior wall of the cavernous sinus, anteriorly with the dura covering the concave surface of the greater wing of the sphenoid bone, and posteriorly with the tentorium. The external layer of dura is thicker, and the internal layer is thin and contains CN III, IV, and V as they course toward the SOF. The limits of the lateral wall of the cavernous sinus are the anterior petroclinoid ligament superiorly, the superior border of the maxillary nerve inferiorly, the SOF anteriorly, and an imaginary line that lies flush with the plane of the dorsum sellae posteriorly (Figs. 60.1 and 60.2).

The medial wall represents the lateral limit of the pituitary fossa and is the only wall that consists of a single dural layer. The roof, or superior wall, is the shape of a trapezium with the base to the lateral side. The limits are the lateral limit of the diaphragma sella, medially; the anterior petroclinoid ligament and the lateral border of the anterior clinoid process, laterally; an imaginary line

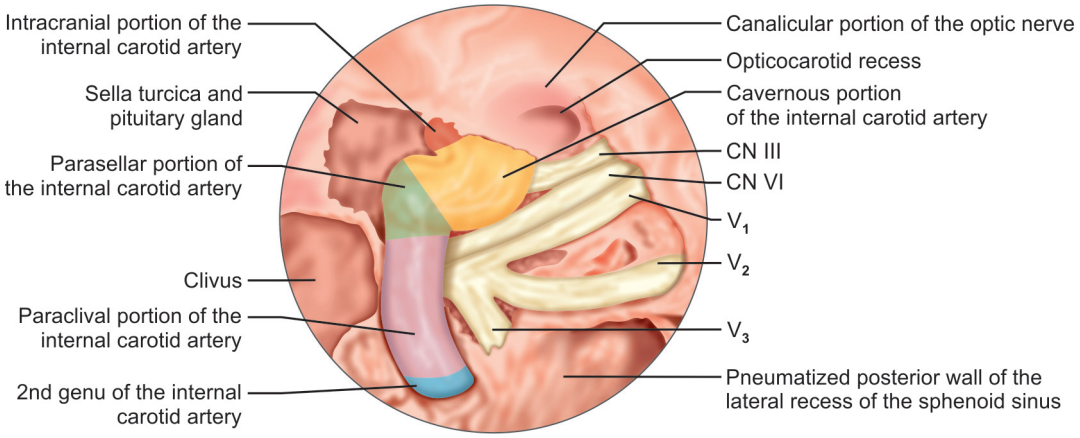


Fig. 60.1: Drawing of the left paraclival and parasellar internal carotid artery (ICA) with the medial layer of cavernous sinus dura removed.
Source: Adapted with permission from Casiano RR. Endoscopic Sinonasal Dissection Guide. New York: Thieme; 2012.

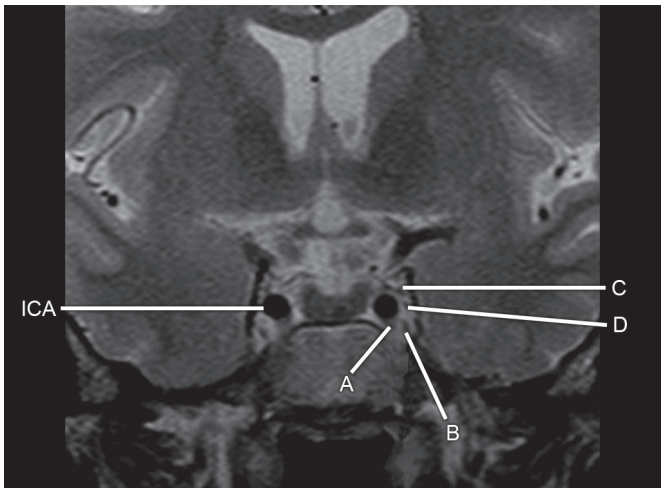


Fig. 60.2: Cavernous sinus anatomy. Coronal T2-weighted magnetic resonance imaging (MRI). A, CN VI; B, CN V2; C, CN V1; D, CN III; ICA, the inferior horizontal portion of the parasellar internal carotid artery. CN IV cannot be seen but should be lying between CN III and CN V1. Also seen but not labeled are the pituitary gland and the optic chiasm.

passing through the base of the anterior clinoid process, anteriorly; and the posterior petroclinoid ligament, posteriorly. The posterior wall is part of the dural covering of the clivus extending medially from the lateral edge of the dorsum sella to laterally at a point just medial to the Meckel's cave. Superiorly the posterior wall extends from the posterior petroclinoid ligament to the superior portion of the petroclival fissure inferiorly.[3-5]

The paired cavernous sinuses are interconnected by superior and inferior intercavernous sinuses. The ICA enters the cavernous sinus at it transitions from the paraclival to the parasellar portion of the ICA, which includes the posterior bend, the inferior horizontal segment, and the anterior ascending segment of the C-shaped carotid siphon, after which it exits the cavernous sinus. While within the cavernous sinus, the ICA gives off an inferolateral branch that supplies portions of CN III, VI, V and VI.[4]

The oculomotor nerve forms the inferior border of the optic strut triangle or optic–carotid recess. This nerve courses anteriorly, lateral to the upper part of the anterior vertical portion of the parasellar ICA to enter the SOF. The trochlear nerve runs lateral to and just inferior to the oculomotor nerve to reach the SOF. The abducens nerve courses anteriorly just lateral to the paraclival ICA and then along the inferior border of the inferior horizontal portion of the parasellar ICA. The ophthalmic division of the trigeminal nerve (V1) lies lateral to the abducens nerve running anteriorly and superiorly to the SOF. The maxillary division of the trigeminal nerve (V2) marks the inferior aspect of the cavernous sinus. This nerve courses anteriorly just lateral to the paraclival ICA to the foramen rotundum.

Petrous Apex

The petrous apex lies at the anteromedial end of the petrous pyramid. It lies anteromedial to the inner ear structures and lateral to the petro-occipital fissure. Coursing along this fissure is the inferior petrosal sinus running from the cavernous sinus to the sigmoid sinus as it becomes the jugular bulb. Along its medial surface, the abducens nerve travels from the brainstem to the SOF. The trigeminal nerve

passes immediately superomedial to the petrous apex. The anterior aspect of the petrous apex contains the horizontal portion of the petrous carotid canal. At the confluence of the anterior aspect of the petrous apex, the basilar portion of the occipital bone and the sphenoid bone sits the foramen lacerum, which is filled with fibrocartilaginous tissue. The petrous apex may or may not be pneumatized (Figs. 60.3 and 60.4).

The borders of the petrous apex are as follows[6]: anteriorly, the bony labyrinth and ICA; posteriorly, the posterior cranial fossa and Dorello's canal (abducens nerve); superiorly, the middle cranial fossa and Meckel's cave; and inferiorly, the jugular bulb and the inferior petrosal sinus.

The most important surgical landmark for the approach to the cavernous sinus and the petrous apex is the carotid artery. After bifurcating in the neck, the cervical segment of the ICA travels toward the skull base to enter through the carotid foramen, just anterior to the jugular foramen and medial to the styloid process. Within the petrous temporal bone, the ICA ascends for a short distance and turns anteriorly in front of the cochlea, which is known as the first or posterior genu. It then courses horizontally in an anteromedial direction to its second or anterior genu, where it turns upward above the foramen lacerum, at which point the ICA is no longer intrapetrous.

After the second (anterior) genu, the ICA runs superiorly as the paraclival carotid. The paraclival carotid starts out extracavernous, and then enters the cavernous sinus as it travels superiorly. At this point, the ICA has a bend anteriorly as it becomes the parasellar portion of the ICA. The parasellar portion of the ICA has an inferior horizontal portion directed anteriorly, a vertical portion, and a superior horizontal portion directed posteriorly, forming a C-shaped bend with its convexity facing anterolaterally. The superior horizontal portion of the parasellar ICA is extracavernous and can be divided into the clinoid segment of the ICA, followed by the cisternal segment of the ICA, which then courses posterosuperiorly to divide into the anterior and middle cerebral arteries[7] (*see* Fig. 60.1).

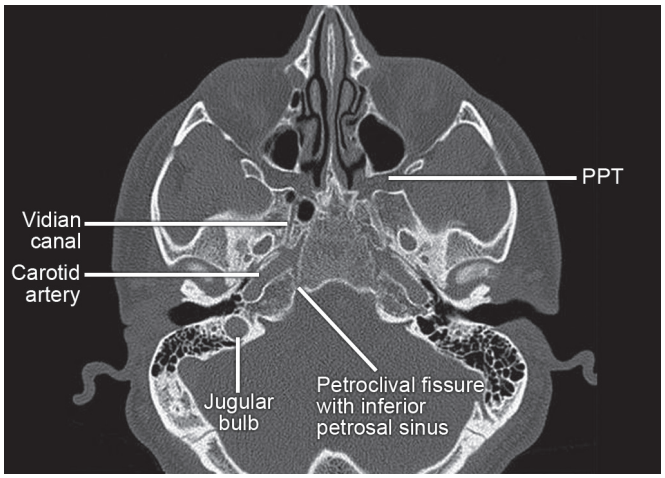
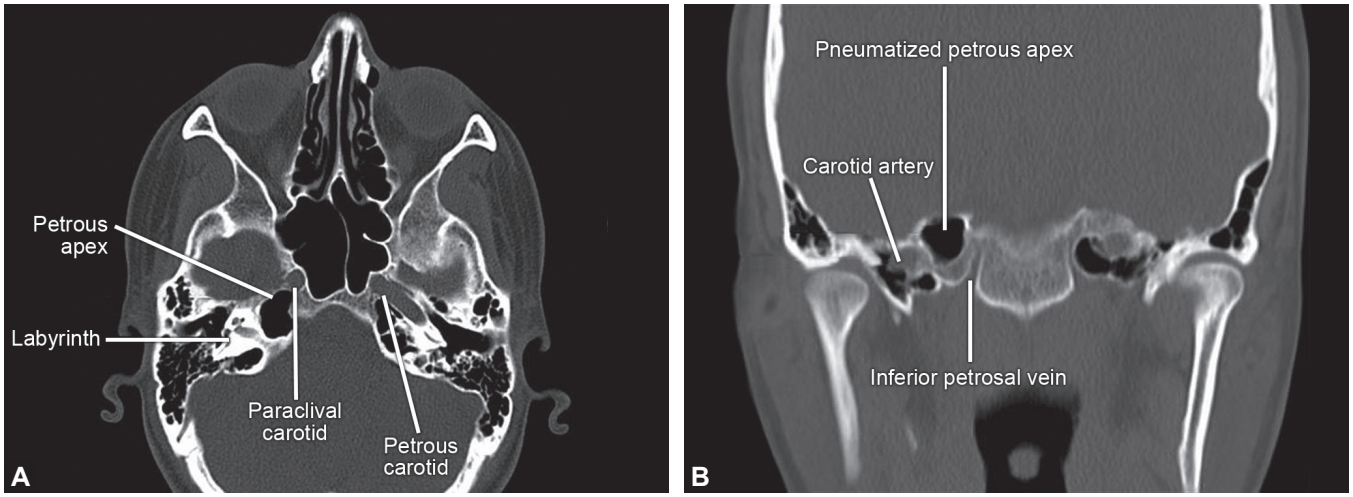


Fig. 60.3: Nonpneumatized petrous apex anatomy. Axial computed tomography (CT). (PPT: Pterygopalatine fossa).

PATHOLOGY

Cavernous Sinus

The cavernous sinus is protected against tumor invasion from the outside by thick dura. However, according to an anatomic study by Kawase et al., there are three weak



Figs. 60.4A and B: Pneumatized petrous apex anatomy. (A) Axial and (B) coronal computed tomography (CT).

points in the cavernous sinus walls: the venous plexus around the SOF where diploic and epidural venous channels through the SOF communicate directly with the cavernous sinus; the meningeal pockets between CN III and CNV where the dural layer is extremely thin or missing; and the medial wall around the pituitary gland as the medial meningeal dura is a single soft layer allowing invasion from or into the pituitary gland. By far, the most common pathology affecting the cavernous sinus is the pituitary macroadenoma with medial cavernous sinus invasion through this single dural layer.[8]

Other cavernous sinus lesions include vascular lesions such as a carotid aneurysm and a carotid-cavernous fistula, infectious/inflammatory lesions such as cavernous sinus thrombosis and sarcoidosis, and benign and malignant neoplastic lesions including chordomas, chondrosarcomas, meningiomas, hemangiomas, hemangiopericytomas, nerve sheath tumors, perineural spread of tumor (e.g. adenoid cystic and squamous cell carcinoma), direct tumor spread (e.g. nasopharyngeal carcinoma), and lymphoma. Presenting symptoms of cavernous sinus lesions include visual loss, diplopia, headache, facial numbness, and extraocular muscle palsy.

Petrous Apex

The petrous apex is rarely involved by disease, and when it is, a diagnosis can often be made by radiology alone. The most common pathology to affect this region is cholesterol granuloma, which is theorized to occur as a result of obstructed air cells within the petrous apex. The obstruction leads to a negative pressure, mucosal edema, and a resultant hemorrhage into the air cells. As the hemoglobin is broken down, the by-products result in cholesterol crystals that incite a granulomatous inflammatory reaction. The differential diagnosis of petrous apex lesion includes congenital lesions (asymmetric fatty marrow, cholesteatoma), infection (petrous apicitis, osteomyelitis), benign obstructive processes (effusion, mucocele, cholesterol granuloma), benign tumor (meningioma, schwannoma), malignant tumor (chordoma, chondrosarcoma, osteosarcoma, squamous cell carcinoma, plasmacytoma, metastatic disease), and miscellaneous lesions (histiocytosis X, Paget disease, fibrous dysplasia, petrous carotid artery aneurysm, meningocele/encephalocele).

Petrous apex lesions are often found either incidentally in asymptomatic patients or after imaging for nonspecific symptoms such as headaches. Often the patient will have associated complaints of retro-orbital pain, vertigo, otalgia, tinnitus, and hearing loss; however, it is not always possible to confirm that the etiology of these symptoms is from the lesion. A decision to operate on a patient with a petrous apex lesion must be made on a case by case basis. More specific symptoms of petrous apex lesions include cranial neuropathies affecting CN III–VII.

INDICATIONS AND PREOPERATIVE CONSIDERATIONS

Cavernous Sinus

As mentioned previously, the vast majority of lesions involving the cavernous sinus will be pituitary macroadenomas with cavernous sinus involvement. Workup should include MR with gadolinium. The use of CT imaging is often useful but not absolutely necessary for every case. In cases other than pituitary adenomas and in cases with potential bony involvement, both imaging modalities are useful for diagnostic purposes and surgical planning. The endoscopic approach is best suited for medial lesions with cavernous sinus involvement such as sellar and clival tumors. The relationship of the tumor to the optic nerve and carotid artery must be closely analyzed. If mobilization of the carotid artery is felt to be necessary to accomplish the surgical goals, the risk of intraoperative hemorrhage and postoperative cranial neuropathy will be increased.

Petrous Apex

The initial reports of the endoscopic approach to the petrous apex generally involved cystic lesions with significant medial extension into the sphenoid sinus. Accessing such lesions is rather straightforward and safe. However, with increasing experience and image guidance technology, it is now possible to safely access less expansile petrous apex lesions.

Workup should include MR with gadolinium and CT imaging that is necessary for both diagnosis and surgical planning. The location of the lesion within the petrous apex, and its relationship to the paraclival carotid, is the most important factor in surgical planning. All approaches, including transtemporal approaches, should be considered. With nonserviceable hearing, a transcochlear or translabyrinthine approach can be considered. If the patient has serviceable hearing, an infralabyrinthine, transcanal infracochlear, or middle cranial fossa approach can be considered. However, in one cadaver and radiologic study, Scopel et al. compared the transcanal infracochlear

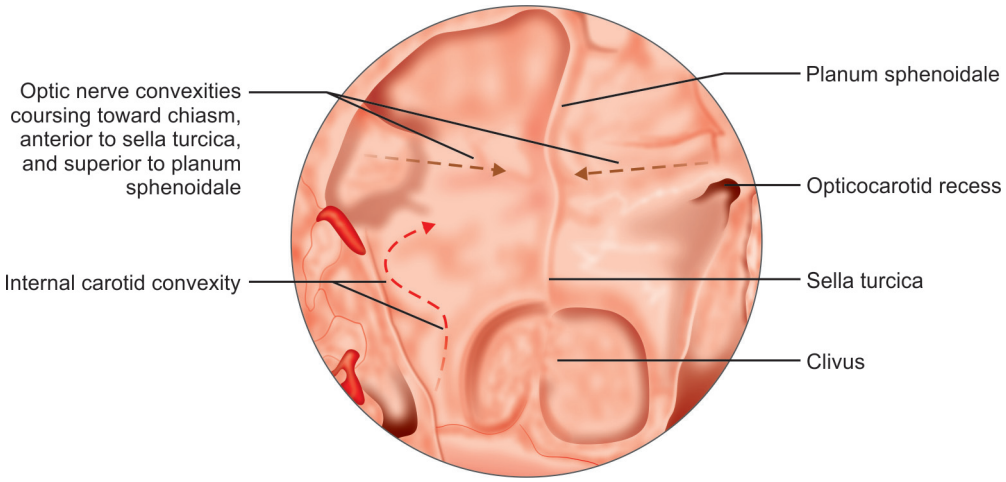


Fig. 60.5: Bony landmarks of sphenoid sinus. After a wide sphenoidotomy, bony landmarks can be seen including the clival recess, sella, planum sphenoidale, internal carotid artery and optic nerve protuberance, and opticocarotid recess.
Source: Adapted with permission from Casiano RR. Endoscopic Sinonasal Dissection Guide. New York: Thieme; 2012.

approach with the endonasal approach to the petrous apex to determine which gave better access for drainage of a cholesterol granuloma. In this study, the authors divided the petrous apex into three zones. The superior petrous apex was defined as between Dorello's canal and the foramen lacerum; the anterior–inferior petrous apex as between the foramen lacerum and the carotid foramen; and the posterior–inferior petrous apex as between the carotid foramen and the jugular foramen. Using the transnasal route, they were able to access all three zones in 90% of specimens, whereas the infracochlear route was only able to access the anterior–inferior petrous apex in 80% of cases, the posterior–inferior petrous apex in 60% and was never able to access the superior petrous apex. In the authors' radiologic analyses, the average maximal drainage window provided by the endonasal approach was three times the area of the infracochlear approach.[9]

SURGICAL TECHNIQUE

The patient is positioned supine on the operating room table. After induction of anesthesia, the head of bed is turned 180° away from anesthesia. The eyes are covered with Tegaderm and kept accessible throughout the procedure. The head is positioned so that it is slightly turned toward the right for right-handed surgeons. Head of bed elevation can be adjusted to assist with the trajectory. Pinning is at the discretion of the surgeons and will also depend on the type of image guidance system that is used. Given the proximity to the carotid artery, we consider image guidance a necessity for these expanded approaches.

The nose is decongested with Afrin-soaked cottonoids, followed by infiltration with 1% lidocaine with 1:100,000 epinephrine in the area of the sphenopalatine foramen bilaterally, the lateral nasal wall, the middle turbinates, and septum. If a cerebrospinal fluid (CSF) leak or exposed ICA is expected, a nasoseptal flap can be harvested at this time and stored in the nasopharynx or maxillary sinus for later use. The nasoseptal flap should be harvested from the side contralateral to that with the more significant pathology, as the pedicle on this side is more easily salvaged.

A bilateral extended sphenoidotomy is performed (Fig. 60.5). The middle turbinates are either lateralized or the inferior third is trimmed to obtain exposure of the superior turbinates and face of the sphenoid sinus. The natural sphenoid ostium can be found just superior to the tail of the superior turbinate, which can be trimmed to aid in exposure. The ostium can be probed gently with a Cottle elevator, starting at the tail of the superior turbinate adjacent to the septum and working superiorly. The sphenoid ostium is first opened inferomedially until the superior and lateral extent of the sphenoid sinus can be visualized. The remaining wall of the face of the sphenoid can then safely be opened while visualizing the carotid and optic protuberances. The lateral optic–carotid recess is a helpful landmark. This recess is bordered superiorly by the optic nerve, inferiorly by the oculomotor nerve, and posteriorly by the parasellar portion of the ICA. Once the sphenoid sinus is widely opened on one side, a Cottle is used to identify the vomerorostral junction that is disarticulated. The sphenoid intersinus septum can then be removed. Depending on the thickness of the septum, it

can be removed with Thru-Cutting Forceps or a drill. From the preoperative imaging, the surgeon should be aware of the insertion of the intersinus septum and any intrasinus septations, given that one or more septations may insert onto the bone overlying the carotid artery. Care is given to minimize the risk of fracturing the bony septations at the carotid attachment point. The contralateral sphenoid sinus is widened as needed to allow exposure of the surgical field and ease of instrumentation. The posterior septectomy can be extended anteriorly as needed to facilitate exposure and maneuverability of the instruments.

At this point, we routinely remove the sphenoid sinus mucosa. The bony landmarks of the sphenoid sinus including the sella, the paraclival ICA, the carotid siphon, and the optic nerve should be evident, and can be confirmed with image guidance.

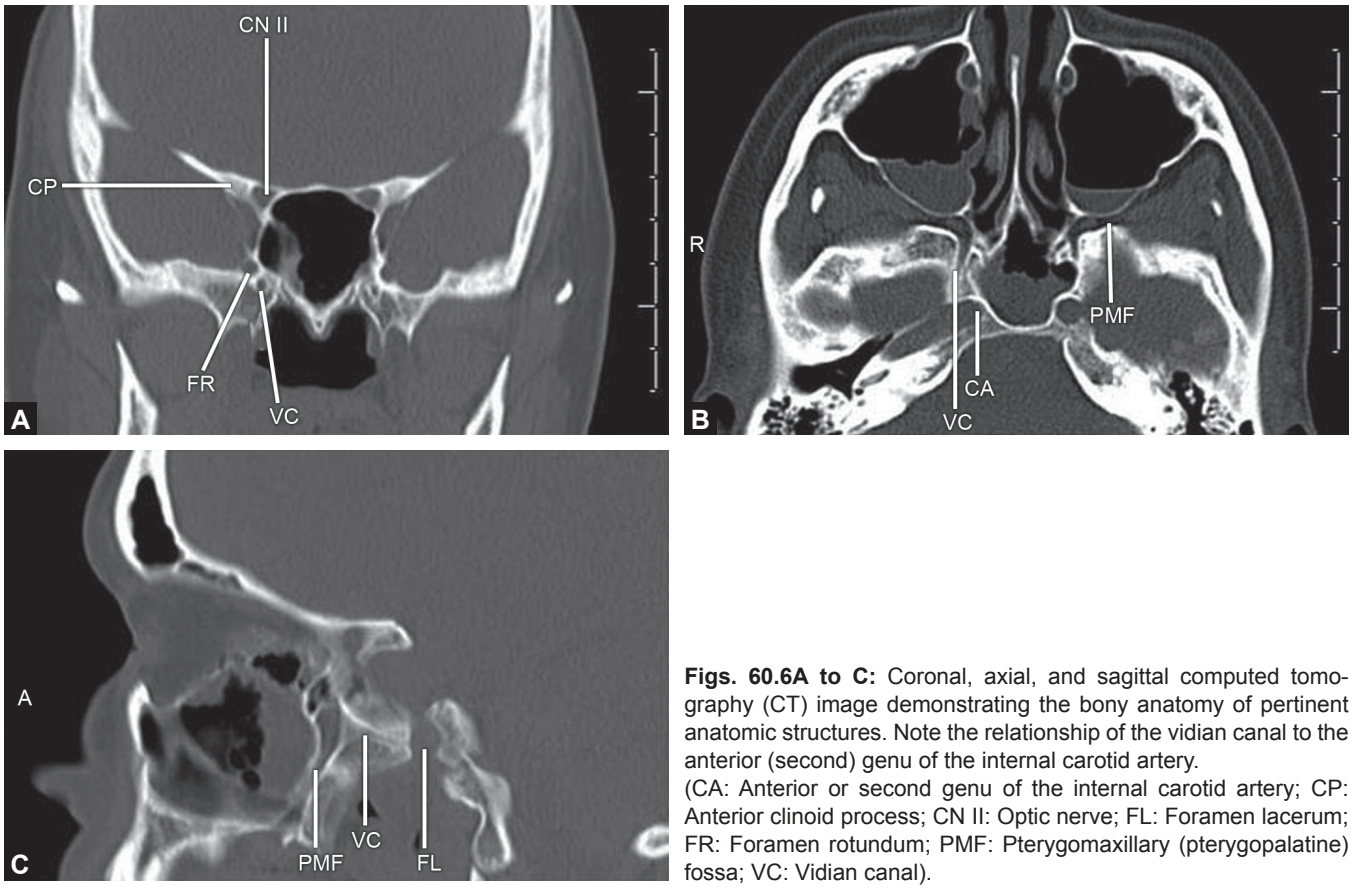
Cavernous Sinus

In cases of minimal cavernous sinus invasion by a pituitary macroadenoma, lateral exposure can be obtained by performing a posterior ethmoidectomy and removing the face of the sphenoid flush with the lateral wall. The bone over the pituitary gland is thinned with a diamond drill, then removed with Kerrison rongeurs. This is started in the midline away from the ICAs and continued laterally to include as much exposure that is necessary to obtain access to the medial cavernous sinus. Cavernous sinus bleeding is controllable with thrombin-soaked Gelfoam and Surgiflo (Ethicon, Somerville, NJ). Elevating the head of the bed is another maneuver that can be helpful in decreasing the bleeding.

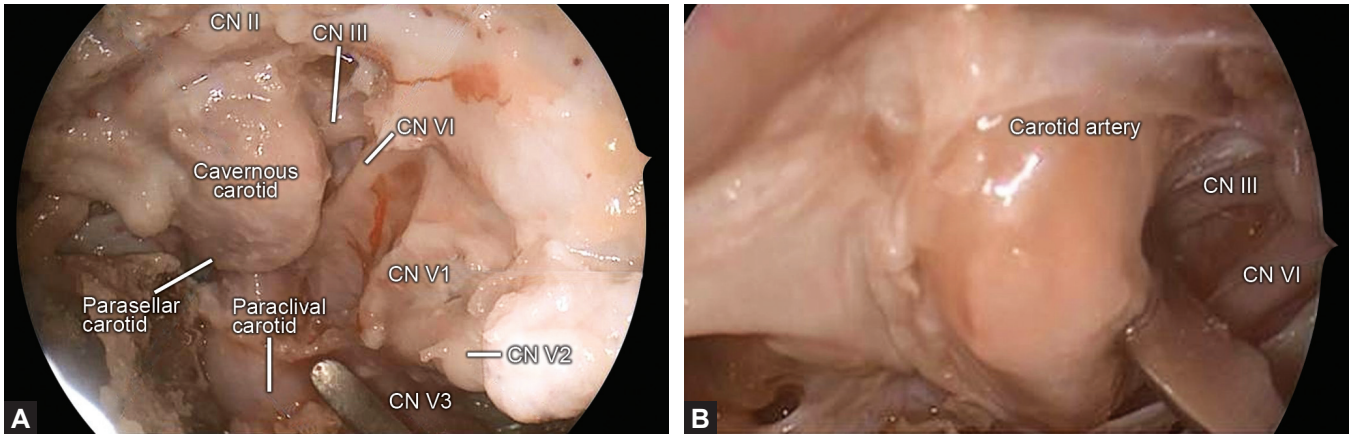
The pituitary gland can gently be retracted medially to expose the medial cavernous sinus wall. The inferior hypophyseal artery coursing from the ICA to supply the gland can sometimes be seen. For additional lateral exposure, the bone over the parasellar ICA can be removed. The safest way to remove bone in this area is to thin it with a diamond drill, followed by removal with either a Kerrison rongeur or a dissector with the force of the movement aimed away from the ICA. With the use of angled scopes, great views can be obtained to ensure that no tumor remains around corners.

For additional exposure laterally or to directly approach the cavernous sinus without opening the sella, a transethmoidal–transsphenoidal route can be utilized. After removal of the middle turbinate, an uncinectomy and maxillary antrostomy is performed for anatomic landmarks. A complete sphenoethmoidectomy is then performed skeletonizing the lamina papyracea and the fovea ethmoidalis while preserving the mucosa on these structures. By starting with the sphenoidotomy, the planum sphenoidale can be identified that represents the most inferior plane of the ventral skull base. Working retrograde, the posterior and anterior ethmoid cells can be quickly opened by staying at or below this level. Once this is performed, the surgeon will have better surgical access and visualization laterally. The mucosa is removed over the bone that will be removed. Depending on the tumor, drilling can begin in the midline or laterally. Working from the medial to lateral, the bone over the parasellar and paraclival ICA and medial cavernous dural can be drilled with a high-speed diamond burr to an eggshell thickness and then removed. An endoscopic Doppler probe is helpful in identifying the course of the cavernous carotid. This approach is generally adequate for a medial corridor to the cavernous sinus (medial to the ICA).

If exposure to the lateral corridor of the cavernous sinus (lateral to the ICA) is necessary, a transmaxillary–transpterygoid approach can be used (Figs. 60.6 and 60.7). A wide maxillary antrostomy is performed on the side of the lesion. A complete sphenoethmoidectomy is performed as above. The sphenopalatine artery is identified at the sphenopalatine foramen and is cauterized or clipped. The palatosphenoidal or palatovaginal canal transmits a pharyngeal branch of the internal maxillary artery and courses from the pterygopalatine fossa to the nasopharynx. This artery will need to be transected and the canal can be a useful landmark for identifying the vidian canal that will lie laterally. The posterior wall of the maxillary sinus is removed that exposes the periosteum overlying the pterygopalatine fossa. This will allow lateralization of the pterygopalatine contents off of the bone of the base of the pterygoid to identify the vidian canal. For better lateralization and less tethering, the bone of the greater palatine canal can be removed to expose the descending palatine neurovascular bundle. Once the vidian canal with its neurovascular bundle is identified, the bone along its superior and medial aspect is drilled. If this neurovascular bundle is followed posteriorly, it will lead to the second genu of the ICA, at the level of the foramen lacerum. Depending on the pneumatization pattern of the sphenoid sinus, there may be a lateral sphenoid recess, which is a pneumatization of the sphenoid sinus into the base of the pterygoid between the maxillary division of the trigeminal nerve (V2) superolaterally and the vidian canal inferomedially. The ICA is exposed as above and



Figs. 60.6A to C: Coronal, axial, and sagittal computed tomography (CT) image demonstrating the bony anatomy of pertinent anatomic structures. Note the relationship of the vidian canal to the anterior (second) genu of the internal carotid artery.
(CA: Anterior or second genu of the internal carotid artery; CP: Anterior clinoid process; CN II: Optic nerve; FL: Foramen lacerum; FR: Foramen rotundum; PMF: Pterygomaxillary (pterygopalatine) fossa; VC: Vidian canal).



Figs. 60.7A and B: Internal carotid artery (ICA) and cavernous sinus. (A) Cadaver dissection demonstrating the paraclival and parasellar carotid artery. The medial cavernous sinus dura has been removed to demonstrate the cranial nerves (CN) within. (B) The cavernous carotid is retracted medially to demonstrate the more proximal cavernous portions of CN III and CN IV.

the dissection continues laterally by drilling the bone over the lateral wall of the sphenoid until it is eggshell thin and then removed with a dissector. The medial cavernous sinus wall can be exposed to its anterior limit at the SOF.

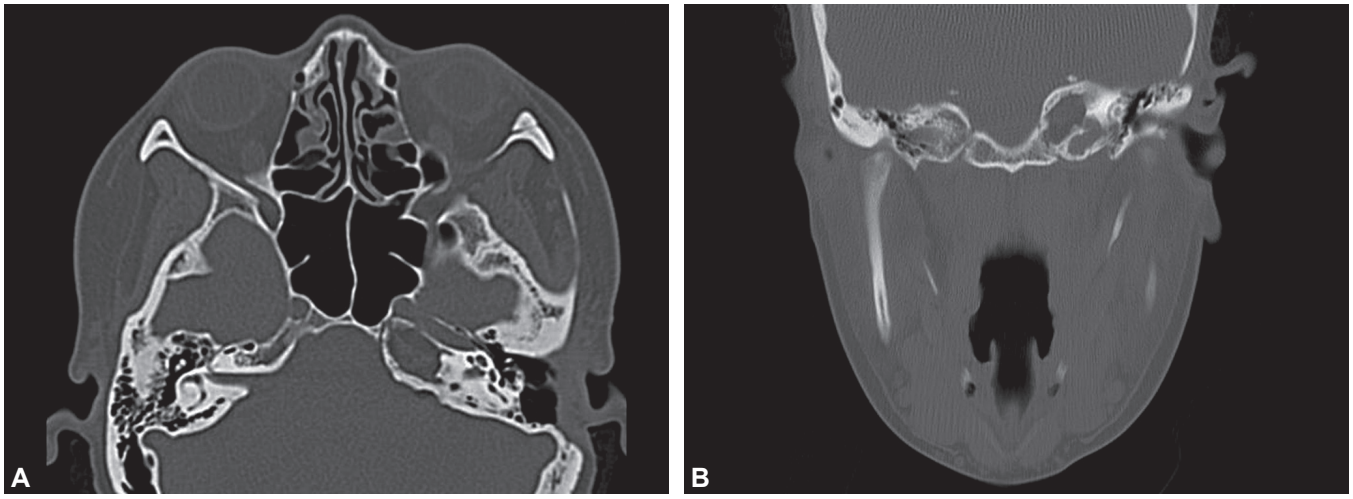
If the cavernous sinus dura is opened, the abducens nerve will be most medial and at greatest risk. It will be seen coursing lateral to the ICA along the inferior edge of the inferior horizontal portion of the carotid siphon.

The oculomotor, trochlear, and ophthalmic nerves are slightly more lateral, running within the lateral wall of the cavernous sinus and, thus, more protected. Medial retraction of the ICA will allow better exposure of the posterior cavernous sinus and the more proximal aspects of the CN (Figs. 60.7A and B). Manipulation of the carotid artery should only be performed if absolutely necessary as this will increase the risk of vessel injury and CN VI dysfunction.

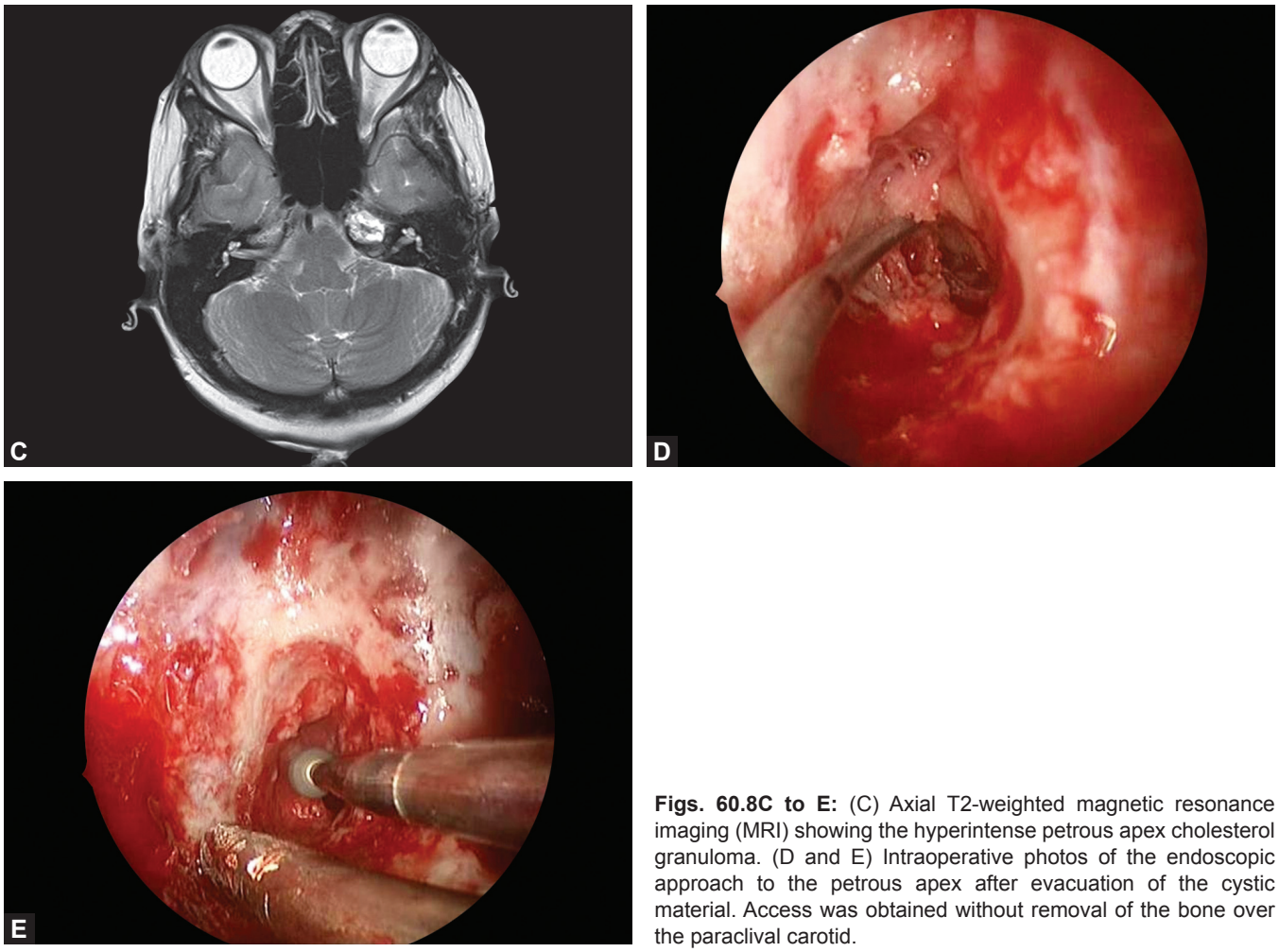
Petrous Apex

In the case of a cystic lesion with medial extension into the sphenoid sinus, the bony medial wall of the lesion can be drilled while keeping the paraclival ICA in view. In the case of a lesion without medial expansion but that sits above the petrous portion of the ICA, the bone over the paraclival ICA can be removed from lateral to medial, using a diamond bur with strokes parallel to the course of the ICA. Once the bone is eggshell thin, it is removed with either a Kerrison rongeur or flicked away with a dissector away from the ICA. Once the bone is removed, the ICA can be gently lateralized to expose the medial portion of the petrous apex. The bone over the lateral portion of the clivus can be drilled down to posterior fossa dura. This will expose the inferior petrosal sinus coursing from the cavernous sinus to the sigmoid sinus. The bone between the paraclival ICA and the inferior petrosal sinus from the foramen lacerum inferiorly to Dorello's canal superiorly can be removed to access the petrous apex (Figs. 60.8 and 60.9).

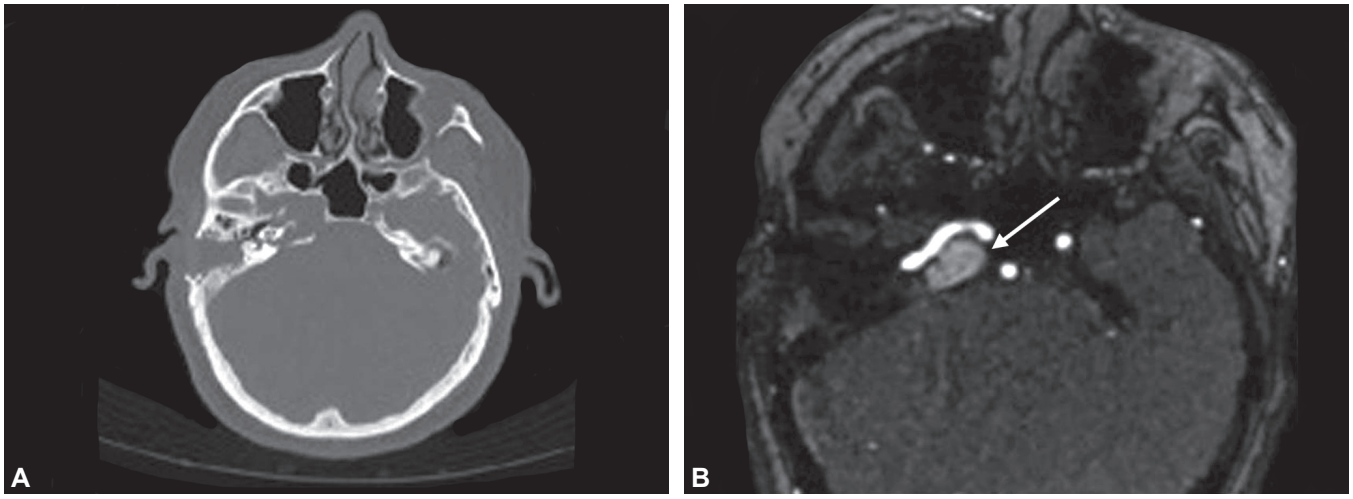
In the case of an inferior petrous apex lesion that extends below the level of the petrous ICA, an infrapetrous approach is necessary. A wide maxillary antrostomy is performed on the side of the lesion. The posterior wall of the maxillary sinus is removed that exposes the periosteum overlying the pterygopalatine fossa. The sphenopalatine artery is identified at the sphenopalatine foramen and is cauterized or clipped. The palatosphenoidal, or palatovaginal, canal that courses from the pterygopalatine fossa to the nasopharynx carries an artery that will need to be transected. This will allow lateralization of the pterygopalatine contents off of the bone of the base of the pterygoid to identify the vidian canal. For better lateralization and less tethering, the bone around the descending palatine canal can be removed. Once the vidian canal with its neurovascular bundle is identified, the bone along its medial and inferior surface is drilled, which will lead back to the second genu of the ICA, at the level of the foramen lacerum. Once the soft fibrocartilaginous tissue of the foramen lacerum is exposed, the bone from the foramen lacerum to the Eustachian tube can be drilled to provide exposure of the inferior petrous apex. If more exposure is needed, the Eustachian tube can be transected and the horizontal portion of the petrous carotid followed posteriorly in the direction of the carotid canal and jugular foramen. It is also important to note that by drilling along the base of the pterygoids laterally, the surgeon will eventually encounter the mandibular branch of the trigeminal nerve (V3) exiting the middle cranial



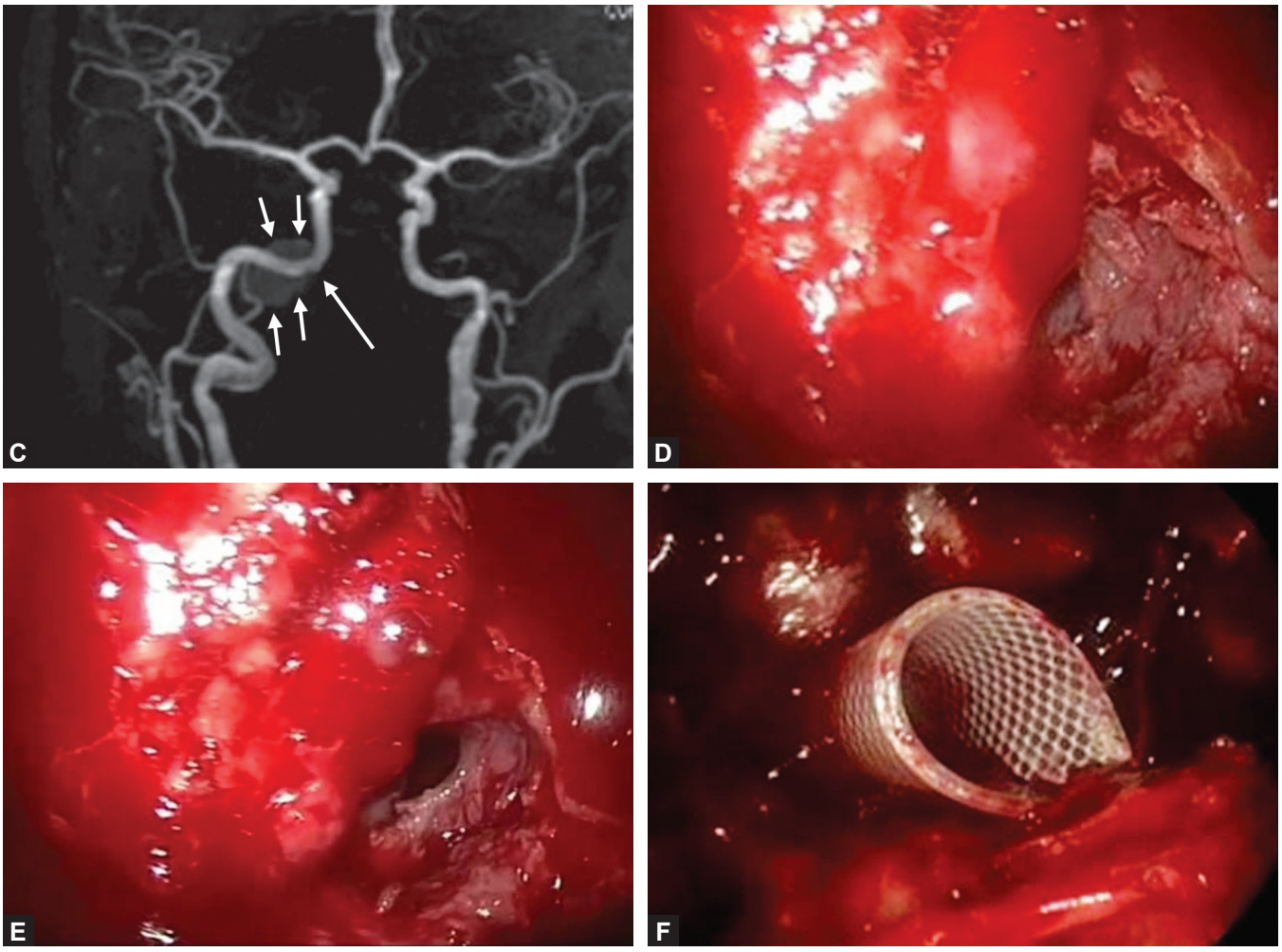
Figs. 60.8A and B: Cholesterol granuloma without removal of bone over paraclival carotid artery. (A) Axial computed tomography (CT) demonstrating left petrous apex cholesterol granuloma. Note the paraclival carotid laterally and the inferior petrosal sinus medially, which represents the limits of the bony window that can be created. (B) Coronal CT showing the lesion.



Figs. 60.8C to E: (C) Axial T2-weighted magnetic resonance imaging (MRI) showing the hyperintense petrous apex cholesterol granuloma. (D and E) Intraoperative photos of the endoscopic approach to the petrous apex after evacuation of the cystic material. Access was obtained without removal of the bone over the paraclival carotid.



Figs. 60.9A and B: Cholesterol granuloma with removal of bone over paraclival carotid artery. (A) Axial computed tomography (CT) showing a right expansile cystic petrous apex lesion that was found to be a cholesterol granuloma. (B) Magnetic resonance imaging (MRI) demonstrating the relationship of the petrous and paraclival portion of the right ICA with the lesion.



Figs. 60.9C to F: (C) MR angiogram demonstrating the relationship of the internal carotid artery (ICA) to the lesion. (D and E) Intraoperative photo of the cavity after evacuation of the cystic fluid. (F) Intraoperative photo after placement of a silastic stent.

fossa at the foramen rotundum to enter the infratemporal fossa. This nerve can be identified early by reflecting the lateral pterygoid muscle off of the lateral side of the lateral pterygoid plate (Fig. 60.10). Depending on the angles and size of the base of the pterygoid, drilling the base of the pterygoids may be necessary to identify this nerve. Bleeding is often encountered while drilling the pterygoid plates. This can be easily controlled with Surgiflo, Gelfoam, and overlying pressure with a cottonoid.

If the lesion is a cholesterol granuloma or other cystic lesion, it is advisable to place a stent to allow for mucosalization of the tract into the sphenoid sinus. We use a piece of rolled silastic, but others have recommended using a silastic pediatric 6-mm tracheal T-Tube. This is left in place for 3–6 months, and then removed in the office.

SKULL BASE RECONSTRUCTION

Skull base reconstruction depends on the extent of the approach, presence of CSF leak, and ICA exposure. For cavernous sinus surgery, there may be no leak, and hemostasis is all that is needed. This can be achieved with Surgiflo, thrombin-soaked Gelfoam, and gentle pressure held with an overlying moist cottonoid. There are several materials that have been used for CSF leak repair including abdominal fat, autologous tissue grafts (e.g. fascia lata), homologous tissue grafts (e.g. Alloderm), pedicled flaps (e.g. nasoseptal flap) as well as a variety of techniques including underlay, overlay, gasket-seal, and fat plug. The most important step in CSF leak closure is the proper placement of the first layer, the goal of which is to create a watertight barrier between the CSF space and the sinonasal cavity.

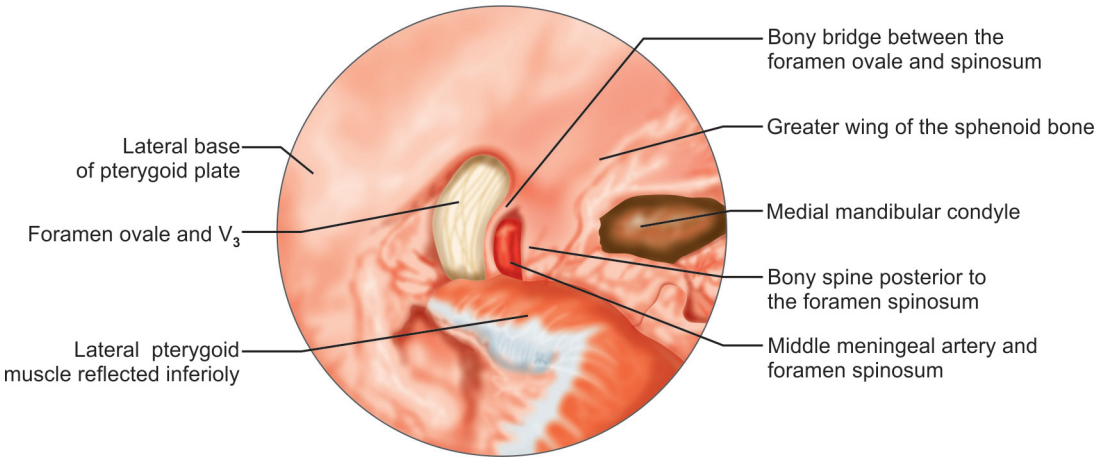


Fig. 60.10: Left infratemporal fossa. A view of the left foramen ovale and cranial nerve (CN) V3 after reflecting the lateral pterygoid muscle off of the lateral pterygoid plate. Not necessary for this approach, with further dissection, the middle meningeal artery can be seen, separated from V3 by a bony spine.
Source: Adapted with permission from Casiano RR. Endoscopic Sinonasal Dissection Guide. New York: Thieme; 2012.

In the case of petrous apex surgery when dealing with a cystic lesion such as cholesterol granuloma, the goal is to create a tract from the cyst into the sphenoid sinus. Therefore, no repair other than placement of a stent is used. If there is a small inadvertent CSF leak from a rent in the posterior fossa dura, a mucosal overlay graft is usually sufficient for repair. If there is a brisk leak, a layered repair including nasoseptal flap may be utilized, remembering that the success of multilayered closures relies on the effectiveness of the first layer that is placed.

While many techniques of bolstering the repair have been described, we use a layer of Gelfoam to completely cover the repair, followed by one or two Merocels (Medtronic Inc., Minneapolis, MN, USA) packed up against the repair. Patients are placed on prophylactic antibiotics, and the Merocels are removed at approximately 7 days after which the patients are started on nasal saline irrigations.

COMPLICATIONS

There are many risks to the endoscopic approach to the petrous apex and cavernous sinus that should be discussed with patients preoperatively. Crusting occurs universally to a varying degree after transnasal approaches to the skull base. Patients should be warned about the real possibility of prolonged crusting that may need to be debrided for many months postoperatively and possibly for a lifetime, especially in patients undergoing postoperative radiation. Other nasal complications include epistaxis, synechiae formation, and loss of smell. Orbital and optic nerve injury is another risk that should be discussed. Patients should be informed of the risk of stroke and even death. CN injury and the sequelae of such injury should also be discussed, including diplopia, blindness, facial numbness, dry eye, and palatal numbness.

One of the most dreaded complications when working in this area is ICA injury, and with manipulation of the ICA this risk increases. The most important aspect of successful management of ICA injury is preparedness, which includes coming up with a protocol of steps to take if such a situation were to occur; this includes having the appropriate discussion with the anesthesia team and surgical staff. The first step is to control the bleeding that can usually be accomplished with packing and pressure over the area. If a significant amount of bone over the skull base has already been removed, and pressure can cause intracranial injury, a more directed pressure should be applied directly over the area of injury. The anesthesiologist will be responsible for controlling blood pressure, and normotension should be maintained to permit adequate cerebral perfusion and prevent a stroke. Once the bleeding is controlled, the patient should undergo angiography either in the operating room or the angiography suite. The endoscopic equipment should be set up in the suite, as the packing may need to be temporarily removed to allow the endovascular specialist to pass a stent or embolize the vessel, depending on the collateral blood flow and the clinical situation. Future developments will hopefully include better stents allowing placement in tortuous areas of the carotid (i.e. cavernous portion) as well as potential transnasal deployment of devices to repair the vessel.

CONCLUSION

A firm understanding of the anatomical landmarks and critical structures, experience in working in these areas, teamwork between otolaryngology and neurosurgery, and proper selection of patients are the most important factors when choosing an endoscopic approach to cavernous sinus or petrous apex lesions, and should allow skull base surgeons to maximize outcomes and minimize morbidity when treating patients with diseases of the skull base.

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CHAPTER

Management of Skull Base Defects: Cerebrospinal Fluid Rhinorrhea, Meningoencephalocele and Endoscopic Skull Base Surgery

61

Edward D McCoul, Abtin Tabaee

INTRODUCTION

The evolution of anterior skull base reconstruction over the past two decades has mirrored advances in transnasal endoscopic surgery. Two fundamental events have occurred during this period that form the basis of modern repair algorithms: the development of an array of transnasal endoscopic techniques and a more sophisticated understanding of the different clinical scenarios in which they are indicated. Whereas the former provides the necessary tools, the latter mediates their successful application. Open skull base surgery approaches, whether through transcranial or transfacial routes, have historically represented the workhorse for repair of cerebrospinal fluid (CSF) rhinorrhea and meningoencephalocele but are limited in terms of patient morbidity, limited visualization, and overall modest success. The adaptation of endoscopic sinus surgery (ESS) techniques for skull base reconstruction improves on these limitations and has largely replaced open approaches. The most recent frontier has been the expansion of endoscopic transnasal surgery to intracranial pathology and the development of more sophisticated repairs to address these larger, more complex defects. The goal of this chapter is to provide a foundation for understanding the pathophysiologic factors, reconstructive tools, and surgical techniques necessary to manage defects of the anterior skull base.

CEREBROSPINAL FLUID PHYSIOLOGY

CSF is a clear, colorless fluid that surrounds the brain parenchyma and spinal column primarily in the subarachnoid and ventricular spaces. Multiple functions are attributed to CSF including cushioning against mechanical forces, providing buoyancy for the brain, regulating intracranial pressure (ICP), and mediating various cerebral homeostatic activities. The normal CSF volume is estimated to be approximately 150 mL in adults with turnover four to five times daily. The hourly production rate of approximately 20 mL and a daily production rate of 400–600 mL can increase in response to chronic loss of CSF volume. The majority of CSF production occurs in the choroid plexus of the lateral ventricles and the 3rd and 4th ventricles. CSF is also partially produced by ependymal cells and parenchymal capillaries. The constituents of the final fluid represent both passive filtration of plasma and active ion transport by the choroid plexus. As such, CSF has the same overall osmolarity, higher levels of sodium, chloride and magnesium, and lower levels of potassium, calcium, glucose and protein when compared to plasma. The cell count is normally between 0–5 cells per cubic millimeter.

The flow of CSF occurs in a unigrade and pulsatile manner. CSF produced in the lateral ventricles flows through the interventricular foramen (of Monro) to the 3rd ventricle and then through the cerebral aqueduct (of Sylvius) to the 4th ventricle. Continued flow to the cisterna magna then occurs through the unpaired median aperture (foramen of Magendie) and the paired lateral apertures (foramina of Luschka). From here CSF flows into one of several intracranial cisterns and caudally to the subarachnoid space of the spinal column. The majority of absorption occurs by the arachnoid villi into the dural venous sinuses (Fig. 61.1). Normal ICP in the prone position is between 5 and 15 mm Hg in adults. Factors that can

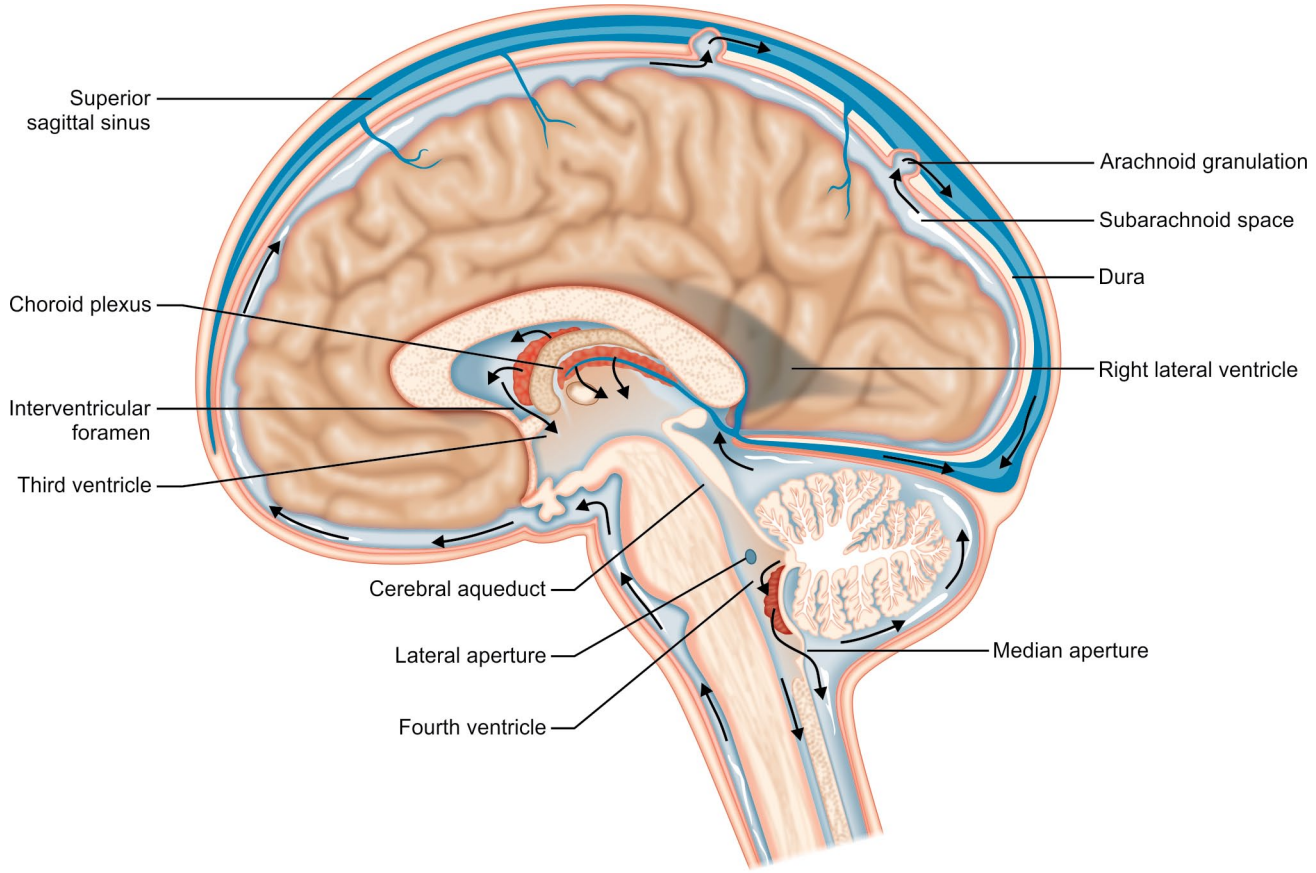


Fig. 61.1: Flow of cerebrospinal fluid.

influence ICP include a mismatch in production versus loss of CSF and changes in the flow of CSF (i.e. obstructive hydrocephalus). ICP modeling by Marmarou[1,2] conveys these influences:

ICP = Resorption of CSF × CSF formation + sagittal sinus pressure + arterial vasogenic component

ETIOLOGY OF CEREBROSPINAL FLUID RHINORRHEA AND MENINGOENCEPHALOCELE

Although multiple classifications have been proposed to describe the etiologies of CSF rhinorrhea, the schema proposed by AK Ommaya in 1976 remains seminal[3] (Table 61.1). The majority of CSF leak events can be classified based on the factors noted in this classification. This allows for a more refined application of specific management concepts. Of note, a given patient may have elements of multiple etiologic factors.

Accidental Trauma

Trauma, whether accidental or iatrogenic, represents approximately 80–90% of CSF leaks.[4] Accidental skull base fractures are defined by several features including location and pattern of the bony fracture, penetrating versus nonpenetrating injury, mechanism and vector of injury, and open versus closed injury. The most common sites of CSF leak in patients with trauma are the sphenoid and frontal sinuses (approximately 30% each), followed by the fovea ethmoidalis and cribriform plate[5] (Fig. 61.2). Of note, CSF rhinorrhea may occur in the setting of a temporal bone fracture with flow of CSF through the Eustachian tube into the nasopharynx. The incidence of CSF rhinorrhea has been estimated to be 2% of all head traumas, 12–30% of skull base fractures, and 25% in patients with facial fractures.[6,7] The leak may be identified in the early post-trauma period or in a delayed fashion; the latter may represent failure to detect a leak that was ongoing throughout the clinical course. Alternatively, a true delay

Table 61.1: Etiology of cerebrospinal fluid rhinorrhea (adapted from Ommaya)[3]

Nontraumatic		
	Normal pressure	
		Congenital
		Skull base neoplasm, infection, inflammation
		Spontaneous
	Elevated pressure	
		Intracranial tumor
		Hydrocephalus
		Benign intracranial hypertension (pseudotumor cerebri)
Traumatic		
	Accidental	
		Skull base fracture, closed head injuries
	Iatrogenic	
		Skull base surgery, endoscopic sinus surgery

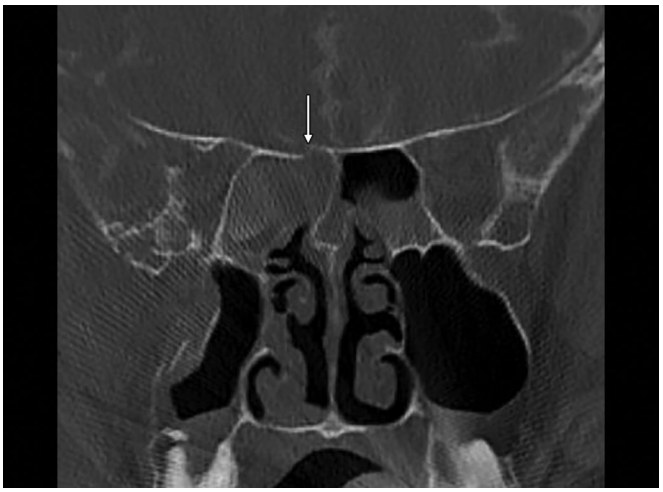


Fig. 61.2: Coronal CT cisternogram of a patient with a cerebrospinal fluid (CSF) leak following a motor vehicle accident. A displaced fracture of the right planum sphenoidale (arrow) and active flow of CSF through the defect into the sphenoid sinus is noted.

in leak onset may occur secondary to increased ICP from brain edema, devascularization of tissue, formation of a fistula tract, and resolution of blood products. A higher risk of meningitis has been linked with trauma-related CSF leak compared to other etiologies, especially if repair is not instituted early.[8]

Endoscopic Sinus Surgery

CSF rhinorrhea complicating ESS has been well described. Indeed, prevention and management of this complication have been the focus of surgical refinements throughout the history of the procedure. The incidence of CSF leak following ESS has decreased over time, likely as a result of improvements in surgical technique and technology. In a large case series published in 1994, May et al. reported major intracranial complication rates of 0.47% in 2,108 of the authors' patients and 0.54% in a separate meta-analysis of 2,583 patients.[9] Although the nature of the intracranial complications was not subcategorized, the authors reported that the majority represented CSF leaks. In a retrospective review of a nationwide database of 62,823 patients undergoing ESS published in 2012, Ramakrishnan et al. reported a 0.17% incidence of CSF leak.[10] The risk of iatrogenic injury is inherent to ESS since the anterior skull base represents a defining boundary of the surgical dissection when addressing the ethmoid, frontal, and sphenoid sinuses. In particular, a complete ethmoidectomy requires removal of obstructive bony partitions and inflammatory tissue abutting the fovea ethmoidalis and lateral lamella of the cribriform. Multiple anatomic and disease variants may predispose to skull base injury and should be routinely assessed on preoperative CT scan: low lying skull base, deep olfactory fossa (Keros 3), skull base dehiscence, and asymmetric depth of the olfactory fossa. Additional factors that increase the likelihood of iatrogenic injury include revision surgery, severe inflammatory changes (polyposis), and extensive surgery.

Skull base defects that occur as a result of ESS are variable in size, location, and dimension based on the mechanism of injury and anatomic factors. The majority of CSF leak events complicating ESS involve the cribriform plate and fovea ethmoidalis, although injury to the planum sphenoidale may also occur (Fig. 61.3). If detected early in the course of the injury, the defect is typically small (< 1cm). A larger defect may occur if the injury is not immediately noted or if powered instrumentation is being used. Intraoperative CSF leak is suggested by the identification of a rush of clear or blood-tinged fluid at the site of the skull base. Pulsatility and "washing" out of blood at the defect site may also be noted. In patients who are not under general anesthesia, acute increase in pain in this setting occurs as a result of dural stimulation. Delayed presentation of ESS-related CSF leak may occur

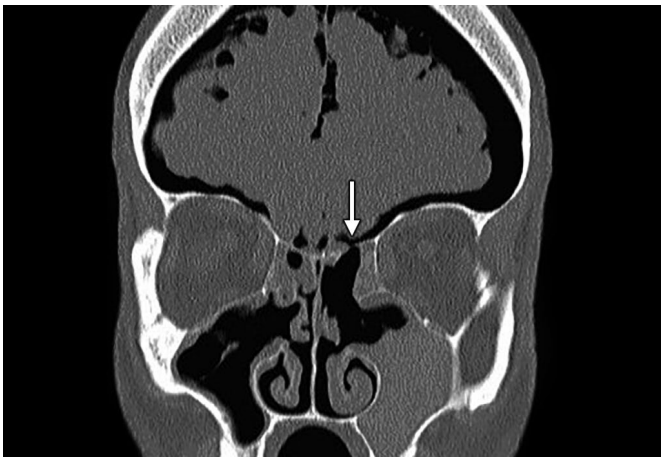


Fig. 61.3: Noncontrast coronal CT sinus in a patient who presented to the emergency room with severe headaches 1 day following endoscopic sinus surgery. There was no clinical evidence of cerebrospinal fluid (CSF) rhinorrhea or mental status changes. However, a defect in the left fovea ethmoidalis (arrow) and extensive pneumocephalus was noted. Intraoperatively, a bony defect with no evidence of dural tear or CSF leak was noted.

if the leak was not identified initially at the time of surgery and is suggested by clear rhinorrhea and headaches during the postoperative period. A change in postoperative mental status potentially suggests additional sequelae of skull base injury including pneumocephalus, meningitis, intracranial vascular, or parenchymal injury.

Nontraumatic, Normal Intracranial Pressure CSF Leaks

Nontraumatic CSF leaks are divided into normal and elevated ICP categories. Nontraumatic, normal pressure etiologies include anatomic dehiscences of the skull base and bony erosion from sinonasal and intracranial lesions. Destructive or expansile lesions may erode the bony skull base creating a communication between the sinonasal and intracranial cavities. Of note, the absence of any bony separation radiographically in this setting often does not result in clinical evidence of a CSF leak. This may occur if the dural layer is intact as it occurs with expansile inflammatory sinonasal lesions (mucoceles and advanced allergic fungal sinusitis). A lack of CSF rhinorrhea may also occur in patients with neoplastic lesions and encephalocele with radiographic and surgical findings of dural involvement and complete absence of bony skull base. In these patients, free efflux of CSF into the nasal cavity may be obstructed by intact sinonasal mucosa, mass effect of the lesion, or fibrotic obstruction of local CSF circulation.

The underlying pathophysiology of "spontaneous" CSF leaks and meningoencephalocele remains debatable. The phrase "spontaneous" has historically been used to signify lesions that do not have any identifiable etiology. However, the results of multiple case series published over the past decade have improved our collective understanding of this category. An underlying etiology may be identified or at least suggested in the majority of these patients. Determination of the etiology has important implications for both treatment planning and prognostication especially in patients with occult increased ICP as they are more likely to fail repair and require adjunctive therapy. Patients with a remote history of major skull trauma and no other identifiable etiology may theoretically have developed a bony skull base defect at the time of the injury that slowly expanded over time by the pressure from normal intracranial pulsation. Definitive evidence of this is often not possible, but may be suggested if prior imaging studies are available for comparison.

A second category of previously termed "spontaneous" lesions is based on congenital pneumatization patterns of the paranasal sinuses and dehiscences in the skull base. This purely anatomic basis for a "spontaneous" defect likely accounts for a minority of patients with CSF leak and meningoencephalocele. A high rate of successful surgical repair is expected in this cohort as the CSF physiology is expected to be normal. The osteology of the skull base is complex with contributions from multiple embryologic precursors. The natural fusion points are potentially sites of structural weakness, especially in areas with already thin bone such as the junction of the cribriform plate and fovea ethmoidalis. The embryologic development of the sphenoid bone begins with five distinct cartilaginous precursors each of which undergo ossification and fusion. In addition to bony pits that may be completely dehiscent, two distinct potential areas of incomplete fusion in the sphenoid bone have been described. The central craniopharyngeal canal arises in the midline in the floor of the hypophysis.[11] The lateral craniopharyngeal canal, also termed "Sternberg's canal," arises from the junction of the greater wing of the sphenoid with the presphenoid and basisphenoid.[12,13] CSF leak and meningoencephalocele may occur in these areas and is hypothesized to represent failure of the embryologic precursors to fully fuse, although this theory remains controversial.[12,14] "Spontaneous" skull base dehiscence is also potentially associated with expansive pneumatization patterns of the sphenoid sinus in the floor of the middle cranial fossa.[15,16] The pressure

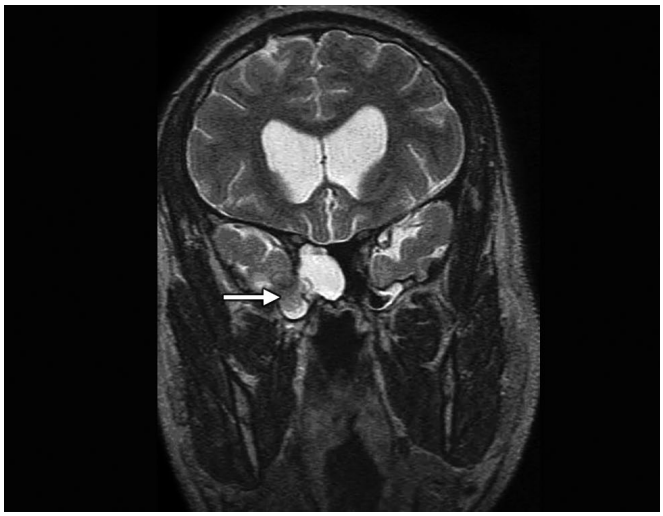


Fig. 61.4: T2-weighted coronal MRI of a patient with long-standing hydrocephalus and a broad-based defect of the right lateral sphenoid sinus (arrow) with herniation of the temporal lobe and high-volume cerebrospinal fluid leak.

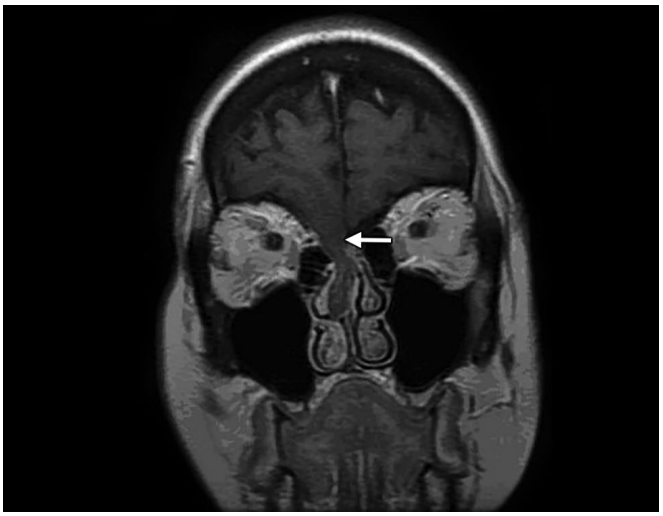


Fig. 61.5: T1-weighted coronal MRI of a patient with benign intracranial hypertension. A broad-based right cribriform defect is noted (arrow).

from normal intracranial pulsations may result in bony dehiscence in this thin bone. Elevated ICP may also be an underlying etiology in these patients.

Nontraumatic, Increased Intracranial Pressure CSF Leaks

CSF leak from increased ICP may occur in patients with an intracranial mass lesion, hydrocephalus, or benign intracranial hypertension. Patients with either of the first two etiologies are routinely identified with neuroimaging (Fig. 61.4). Management of the underlying condition in addition to the CSF leak is critical for successful closure. Benign intracranial hypertension, also termed pseudotumor cerebri, is likely the underlying etiology in a significant number of patients with "spontaneous" CSF leak. The underlying pathophysiology remains poorly understood and has been theorized to involve impaired absorption of CSF. The diagnosis is suggested by patient demographics, clinical symptoms, and signs of increased ICP. These signs include absence of localizing neurologic signs (except possibly an isolated sixth nerve palsy), increased CSF pressure, normal CSF cell count and chemistries, papilledema on examination of the fundi, and no other identified etiology of increased ICP (including mass lesion or hydrocephalus on imaging).[17] Demographic hallmarks include female gender (approximately 9:1 female to male ratio), middle age, and central obesity. Clinical symptoms include headache, episodic blurry vision, diplopia and pulsatile tinnitus. The clinical symptoms are sensitive to postural changes and Valsalva maneuver. Measurement of an opening pressure of 25 cm H_2O at the time of lumbar puncture is diagnostic. Of note, the presence of a meningoencephalocele may act as an escape valve and lower the ICP, especially if associated with active CSF leak. In this setting, clinical signs and symptoms of elevated ICP may be absent and the opening CSF pressure may not be accurate. The lateral recess of the sphenoid sinus and fovea ethmoidalis/cribriform plate represent the most common locations of the skull base defect (Fig. 61.5). Multiple skull base defects in a single patient may occur in approximately one-third of cases.[18] The occurrence of meningoencephalocele in addition to CSF rhinorrhea is nearly universal in this cohort and is best assessed with MRI. Radiographic findings of empty sella, though not diagnostic for increased ICP, are a common association. This represents herniation of meninges and CSF through the diaphragmatic sella with displacement of the pituitary gland. Treatment strategies for increased ICP are reviewed in this chapter and involve both closure of the defect and management of the abnormal CSF physiology. Continued monitoring of CSF pressure and clinical findings in the early postoperative period may assist in identifying patients with occult increased ICP that become unmasked following successful repair.[19,20] A higher rate of adjunctive therapy for CSF leak is expected in this cohort and attentive evaluation and counseling is critical.

Endoscopic Skull Base Surgery

The past 20 years has witnessed the rapid development and widespread adoption of transnasal endoscopic approaches to a variety of complex pathologies of the sinonasal tract, anterior skull base, and intracranial compartments. As endoscopic instruments and techniques for inflammatory sinus disease were adapted for increasingly advanced lesions and complex anatomic subsites, a number of challenges were encountered. Integral to all endoscopic transnasal approaches to anterior skull base and intracranial lesions is the ability to repair skull base defects with a high degree of reproducible success and minimal morbidity. Failure to repair the skull base at the time of tumor extirpation is associated with the potential for significant morbidity including need for additional procedures, postoperative CSF leak, pneumocephalus, and meningitis. Indeed, the rate of postoperative CSF leak represents a hallmark outcome measure for these procedures and has, appropriately, been a major focus of surgical refinement in the brief history of endoscopic skull base surgery.

A number of challenges are associated with achieving successful repair following endoscopic skull base surgery. The variability in the location and size of the defects necessitates versatility in repair methods and a working knowledge of how to integrate the various available techniques into different surgical settings. The surgical site is accessible only through deeply recessed corridors and therefore the ability to inset and secure reparative grafts can only be done with endoscopic techniques. Certain basic and quintessential techniques in open surgery (i.e. suturing) are not technically practical. Regardless, the repair method of choice has to be immediately watertight and durable enough to withstand stress from ICP, gravity, and sinonasal function. These goals are especially challenging in patients with advanced intracranial lesions that require large skull base and dural resections for exposure. Tissue integration and fibrosis have to occur within a short period of time to allow for return to normal function and initiate adjuvant therapy in select cases.

EVALUATION AND DIAGNOSTIC STUDIES

Clinical Evaluation

The clinical presentation of CSF leak varies according to patient and disease variables. Clinical symptoms for CSF leak are of heightened concern in patients presenting with a known etiologic event such as recent trauma or surgery. However, a significant percentage of patients do not have a history of a causative event at the time of initial presentation and the underlying etiology will require evaluation. Common clinical symptoms include clear, watery rhinorrhea that is most often unilateral and described as salty or sweet. The volume and pattern of drainage are variable and may occur constantly, intermittently or with positional changes. Nonspecific headache symptoms may accompany the leak. Severe headaches, fevers, mental status changes and meningitis symptoms may portend intracranial complications from the CSF leak, including meningitis and pneumocephalus. An antecedent history of trauma or sinonasal surgery should be queried in patients with suspected leak. A past meningitis event may also signify the presence of an occult skull base defect. In patients with a possible spontaneous CSF leak, the clinical evaluation focuses on symptoms and signs of possible benign increased ICP as discussed previously.

Evaluation of patients with possible CSF leak or meningoencephalocele involves routine otolaryngologic and neurologic examination. Positional provocation of rhinorrhea is achieved with downward face position and a several-minute period of observation. Identification of clear, unilateral fluid is suggestive of CSF leak. The fluid may be collected for biochemical analysis. Papilledema on examination of the fundus may be noted in patients with benign increased ICP. Nasal endoscopy is indicated for assessment of sinonasal anatomy, evaluation of other sinonasal disorders including rhinitis and sinusitis, and potential identification of the site of the defect. In patients without a prior history of sinonasal surgery, the skull base defect is often not visible with routine endoscopy. However, localization of an area of clear fluid or a herniating meningoencephalocele is possible in certain patients. A leak site may be readily identifiable in patients with a prior history of sinonasal surgery. Endoscopy additionally allows for visualization of sinonasal anatomy that may be relevant at the time of surgery.

Diagnostic Studies

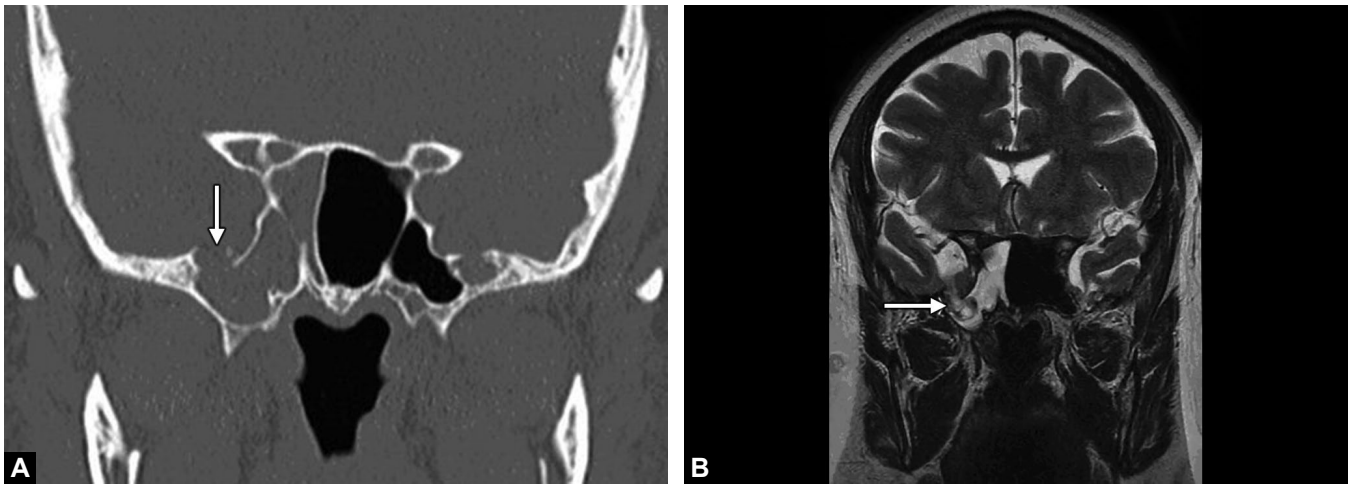
The application of various diagnostic tests to a patient with a suspected CSF leak requires an understanding of their limitation and clinical utility. Not all patients require every study, especially if there is a clear etiologic event and a clinical picture consistent with a CSF leak. Conversely, the diagnosis and location may be elusive in certain patients despite utilization of multiple studies.

A number of tests with unacceptably poor sensitivity and specificity have largely fallen out of favor. This includes the "halo" sign (clear ring surrounding a central blood spot) and measurement of rhinorrhea fluid for glucose, protein, and electrolyte levels. Accurate diagnosis is based on assessment of clinical factors, detection of CSF-specific fluid markers, and use of radiographic studies. Identification of beta-2 transferrin in rhinorrhea fluid is highly specific for CSF, as the only other natural locations are perilymph and vitreous humor. Beta-2 transferrin is produced by desialization (partial loss of sialic acids) of beta-1 transferrin by cerebral neuraminidase. False negatives can occur, especially if the CSF leak is intermittent. False-positive results, although rare, can also occur especially in patients with chronic liver disease.[21] An additional limitation of the test is the duration of time required for a result since the majority of medical centers send the test to specialized laboratories for analysis. Beta-trace protein is also a highly sensitive and specific marker of CSF. Although it is present in other body fluids including serum, the concentrations outside of CSF are substantially lower. The lack of widespread availability and potential for inaccuracy in patients with renal insufficiency and bacterial meningitis limit the utility of the test.[22]

The primary goals of radiographic studies in patients with suspected CSF leak and meningoencephalocele are diagnostic confirmation of active leakage, anatomic description of the defect and surrounding structures, evaluation of underlying etiologies, and detection of intracranial complications. To this end, different radiographic studies have different utility, and their application should be individualized based on the patient and disease factors. A step-wise approach with an understanding of the indications and limitations of each study is necessary. Plain X-ray radiography has a limited role for this disorder, given its poor anatomic resolution. In trauma patients too critical to undergo additional radiographic studies, plain films of the skull and paranasal sinuses may identify fractures and intracranial air. The primary initial study for the majority of patients is noncontrast paranasal sinus CT with fine cuts in the area of the skull base. Triplanar images are reviewed for evidence of skull base dehiscence, soft tissue herniation, air–fluid levels within dependent sinuses, surrounding paranasal sinus anatomy, presence of intracranial air, and other general intracranial findings. In patients with clinical evidence of CSF leak in the correct clinical setting, diagnostic findings on CT scan may be adequate to proceed with treatment planning. False negative and nondiagnostic results may occur from CT, especially in patients with small bony defects. False-positive results may occur from volume averaging or the presence of nonsignificant bony thinning of the skull base. CT may also be associated with limited definition of intracranial findings and inability to characterize soft tissue opacification within the paranasal sinuses (e.g. inflammatory polyp vs. meningoencephalocele). These issues are better addressed with MRI and its inclusion is especially indicated in patients with spontaneous CSF leak and meningoencephalocele. MRI in this setting is critical to assess potential findings of hydrocephalus and intracranial lesion. The primary limitation of MRI is the inferior resolution of the bony anatomy of the skull base and paranasal sinuses (Figs. 61.6A and B).

Suspicious findings on CT and MRI scans in the setting of a strong clinical history and positive biochemical testing of rhinorrhea fluid are often adequate to proceed with surgical exploration. However, certain clinical situations warrant the use of dynamic imaging including cisternography and radionuclide studies. CT cisternography involves intrathecal injection of contrast agents such as iohexol (previously metrizamide) followed by high-resolution CT scan. The phrase MR "cisternography" is potentially confusing as it is used interchangeably for two different procedures. The first involves the intrathecal injection of gadolinium-contrast agent followed by MR scanning, similar to CT cisternography. More commonly, the phrase is used to denote a scanning protocol that involves heavily weighted T2 images with fat suppression and image reversal, all of which better highlight CSF without any intrathecal injection.[23] Regardless of modality, a positive study is suggested by visualization of flow of contrast material through the site of a skull base defect. Supportive findings also include pooling of contrast within a dependent paranasal sinus. The sensitivity of cisternography studies are variable and largely correlates with how active and high-volume the CSF leak is at the time of the study. The need for lumbar puncture in patients undergoing intrathecal injection is also associated with patient discomfort and invasiveness. Cisternography may be most useful in patients with clinical suspicion of CSF leak from any cause without an identified anatomic source on high-resolution CT and MRI.

Radionuclide cisternography involves the intrathecal injection of a radionuclide agent (most commonly technetium^{99}) followed by either gamma camera imaging or measurement of radioactivity on nasal pledgets placed



Figs. 61.6A and B: Noncontrast coronal CT sinus (A) demonstrating an opacified right sphenoid sinus and a lateral bony defect (arrow). The nature of the opacification is nonspecific and is confirmed on T2 weighted coronal MRI image (B) to be a combination of cerebrospinal fluid and meningoencephalocele (arrow).

in the nasal cavity for several hours or days. The primary role of radionuclide cisternography is to diagnose the presence of a CSF leak in patients with a possible low volume or intermittent leak. Radionuclide studies are limited in a number of ways including invasiveness, exposure to radiation, moderate sensitivity, potential for false-positive findings, and poor anatomic localization.[24] This study may be most appropriate for patients with otherwise nondiagnostic radiographic studies and with an unclear clinical picture about the nature of the rhinorrhea fluid.

Although the intrathecal injection of fluorescein to stain the normally clear CSF a fluorescent green has been described for over 50 years, its clinical utility and safety profile have dramatically evolved in the endoscopic skull base surgery era. Historically, this was used as a diagnostic tool to identify the presence and side of a CSF leak. In this setting, the patient is awake during the injection and the nose is subsequently inspected for evidence of green fluid. Although the presence of leak may be confirmed, anatomic localization is limited. This technique has also historically been associated with a risk of rare, transient, but potentially morbid complications related to meningeal inflammation from fluorescein: seizure, lower extremity weakness and numbness, cranial nerve paresis, and hemiparesis. As the other diagnostic studies with less morbidity and improved utility for CSF leak developed, the use of intrathecal fluorescein in this setting waned. Renewed interest in the endoscopic era is based on its use intraoperatively rather than preoperatively. The safety profile in this setting is markedly improved since it is administered following induction of general anesthesia and premedication with intravenous corticosteroids and diphenhydramine. The meningismus effect is additionally minimized with a lower dosage of fluorescein (25 mg diluted with 10 cc of CSF) and slow intrathecal injection. Multiple benefits of fluorescein have been identified in patients undergoing endoscopic surgery for closure of CSF leak and meningoencephalocele. The leak site is more readily identified with confidence given the unique coloration of the fluid. In rare cases, a second leak site may also be more readily identified. Following identification, the defect is stratified (low vs. high volume), possibly altering the method of repair. Finally, following closure of the defect, the wound is carefully reinspected for evidence of continued leak. If a leak is noted intraoperatively, the reconstruction can be revised. In patients undergoing endoscopic surgery for resection of a skull base tumor, intrathecal fluorescein has these benefits and the additional advantage of assisting in determining whether there was any leak during the course of the surgery. The product is not currently FDA approved for intrathecal usage and therefore patient counseling and informed consent should entail a discussion of its risks, benefits, alternatives, and off-label usage.[25,26]

SKULL BASE RECONSTRUCTION

A variety of reconstruction materials, repair techniques, and surgical adjuncts are available for management of skull base defects. Familiarity with these different tools is critical to maximize successful reconstruction in the

various clinical scenarios. It is likely that several different options are effective in a given setting and a degree of surgeon preference is appropriate. The following sections review the different methods of skull base repair and provide a practical approach to common surgical indications.

Reconstruction Materials

A variety of materials are available for use during skull base reconstruction. Repair materials can be classified based on source as autologous versus nonautologous. Autologous grafts are subclassified as either free tissue versus vascularized pedicled flaps. Nonautologous grafts are subclassified as either biologic (homograft, xenograft) or synthetic material. Regardless of the specific graft, reconstruction materials can also be classified by function: filling a space by mass effect (fat), recreating a watertight layer (fascia, acellular dermis, mucosal grafts, rotational flaps), acting as a rigid buttress (cartilage, bone, synthetic miniplates), and stabilization of the wound edges (oxidized cellulose, gelatin sponge, tissue sealant). Common endoscopic reconstructive materials are summarized in Table 61.2.

Autologous fat has been a mainstay of cranial surgery for decades. The abdomen and lateral thigh provide an abundant supply that can be harvested with little morbidity. Advantages of fat include low morbidity of harvest, flexibility in size, and conformity to different three-dimensional cavities. Large fat grafts may be used to obliterate intracranial dead space following tumor extirpation. Smaller grafts may be useful to plug dural defects in conjunction with other materials.

Fibrous, watertight reconstruction grafts create a functional replacement for dura. Autologous fascia lata provides a versatile option, particularly if the defect is large. This is a low-cost option with excellent tissue compatibility, though it carries the disadvantage of potential donor site morbidity. Allogeneic products such as hydrated acellular dermis, marketed as Alloderm (LifeCell Corporation, Branchburg, NJ), provide an alternative, though at an increased cost. Grafts engineered from bovine pericardium (DuraGuard, Synovis, St. Paul, MN), bovine Achilles tendon (DuraGen, Integra Neurosciences, Plainsboro, NJ), and other sources are also available. Superiority of one product over another has not been demonstrated, although surgeon preference is common with the use of these products.

Table 61.2: Common reconstructive materials

Autologous	*Nonautologous*
Fat (abdomen, lateral thigh)	Acellular dermis
Fascia (lateral thigh, temporalis)	Collagen matrix products
Mucosa (nasal)	Gelatin sponge
Cartilage (nasal septum, auricular)	Oxidized cellulose
Bone (nasal septum, calvarium)	Porous polyethylene
Vascularized pedicled soft tissue flaps (nasal septum, inferior turbinate, middle turbinate, palate)	Titanium mesh/plate

A number of grafts are available for rigid reconstruction of the bony skull base. The most widely used autologous tissues for this purpose are the bony vomer and nasal septal cartilage, although conchal cartilage, calvarial bone, and other sites may provide alternatives. Tissue compatibility and extrusion are not significant concerns with these materials, though limitations in graft availability and customizing the shape may prove difficult. Titanium plates and titanium mesh are widely used in other aspects of craniofacial repair, and were employed prior to the development of local vascularized flaps.[27] An alternative to metallic hardware is porous polyethylene (Medpor, Stryker Corporation, Newnan, GA), which can be trimmed to an appropriate size and may facilitate subsequent in-growth of native tissue. Potential advantages of synthetic rigid support include malleability, visibility on imaging studies, and low risk of intradural or extracranial graft migration. Disadvantages include risk to neurovascular structures during placement, potential for extrusion, and difficulty with removal at the time of reoperation.

Nonvascularized Techniques

Nonvascularized techniques have historically been a cornerstone of endoscopic skull base reconstruction. The first report by Wigand and Hosemann utilized free tissue grafts for endoscopic closure of CSF fistulae.[28] Nonvascularized reconstruction may be achieved with a wide variety of materials, used either in isolation for low-volume, small defects or in conjunction with vascularized reconstructive techniques in more complex defects.

Bath-plug Technique

The "Bath-plug" technique involves repair of a skull base defect with a single autologous fat graft. A portion of the graft is placed intracranially and the remainder is positioned in the paranasal sinus; a suture may be used to

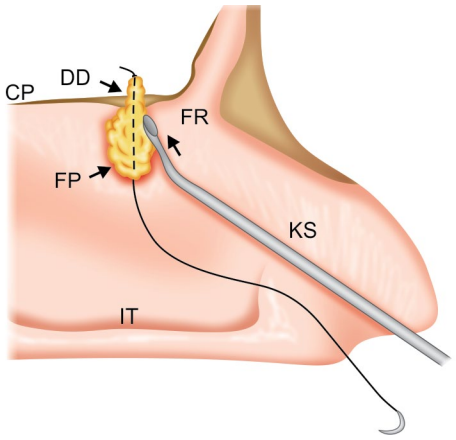


Fig. 61.7: An autologous fat graft placed with the Bath-plug technique through a cribriform defect. (CP: Cribriform plate; DD: Dural defect; FP: Fat plug; FR: Frontal recess; IT: Inferior turbinate; KS: Kuhn seeker).

cinch the intracranial portion against the skull base. The central portion spans the bony defect, stabilizes the graft, and plugs the defect[29] (Fig. 61.7). This type of repair is appropriate for small, low-volume CSF leaks.

Onlay Grafts

Onlay grafts are defined by their extracranial placement within the paranasal sinuses abutting the skull base defect. Early efforts at endoscopic reconstruction utilized free mucosal grafts harvested from intranasal structures, including the nasal septum mucosa and inferior and middle turbinates. Middle turbinate mucosal grafts have a reported success rate ranging from 83% to 94% for closure of traumatic or idiopathic CSF leaks.[30,31] Mucoperichondrial or mucoperiosteal free grafts from the nasal septum have a success rate up to 89% in closing CSF fistulae and encephaloceles.[32] Advantages include ease of harvest and availability of significant surface area. Care is taken to aim the mucosal surface away from the skull base defect to minimize the risk of mucocele formation. Fascia lata and acellular dermis may also be used as onlay grafts, particularly when sinonasal structures are sacrificed during the surgical approach.

When used as a single-layer repair, onlay grafts have a limited role and may be used in the reconstruction of small, low-flow defects at the anterior skull base (Figs. 61.8A to D). However, their use in isolation is limited, since the free edges of the graft are not affixed to the skull base and may be outwardly displaced by ICP. In modern surgery, the onlay graft is most commonly employed as part of a multilayer reconstruction.

Inlay Grafts

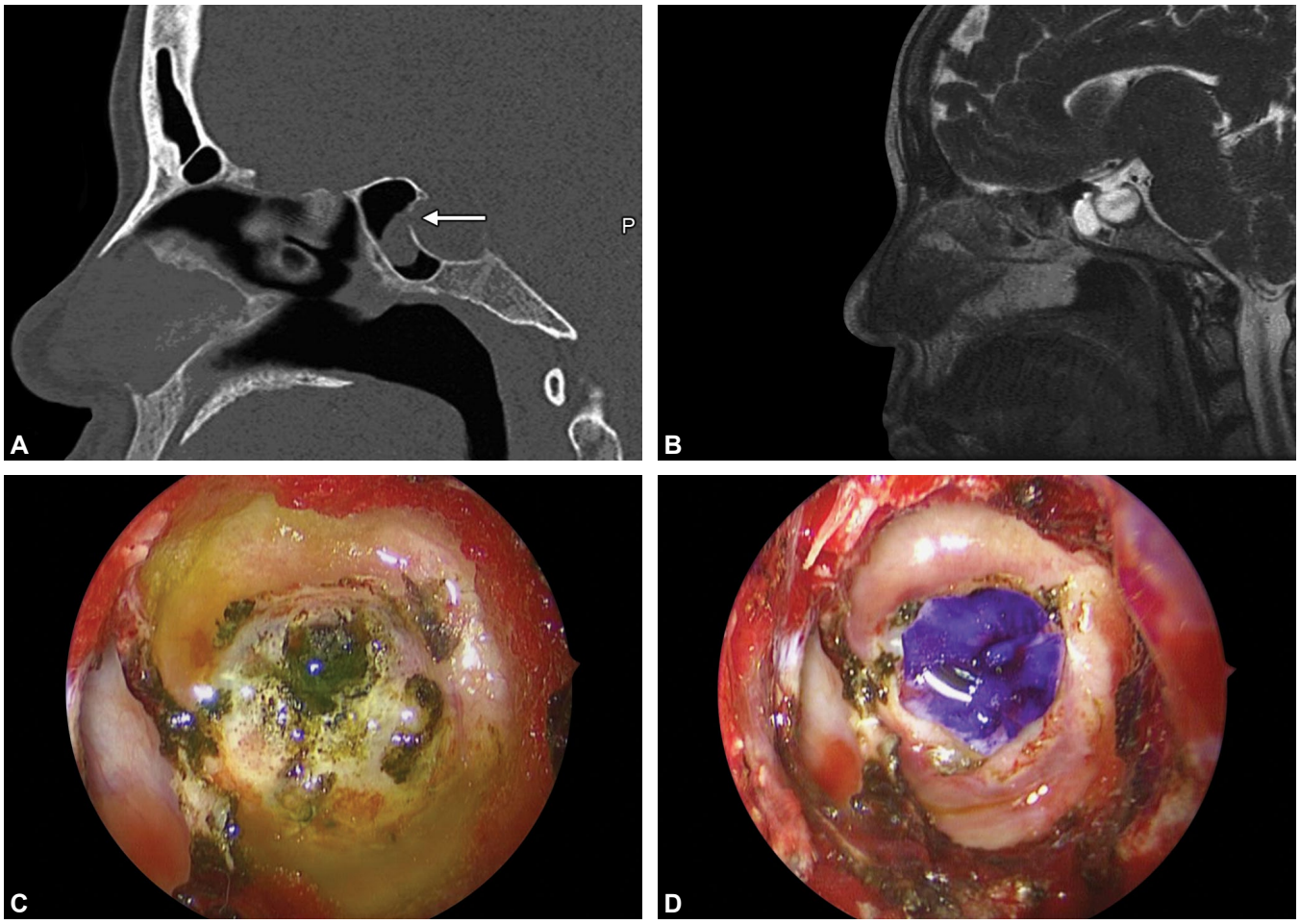
Inlay grafting, also termed "underlay" grafting, refers to the application of reconstructive material within the intracranial space, between bone and dura. The presence of a circumferential bony ledge is typically required to permit secure application of an inlay graft; otherwise, outward displacement and graft failure are likely. Once the bony margins have been defined, a graft is trimmed to allow the edges to be tucked intracranially using a probe. The intracranial contents provide pressure that keeps the graft buttressed against the skull base (Figs. 61.9A and B). As such, retraction of intracranial contents and displacement of the graft may occur in the setting of CSF hypovolemia.

Inlay placement of a graft can be done for either a fibrous, watertight repair of the dura or a rigid repair of the bony skull base. Inlay placement of a watertight fibrous graft including autologous fascia, acellular dermis, and dural substitute can recreate the functionality of intact dura. Application of collagen sponge at the wound edge may form a base layer for reconstruction, on the presumption that it provides a scaffold for subsequent fibroblast activity.[33,34] Inlay dural repair grafts may be used as a single layer in patients with low-volume CSF leaks in a number of different settings including iatrogenic, surgical, and spontaneous defects. More commonly, inlay grafts are used in conjunction with other layers.

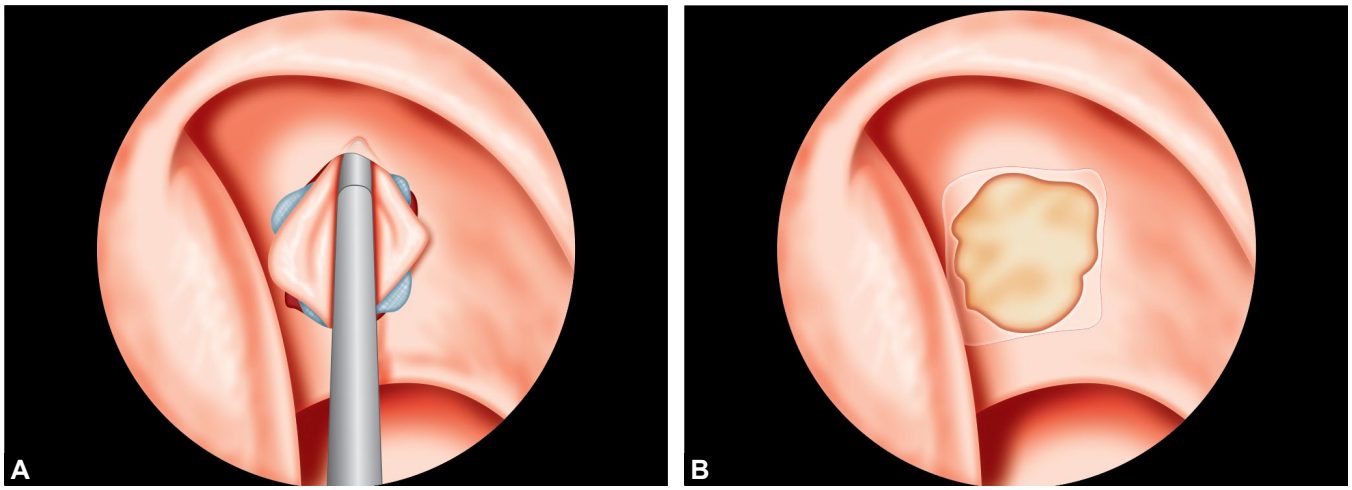
Inlay placement of a rigid buttress aims to reconstruct the bony skull base. The primary benefit is stabilizing the other repair layers and preventing displacement from intracranial pulsation. As the rigid materials are not watertight, other layers are typically required. Although repair of the bony skull base defect with a structure of similar integrity seems inherently important, its necessity is controversial. Inclusion of a rigid buttress is likely beneficial in patients with large skull base defects following tumor resection. Some authors have advocated for the use of rigid buttressing for repair of all CSF leaks confirmed by Valsalva maneuver.[35] A selective role for rigid buttressing may be found in cases in which elevated ICP is present, since these cases have a higher incidence of reconstructive failure.[20]

Composite Grafts

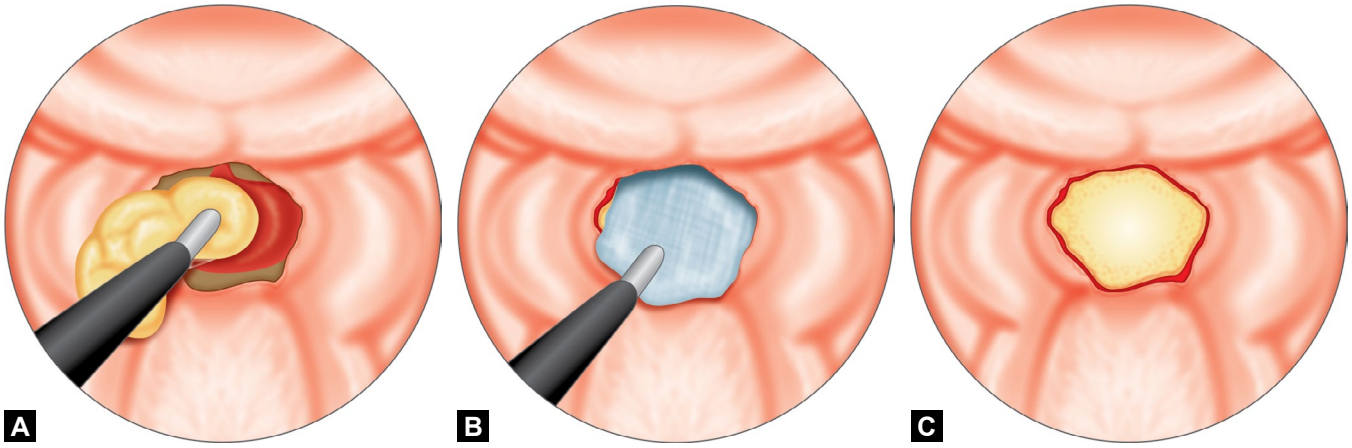
The workhorse in skull base reconstruction for moderate-sized defects with active CSF leakage is the composite graft composed of two or more free tissue grafts placed in a specific manner. Most commonly, a composite graft



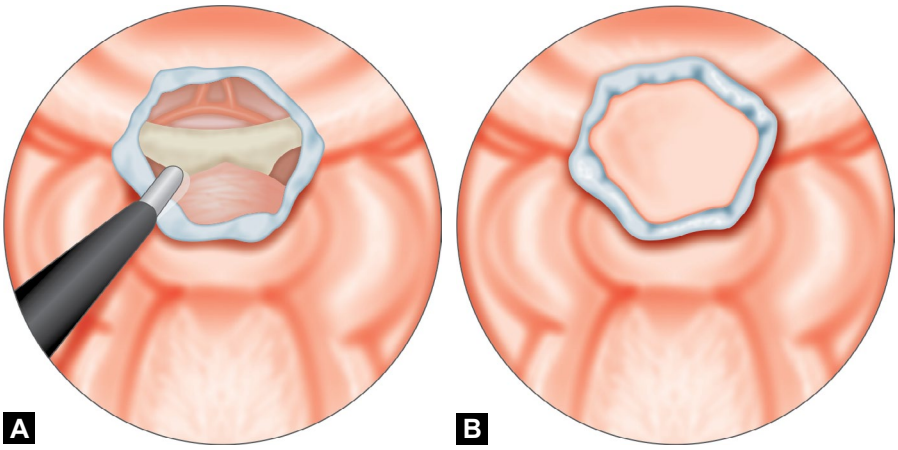
Figs. 61.8A to D: Onlay repair of a patient with spontaneous cerebrospinal fluid (CSF) leak and meningocele from a small paramedian defect of the sella as noted on sagittal CT (A) and T2-weighted MRI (B). A small bony defect and active fluorescein-stained CSF leak was noted at the time of surgery (C). Mucosal onlay graft of inferior turbinate mucosa was used for primary closure (D). The mucosal surface is marked with a marking pen to ensure that it is identified throughout the closure. Correct placement toward the sphenoid sinus and away from the intracranial opening is necessary to minimize the risk of mucocele formation.



Figs. 61.9A and B: Inlay graft placement of fascia or acellular dermis.



Figs. 61.10A to C: A multilayer repair encompassing a fat graft placed in the intracranial cavity to fill the dead space and plug dural tears (A), dural substitute (fascia lata or acellular dermis) underlay graft to act as a watertight layer (B) and rigid reconstruction of the bony skull base (C). An additional onlay graft of free mucosal tissue or a local vascularized flap such as the nasoseptal flap is considered. Tissue sealant and packing material are placed over the repair.



Figs. 61.11A and B: A multilayer repair placed with gasket seal technique. An oversized piece of dural substitute (fascia lata or acellular dermis) (A) is placed as an onlay graft and countersunk into the defect with a rigid buttress (B).

consists of a combination of inlay and onlay grafts, tissue sealant, and supporting material. This may involve some or all of the following elements: a fat graft placed intracranially to fill a potential dead space, a watertight fibrous layer to reconstitute the dura, a rigid buttress placed as an inlay to repair the bony defect, a mucosal onlay graft, and tissue sealant over the entire repair. Variants of this involve excluding one or more of the layers (Figs. 61.10A to C). The composite graft is a versatile option for different skull base defect locations, dimensions, and underlying etiologies. The composite graft is likely unnecessary in patients with small defects with low-volume CSF leak. For patients with large defects and high-volume CSF leaks, a composite graft may be combined with a pedicled vascular flap.

Leng et al. introduced a variant of a composite graft for closure of high-flow CSF leaks that combined rigid and soft components into a "gasket seal" closure.[36] In this technique, a pre-cut piece of bone is countersunk against a fascia lata graft to create a watertight seal at the skull base (Figs. 61.11A and B). They reported no postoperative leak in an initial series of 10 patients. This technique has been modified to use a buttress of Medpor instead of bone. A subsequent series of 57 consecutive cases of gasket seal closure following resection of intracranial pathology by the same authors has been associated with a postoperative leak rate of 6.8%.

One application for the gasket seal is reconstruction of high-flow leaks following transtuberculum resection of a craniopharyngioma, where placement of a fat graft

within the cavity carries the risk of optic chiasm compression and third ventricular obstruction. Eloy et al. reported a postoperative leak rate of 13.6% for a series of 22 transplanum and transtuberculum resections that were reconstructed with an onlay graft and nasoseptal flap.[37] This contrasts with a series by Schwartz et al. (unpublished data) in which 47 consecutive gasket seal closures after suprasellar tumor resection achieved a postoperative leak rate of 6.4%.

Luginbuhl et al. described a technique for closure of high-flow CSF leaks using a bilayer "button" as a composite graft.[38] This technique involves suturing two layers of fascia lata or acellular dermis together. One leaf of the graft is tucked on the intracranial side of the skull base defect as an underlay graft and the other is positioned on the sinonasal surface as an onlay graft. A circumferential rim of intact skull base bone is required to support the graft. Advantages of this repair include its stability, utilization of two watertight layers, and flexibility for skull base defects of variable size and dimensions. For this "button closure," Luginbuhl et al. reported a postoperative leak rate of 10% for 20 cases of open-cistern CSF leak following resection of mostly meningiomas and craniopharyngiomas. The majority of these cases were also treated concurrently with a vascularized septal flap.

Other Techniques

Cukurova et al. described the endoscopic repair of ethmoid roof CSF leaks <1.2 cm^2 by suturing the dura under endoscopic visualization.[39] The applications for this technique appear to be limited to cases with a large bony defect and a relatively small dural defect that can be subjected to a tension-free closure. The technical difficulty in endoscopic suture placement and the success of other techniques has historically precluded suturing as a viable option.

Endoscopic closure of skull base defects using laser tissue welding may hold promise for the future. Bleier et al. described an initial human experience with a chromophore-containing biological solder, which is applied topically to the defect and exposed to a laser beam.[40,41] They found that this technique has a strength that exceeds that of common tissue sealants, with no significant thermal or inflammatory sequelae. Further study is needed to demonstrate the role of this technique in a routine clinical setting.

Vascularized Techniques

Local vascularized flaps represent a newer addition to the reconstructive capabilities of the endoscopic surgeon. A major limitation of intranasal free grafts is their random blood supply, which limits the viability of large grafts. In contrast, vascularized flaps utilize an axial blood supply, which improves the viability and surface area of the flap. Integral to successful flap insetting are adequate length, arc of rotation, and torsional forces. The majority of these flaps do not require an external incision. Table 61.3 lists available options for vascularized endoscopic reconstruction.

Nasoseptal Flap

The vascularized nasoseptal flap, also called the Hadad-Bassagasteguy flap, is a mucoperichondrial and mucoperiosteal flap that is based on the posterior septal branch of the sphenopalatine artery (Fig. 61.12). Since its initial description, the nasoseptal flap has been identified as a major advance in endoscopic skull base reconstruction, ultimately allowing for a higher rate of successful repair of complex skull base defects.[42] Its advantages include ease of harvest, limited patient morbidity, large mucosal surface and favorable arcs of rotation for coverage of

Table 61.3: Vascularized flaps available for endoscopic reconstruction

Name	*Pedicle site*	*Relative size*	*Suitable defects*
Nasoseptal flap	Posterior	Large	Anterior, central, posterior
Inferior turbinate flap	Posterior	Small	Posterior, central
Lateral nasal wall flap	Anterior	Medium	Anterior
Middle turbinate flap	Posterior	Small	Central
Palatal flap	Inferior–posterior	Large	Posterior, central
Double nasoseptal flap	Posterior	Large	Anterior, central, posterior
Tunneled pericranial flap	Superior	Large	Anterior, central
Tunneled temporoparietal flap	Lateral	Large	Anterior, central, posterior

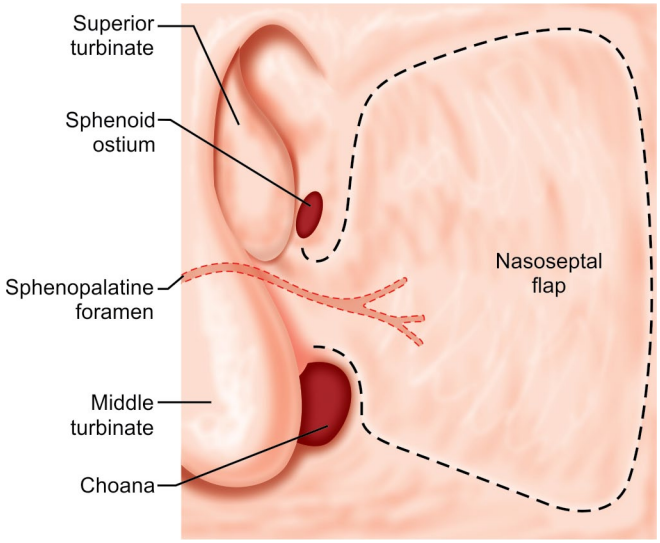


Fig. 61.12: A right nasoseptal flap, including the neurovascular pedicle (posterior nasal septal branch of the sphenopalatine artery).

sellar, suprasellar, clival, and anterior skull base defects. Cadaveric study[43] has reported the surface area of the flap at 22–27 cm^2.

The decision to harvest a nasoseptal flap must be made preoperatively, particularly if a posterior septectomy is planned for the approach and exposure. The presence of a prior septal perforation or the involvement of septal mucosa with malignant disease may contraindicate the use of a nasoseptal flap. Prior septoplasty does not preclude the harvesting of a nasoseptal flap, although it may prove more technically challenging. In cases where a prior bilateral sphenoidotomy has been performed, the viability of a proposed flap pedicle may be assessed using acoustic Doppler sonography.[44] An additional limitation of the nasoseptal flap is its difficulty in reaching far anterior defects. The flap should be designed contralateral to the site of the lesion in patients undergoing surgery of the pterygopalatine fossa or sphenoid rostrum, since the vascular supply on the ipsilateral side is expected to be compromised during the surgery. Avoidance of a nasoseptal spur is prudent given the risk of flap perforation.

The nasoseptal flap is harvested at the onset of the case to ensure viability of the neurovascular pedicle. Harvesting of the flap involves an inferior horizontal incision at the level of the floor of the nasal cavity, a superior horizontal incision high in the nasal cavity and a single vertical incision anteriorly in the mucocutaneous junction of the nasal vestibule. Maximizing the surface area of the flap by appropriate placement of the incisions is critical. Following initial incisions, the flap is elevated in the mucoperichondrial and mucoperiosteal layers until the area of the pedicle is identified. Additional releasing incisions are often required in the posterior-most aspect of the vomer to allow for flap rotation. Following harvest, the flap is stored away from the site of surgical dissection until needed, often in the nasopharynx given its proximity to the pedicle and location away from the sella and anterior skull base. In patients undergoing resection of clival lesions, the flap can be stored within the ipsilateral maxillary sinus until needed. Following tumor resection, the flap is rotated into place to cover the skull base defect either as a single layer, or most commonly as the last layer of a multilayered reconstruction. In cases where it is harvested initially but is ultimately not used, the flap may be repositioned and secured on the nasal septum.

Potential adverse effects of nasoseptal flap usage include donor site morbidity, flap displacement, and flap necrosis due to torsion or interruption of vascular pedicle blood supply. A sphenoid sinus mucocele may also occur in the event of incomplete removal of mucosa from the sinus cavity before insetting the flap. Takedown and reuse of the nasoseptal flap have been described for revision cases.[45]

Inferior Turbinate Flap

When a nasal septal flap is unavailable, other methods of vascularized reconstruction are possible. The posterior-pedicle inferior turbinate flap, first described by Fortes et al.,[46] is an option for coverage of posterior and central skull base defects, particularly the clivus. This flap is based on the posterior lateral nasal artery, a branch of the sphenopalatine artery, with a posterior pedicle and a surface area of approximately 5 cm^2. Other studies have confirmed the role for the inferior turbinate flap in reconstruction at the posterior cranial fossa, with less reliable coverage of anterior fossa defects.[47] Prolonged postoperative crusting over the turbinate site is a potential disadvantage.

A vascularized lateral nasal wall flap has also been described[48] that incorporates the inferior turbinate and nasal floor mucosa, with a pedicle based anteriorly on the facial (angular) artery and anterior ethmoidal artery. This may be suitable for reconstruction of larger anterior fossa defects.

Middle Turbinate Flap

The vascularized middle turbinate flap, as described by Prevedello et al.,[49] has potential for coverage of sellar defects. In this technique, mucoperiosteum is dissected

from the medial and lateral surfaces of the turbinate bone to create a single broad flap that is pedicled posteriorly on the middle turbinate branch of the sphenopalatine artery. This flap yields a surface area of up to 6 cm^2, though it may have the disadvantage of a less acute arc of rotation compared to a nasoseptal flap.[50]

Palatal Flap

Oliver et al.[51] described the use of a pedicled flap of palatal mucosa for coverage of defects of the planum, sella and clivus. This technique involves mobilizing the descending palatine vessels from the greater palatine foramen to their origin in the pterygopalatine fossa. This flap is described as having a 3 cm pedicle with a maximum surface area of 18 cm^2. Potential disadvantages are the technical difficulty, which includes extensive dissection and drilling, and donor site morbidity. To date, clinical application of this technique has been limited.[52]

Tunneled Flaps

Certain external techniques have been modified to fit the goals of the endoscopic approach. Zanation et al.[53] described raising a pericranial flap through limited brow incisions and tunneling it into an epidural plane using endoscopic instrumentation. This type of reconstruction may be desirable in cases of anterior cranial malignancy such as esthesioneuroblastoma that are being resected endoscopically. A multi-institutional series of 10 cases utilizing this technique included no postoperative CSF leaks or other major complications.[54] Fortes et al.[55] described a tunneled temporoparietal fascia flap that is raised through a hemicoronal incision and passed through a bone window created by an endonasal transpterygoidal approach. This technique may be useful for cases of clival pathology with a large dural defect and previous radiotherapy.

Other regional vascularized flaps have been described, including the pedicled facial buccinator flap and the pedicled occipital galeopericranial flap.[56] Although clinical application has been limited, the expansion of reconstructive requirements suggests a future role for these and other novel options for the skull base surgeon.

Surgical Adjuncts

Tissue Sealants

A variety of tissue sealants are commercially available for use in endoscopic skull base reconstruction. Compounds based on a fibrin matrix include Tisseel (Baxter Healthcare, Deerfield, IL) and Evicel (Ethicon). These target the final steps of the coagulation cascade and may assist with hemostasis. Nonfibrin-based synthetic tissue sealants may also be employed.[57] These include BioGlue (Cryolife, Kennesaw, GA), a compound of bovine albumin and glutaraldehyde, and synthetic polyethylene hydrogels, such as Duraseal (Covidien, Mansfield, MA), CoSeal (Cohesion Technologies, Beaufort, SC), and AdvaSeal-S (Genzyme Corp, Cambridge, MA).

Synthetic tissue sealants often play a role in endoscopic skull base reconstruction, although their necessity remains unclear. In general, tissue sealants do not provide reliable closure of CSF leaks when used in isolation, but may help to stabilize other reconstructive materials when applied as the final layer of a multilayered repair.[35,58] Eloy et al. reported on a series of 74 high-flow CSF leaks treated with a multilayered reconstruction including a vascularized nasoseptal flap, 42 of which received a final layer of Duraseal and 32 of which did not.[59] The overall postoperative leak rate was 1.4%, with no significant difference between the two groups. An additional potential drawback of tissue sealants is their high cost, which could mitigate decisions about their necessity in routine skull base reconstructions.

Lumbar Drain

The role of lumbar drainage in the setting of endoscopic skull base surgery remains incompletely defined. The primary benefit of diverting CSF through a lumbar drain is reduction in pressure at the skull base repair site during the early postoperative period. This would potentially improve wound stabilization and overall closure rate. However, the efficacy of this intervention has not been completely evaluated in the literature. The risks associated with the use of lumbar drain, however, are well described and include infection at the catheter site, meningitis, pneumocephalus, chronic headache, and retained catheter material. Specialized nursing care is required to minimize the risk of accidental over-drainage and associated cerebellar herniation. Finally, lumbar drainage is associated with a delay in mobilization and discharge from the hospital. Indeed, the risk–benefit assessment of lumbar drainage remains complicated given the unclear impact on outcomes.[60]

What has borne out of the collective experience over the past two decades is that the primary determinants of whether a given skull base reconstruction will be successful are patient comorbidities, etiology of the leak, size of the defect, volume of active CSF drainage and, most

of all, the design and execution of the repair, rather than lumbar drainage. Additionally, the majority of repairs will be successful without lumbar drainage.[61,62] Given these considerations and the potential for morbidity, lumbar drainage may be considered an adjunct to be used in select situations. Although surgeon preference and a case-by-case analysis are appropriate, several indications warrant consideration of a drain: complex skull base defects with high-volume intraoperative leaks, increased ICP (both for therapeutic and diagnostic purposes), and the presence of a high-volume CSF leak preoperatively. Lumbar drainage may also be considered as primary treatment when CSF leak occurs in the postoperative period following skull base surgery or trauma.[62-64]

Intracranial Approach

Although the majority of anterior CSF leaks and skull base defects can be managed from an endoscopic, endonasal approach, there is still a role for intracranial surgery. The indications are determined individually and may include large, broad-based or multifocal defects, high-pressure CSF leaks, comminuted skull base fractures, large tumors with intracranial extension, CSF leaks refractory to attempted endoscopic repair, and far-lateral CSF leaks of the frontal and sphenoid sinuses. Distinct advantages of the open approach stem from direct exposure, which permits placement of large vascularized pericranial flaps and simultaneous reduction in meningoencephaloceles while addressing elevated ICP.

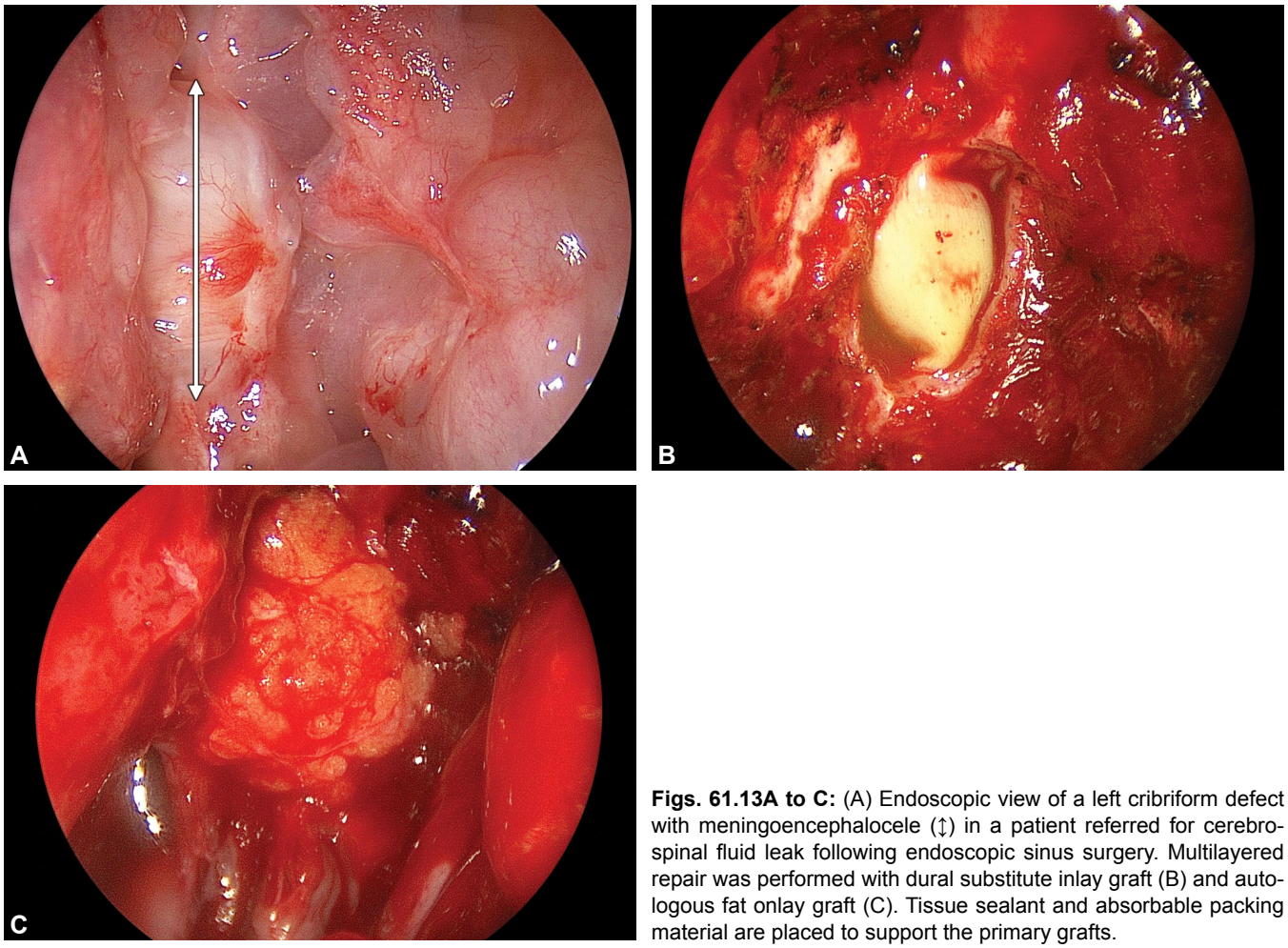
COMMON CLINICAL SCENARIOS

Regardless of the specific etiology and characteristics of the skull base defect, certain general principles apply. Careful consideration should be given to the underlying etiology and CSF dynamics of each patient as different repair methods and use of adjuncts are variably indicated. This is especially true in patients with spontaneous CSF leaks. The defect itself should be closely assessed at the time of surgery including the size of the bony defect, the integrity of the dura, the volume of active CSF leakage, and potential continuity with cisternal spaces. Hemostasis is attained and any sinonasal mucosal tissue near the wound edges is cleared. In patients with long-standing CSF leaks, the wound edge of the fistula is roughened to promote granulation. Herniating meningoencephalocele is reduced using a combination of bipolar cautery and tissue dissection. These steps allow for a complete assessment of the defect and allow for determination of which repair techniques/materials are likely to be indicated. A variety of reconstruction options and graft types are available as outlined in this chapter. Following graft placement, the wound edges are assessed for complete cessation of CSF egress. Revision of the repair is indicated if continued CSF leak is noted. As a final step, the graft is supported with tissue sealant and packing material. Postoperative care includes precautions to avoid strenuous activity, straining, nose blowing, and Valsalva maneuver. Following an observation period of several weeks, office-based debridements and use of nasal saline irrigation assist in restoration of normal sinonasal function. Maturation of the repair site including remucosalization is expected to occur over a 6–8 week period of time.

CSF leak Following Endoscopic Sinus Surgery

Intracranial injury is a well described risk of ESS and any surgeon endeavoring in this procedure should be well-versed in prevention and management strategies. The anatomy of the skull base should be closely inspected on preoperative CT scan as a routine step in preparation for surgery. This includes reviewing the position of the cribriform plate, fovea ethmoidalis and planum sphenoidale with respect to the paranasal sinuses, the slope of the fovea ethmoidalis (sagittal images), and any areas of potential dehiscence. A heightened degree of risk is identified in patients undergoing revision surgery, advanced surgery (i.e. endoscopic Draf III), or surgery for complex pathology (polypoid chronic rhinosinusitis, hyperostosis, neoplasm). During the surgical dissection, care should be taken in dissecting near the skull base including constant confirmation of orientation, maintenance of excellent visualization and judicious use of powered instruments.

If a skull base injury occurs during ESS, immediate repair should be performed. There are a number of advantages to immediate management: the location of the injury is typically well exposed and apparent to the operating surgeon; the patient is already under anesthesia and surgical instrumentation is readily available; the defect has not had the opportunity to develop into a true fistula tract and is therefore more amenable to closure; there has not yet been a compensatory increase in CSF production as may occur with a long-standing high-volume leak; and



Figs. 61.13A to C: (A) Endoscopic view of a left cribriform defect with meningoencephalocele (↕) in a patient referred for cerebrospinal fluid leak following endoscopic sinus surgery. Multilayered repair was performed with dural substitute inlay graft (B) and autologous fat onlay graft (C). Tissue sealant and absorbable packing material are placed to support the primary grafts.

the risk of additional sequelae from the injury (pneumocephalus, intracranial infection) is minimized. Therefore, delaying repair or hoping for spontaneous closure is not indicated. Once an injury is suspected, the surgeon should take a few minutes to assess the injury, discuss the unplanned event with the surgical and anesthesia team, and consider the various reconstruction options. The location, extent and nature of the injury should be determined. Hemostasis is achieved and any obstructive mucosal tissue near the injury site should be cleared. The majority of intraoperative defects caused by cold steel instruments tend to be small (1 cm or less) and readily amenable to any number of repair options including a mucosal onlay graft (harvested turbinate tissue), supported by gelatin sponge and tissue sealant. The defect should not be enlarged with the hopes of accommodating an inlay graft as this risks further injury. A Bath-plug graft of fat may also be effective, but this requires harvesting from a separate donor site. A multilayered composite graft should be considered for injuries larger than 1 cm (Figs. 61.13A to C).

Immediate hospitalization for further evaluation and neurologic observation is indicated following the injury even if this requires transferring from an ambulatory facility to an inpatient hospital. A CT scan of the head is performed to evaluate the extent of the injury including assessing for pneumocephalus or intracranial hemorrhage. Early neurosurgical consultation is indicated even if no other care is likely to be necessary. Lumbar drain is not routinely necessary in this setting, especially if the repair was felt to be durable, but may be considered if the repair is thought to be tenuous.

"Spontaneous" CSF Leak

Management of "spontaneous" CSF leak requires a systematic approach as this is a heterogeneous group of

disorders with different underlying pathophysiologies, management requirements and prognosis. Following confirmation of the presence of a CSF leak and/or meningoencephalocele, detailed consideration should be given to assessing the etiology. An underlying history of intracranial pathology including neoplastic lesion or hydrocephalus should be assessed on MRI. Dehiscences following old trauma events and congenital anatomic defects represent a subset of patients with spontaneous CSF leaks and are highly amenable to endoscopic repair. A critical aspect of successful management of a patient with a spontaneous CSF leak is assessing for increased ICP as the underlying etiology. This is described previously in this chapter and requires clinical evaluation and application of diagnostic studies including intracranial imaging and measurement of ICP. The method of repair in these patients is similar to other etiologies and encompasses multilayered composite grafts. Use of a rigid buttress as one of the layers is appropriate to counteract intracranial pulsation. Unique to these patients is careful surveillance for increased ICP. In patients with active high-volume leakage, the manifestations of increased ICP may be masked until the repair has been performed. Measurement of ICP in the immediate postoperative period with a lumbar drain may identify this cohort.[65] Lumbar drainage is also especially helpful in this cohort to minimize pressure on the repair site in the early postoperative period. If elevated ICP is noted following surgery, adjunctive therapy including acetazolamide and CSF shunt procedures should be considered.[20] Patient counseling in this cohort is imperative given the complexity of the clinical issue, lower success rate of CSF leak closure and higher need for adjuvant therapies.[5,66] Limited reports of resolved CSF rhinorrhea following gastric bypass supports the pathophysiologic link between obesity and increased ICP, though further research is required.[67,68]

Reconstruction Following Endoscopic Skull Base Surgery

Endoscopic skull base surgery can be divided into the following elements: preoperative planning, approach, tumor resection, skull base reconstruction, and postoperative care. The primary goal of reconstruction is the creation of a durable, watertight separation between the skull base and sinonasal cavity with minimal morbidity and rapid healing of the sinonasal cavity. An algorithmic approach is recommended based on the nature of the surgery, patient and tumor variables and intraoperative findings (Table 61.4).

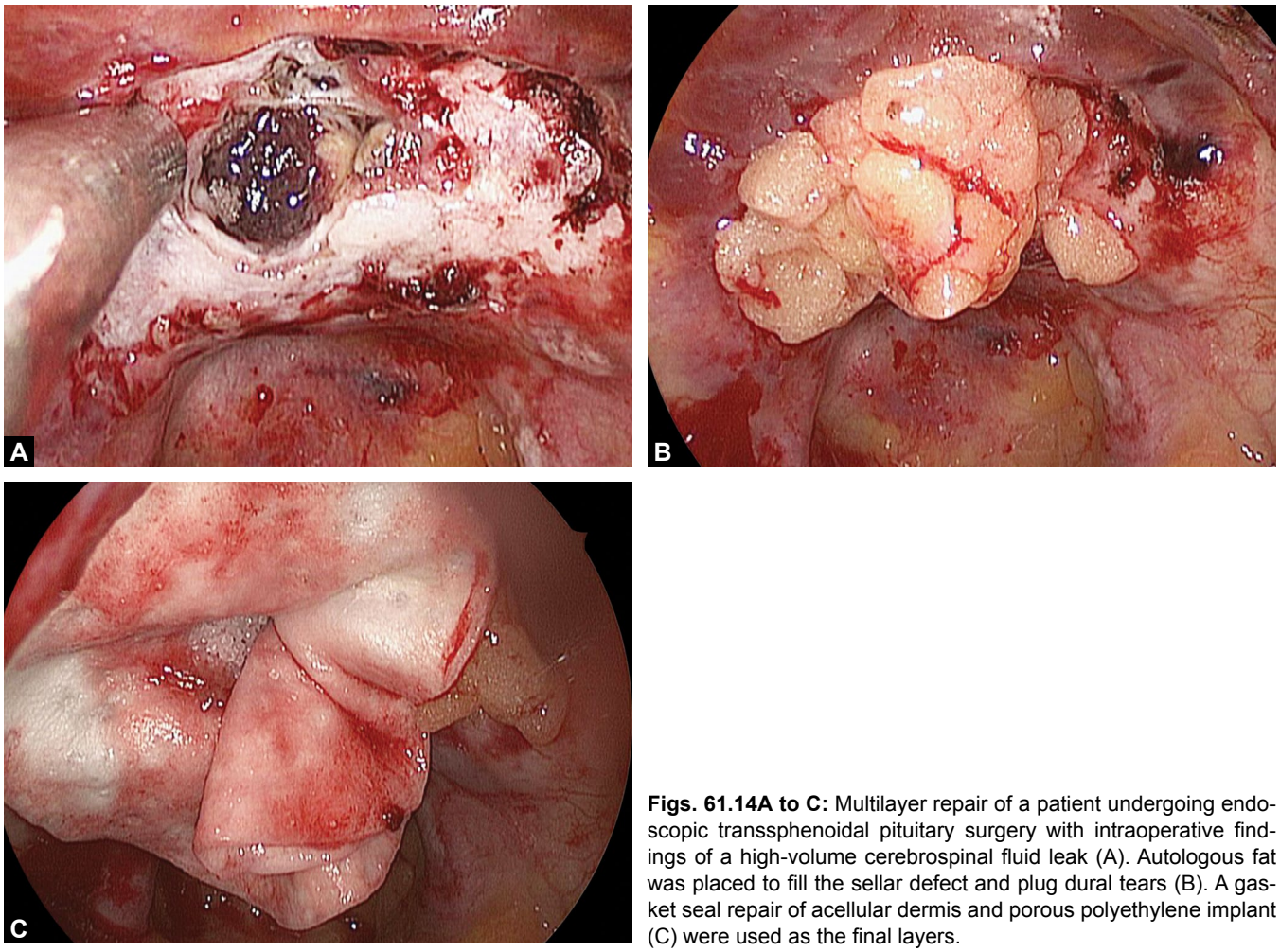
Several determinants should be considered in designing an appropriate repair. Patient related factors that may impair wound healing include tobacco use, prior sinonasal history, surgery or infection, and medical comorbidities such as diabetes, radiation history or Cushing's syndrome. The size, location and dimensions of the skull base defect should be determined. The intracranial depth should be defined: extracranial, intracranial–extradural, intracranial–intradural–extra-arachnoid, or intracranial–intradural–intra-arachnoid. Finally, a determination of low- versus high-volume leakage is critical.

No formal repair is necessary in patients undergoing resection of a primary sinonasal lesion where the bony skull base is not violated. Common examples include

Table 61.4: Algorithm for reconstruction following endoscopic skull base surgery

Indication	*Repair method*
Extracranial dissection with no exposure of dura and no CSF leak	No formal repair necessary
Sellar defect with no intraoperative evidence of CSF leak	Formal repair not mandatory. Consider single layer repair with autologous fat or gelatin sponge +/- rigid support.
Sellar defect with intraoperative CSF leak	Multiple options. Formal multilayer repair with free tissue or composite graft +/- rigid support (Figs. 61.10 and 61.11). Consider nasoseptal flap for high-volume leak, large defects or complex lesions (craniopharyngioma).
Small anterior skull base defect (extra-sellar) with low-volume CSF leak	Multiple options. Formal repair with single or multiple layers including bathplug graft, inlay graft, onlay graft, or composite grafts.
Large anterior skull base defect (extra-sellar) with high-volume CSF leak	Multiple options. Formal multilayer repair with composite graft +/- rigid support with inclusion of vascularized, pedicled flaps (nasoseptal flap).

(CSF: Cerebrospinal fluid).



Figs. 61.14A to C: Multilayer repair of a patient undergoing endoscopic transsphenoidal pituitary surgery with intraoperative findings of a high-volume cerebrospinal fluid leak (A). Autologous fat was placed to fill the sellar defect and plug dural tears (B). A gasket seal repair of acellular dermis and porous polyethylene implant (C) were used as the final layers.

surgery for inverted papilloma and juvenile nasopharyngeal angiofibroma. In patients undergoing endoscopic pituitary surgery, reconstruction is stratified based on intraoperative findings including presence of CSF leak and volume of the leak (low vs. high). In cases without an intraoperative CSF leak, some authors have suggested that no formal reconstruction is necessary.[69] Other authors have advocated the use of a simple, single-layer closure in such instances.[70,71] As a general rule, whenever a CSF leak is identified, formal reconstruction is indicated. Depending on the characteristics of the leak, single-layer or multilayer closure may be appropriate. In many cases, the optimal type of reconstruction remains a matter of debate. In patients with low-volume CSF leak identified during the course of surgery, several options exist. The primary goals of repair are to plug the dural defect and stabilize the reconstruction. One strategy includes a composite graft comprised of autologous fat within the sella and a rigid onlay graft to reconstruct the sellar floor. A bathplug graft of fat or a mucosal free-tissue onlay graft may also be effective. Although vascularized pedicled flaps such as the nasoseptal flap are effective in this setting, they are more commonly reserved for more challenging defects.

In patients undergoing endoscopic pituitary surgery where a high-volume CSF leak is identified, a multilayered repair is indicated. Effective options include autologous fat within the sella, supported by a rigid buttress and covered by mucosal graft. Fascia or acellular dermis may also be used either as an inlay graft as part of this multilayered repair or as part of a "gasket" seal repair (Figs. 61.14A to C). Pedicled nasoseptal flaps are also useful in this setting as the final layer of a multilayered technique. However, anticipation of a possible need for this flap is necessary at the onset of the case as harvest needs to be performed prior to creation of the sphenoidotomies and

violation of the posterior nasal septal artery. Of note, fat has also been used historically to fill the entire sphenoid sinus cavity, especially in the microscopic era. This practice has been questioned based on the lack of targeted placement, potential for graft infection, and obstruction of sphenoid sinus mucosal function leading to postoperative sinusitis and mucocele formation.

Endoscopic reconstruction for patients undergoing endoscopic resection of a skull base or intracranial tumor is associated with unique challenges given the large, multidimensional defect and high-volume nature of the defects. Various multilayered reconstructions have been described, primarily variants of composite grafts and pedicled flaps. The superiority of one technique over another has not been identified, suggesting that multiple approaches may be successful. Principles of successful repair for these complex defects include surgical experience and knowledge of the different repair options, assessment of the defect characteristics, successful placement of a watertight and durable repair, and appropriate postoperative care.

Tabaee et al.[62] proposed an algorithm for endoscopic reconstruction based on their experience with 127 patients using nonvascularized techniques. Under that system, small extrasellar skull base defects (such as from iatrogenic CSF leak) were closed with a single layer of autologous fat or fascia followed by tissue sealant. Sellar defects without intraoperative leak were closed with compressed gelatin sponge followed by rigid buttressing and tissue sealant, whereas sellar defects with a leak substituted autologous fat as the deepest layer. Defects resulting from resection of extrasellar pathology with a high-flow leak added an inlay of autologous fascia lata between the fat and the rigid buttress. The presence of direct communication between the ventricular spaces and tumor cavity dictated the omission of the fat packing to minimize the risk of iatrogenic hydrocephalus.

The availability of vascularized techniques has allowed expansion of this algorithm. Vascularized reconstruction may now be favored in cases where a significant intraoperative CSF leak is anticipated, such as meningiomas, craniopharyngiomas, chordomas with intradural extension, and large macroadenomas that extend >1 cm above the planum sphenoidale. When the nasoseptal flap is not available, anterior or central skull base defects may be managed with a middle turbinate flap (if small) or an endoscopically harvested pericranial flap (if large), while clival defects may be managed with an inferior turbinate flap.

The stratification into low- and high-flow CSF leaks has been supported by numerous authors.[35,72] Low-flow leaks at the sella or defects <1 cm in diameter may be managed with an obliterative fat graft or fascia onlay graft. Larger extrasellar defects with a low-flow leak may be closed with an inlay graft, with an optional vascularized flap. Sellar defects with a high-flow intraoperative CSF leak may be repaired with placement of a fat graft within the dead space of the enlarged sella, followed by a rigid buttress such as Medpor to prevent graft extrusion, plus a vascularized flap. For nonsellar high-flow leaks, the bony defect should be circumferentially sealed with soft tissue, with or without a rigid buttress, followed by vascularized tissue. The gasket seal is an appealing option in this regard, although other multilayered grafting techniques may also be considered since the superiority of one technique over the other has not been studied. Tissue sealants may be optionally applied as a final layer to stabilize the reconstruction.

In an interesting variant, the technique described by Germani et al. utilizes a single 1 mm thickness graft of Alloderm for repair of anterior cranial fossa defects.[73] The graft is sized for circumferential inlay coverage of the bony edges, with >1 cm excess to permit infolding into the sinonasal compartment. The graft edges are held in place with multiple pieces of compressed gelatin sponge tucked into the periphery of the graft. A series of 30 cases closed with this technique had a postoperative leak rate of 3%, which was not significantly different from a comparison group of 25 cases closed by other techniques. Although the results of this series support its use, relying on a single layer for reconstruction may pose a concern.

OUTCOME STUDIES

Assessment of the outcomes following endoscopic skull base reconstruction has been largely limited to single institutional case series with a low evidence level. Several systematic reviews of the literature have been published that suggest efficacy across studies. A meta-analysis by Hegazy et al. in 2000 found that endoscopic repair of CSF leaks was successful in 90% of cases after a first attempt, and 57% of persistent leaks were closed after a second attempt (14 studies, n = 289).[74] They did not find any significant difference between materials or closure techniques.

In a systematic review of endoscopic pituitary surgery, Tabaee et al. analyzed 9 studies encompassing 821 patients, which reported a pooled CSF leak rate of 2%.[75] A systematic review by Rotenberg et al. of publications directly

comparing the endoscopic and microscopic approaches reported no difference in postoperative CSF leak rates in 6 of 7 included studies.[76] A more recent meta-analysis by DeKlotz et al. compared patients undergoing pituitary surgery via an endoscopic approach (n = 2,298) versus a sublabial approach (n = 2,150). They reported a lower rate of postoperative CSF leak in the endoscopic group (5% vs. 7%, p = 0.0059). Additional analysis indicated no statistical difference in operative time or the rate of postoperative meningitis, and a significantly shorter length of hospitalization after the endoscopic approach (3.3 vs. 5.9 days, p = 0.01).[77] A meta-analysis by Harvey et al. included studies of endoscopic reconstruction of large dural defects (38 studies, n = 609), excluding purely sellar defects. They found an overall postoperative CSF leak rate of 11.5%, including a 15.6% leak rate for free graft reconstruction and a 6.7% leak rate when a vascularized reconstruction was employed (p = 0.001).[78]

Recent reviews have compared the results of endoscopic skull base approaches with open transcranial approaches for various pathologies as reported in the literature between 1950 and 2010.[79,80] Giant pituitary adenomas were associated with a postoperative CSF leak rate of 7.1% following open transcranial approach (66 cases), 5.1% following transsphenoidal microscopic approach (304 cases), and 0% following endoscopic endonasal approach (106 cases). Clival chordomas were associated with a postoperative leak rate of 10.7% following open transcranial approach (639 cases) and 5.0% following endoscopic endonasal approach (127 cases; p = 0.08). Esthesioneuroblastoma had comparable postoperative leak rates following anterior craniofacial approach (6.0%; 318 cases) and endoscopic endonasal approach (7.4%; 102 cases), and significantly higher leak rates following cranionasal approach (18.2%; 33 cases). Craniopharyngioma resection was associated with higher postoperative leak rates following endoscopic endonasal resection (18.4%; 149 cases) than either transsphenoidal microscopic (9.0%; 354 cases; p = 0.02) or open transcranial approaches (2.6%; 2967 cases; p < 0.003). Olfactory groove meningiomas resection via the endoscopic endonasal route (19 cases) had a postoperative leak rate of 31.6% versus a rate of 6.0% via the open transcranial approach (474 cases; p < 0.001). Similar results were found following resection of tuberculum sellae or planum sphenoidale meningiomas (21.3% for endoscopic endonasal approach (93 cases) vs. 4.3% for open transcranial approach (840 cases; p < 0.001)). This analysis suggests that the success of endoscopic reconstruction is favorable following surgery for pituitary macroadenomas and clival chordomas, whereas reconstruction following excision of other skull base tumors is less consistently successful compared with traditional open approaches. In these latter cases, the choice of surgical approach should be weighed against other factors, such as the expected completeness of tumor resection, expected morbidity, and patient acceptance.

The introduction of the nasoseptal flap represented a significant advancement in reconstructive options. This flap was first described in a series of patients undergoing surgery for idiopathic CSF leaks, meningoencephaloceles and pituitary tumors. A multilayered reconstruction was used, entailing an inlay graft with or without an onlay graft, and bolstering of the flap with a Foley balloon catheter. They reported a postoperative leak in 2 of 44 patients, and noted few other complications.[42]

Kassam et al. reported on a series of 75 patients who underwent repair with the nasoseptal flap following endoscopic tumor resection. They described a postoperative leak rate of 10.7% among all cases, and 14.5% for cases that involved intra-arachnoidal dissection. They also noted a learning curve, wherein 75% of postoperative leaks in that series occurred in the first 25 cases.[81] Multivariate analysis indicated that reconstructive failure with the nasoseptal flap was more likely to occur in pediatric patients who had a high-flow intraoperative leak.[82]

McCoul et al. described the outcomes for a series of 210 consecutive cases of endoscopic skull base tumor resection, which included 96 nasoseptal flap reconstructions. The cumulative postoperative leak rate for the nasoseptal flap group (3.1%) did not differ significantly from the nonflap group (2.6%). Comparison was also made to a group of 205 consecutive cases performed by the same surgeons prior to the adoption of the vascularized nasoseptal flap. In that analysis, the postoperative leak rate in the older group (5.9%) was significantly higher than in either of the newer cohorts. They also reported that after adoption of the nasoseptal flap to the reconstructive protocol, the rate of postoperative leak improved for both high-volume leaks (4.9% vs. 9.0%; p < 0.001) and low-volume leaks (0.8% vs. 4.0%; p < 0.001). No cases of flap failure were encountered.[83] This suggests that selective application of vascularized tissue to defects stratified by leak volume can improve the likelihood of successful closure.

Eloy et al. described a series of 59 high-flow CSF leaks, including 32 pituitary adenomas, repaired with a nasoseptal flap without CSF diversion. Their technique involved an inlay graft of autologous or nonautologous material, followed by the flap and a layer of oxidized cellulose, with or without tissue sealant. No postoperative leaks were reported.[84] A subsequent study from the same authors compared 69 high-flow CSF leaks, including 37 trans-sellar approaches and 32 expanded endonasal approaches. There was no significant difference in postoperative leak between the two groups, with an overall leak rate of 1.4%.[85]

Nyquist et al. proposed the use of bilateral nasoseptal flaps, which they termed the "Janus flap," for coverage of defects for which a single flap would be insufficient. Their initial series of five patients demonstrated the feasibility of this technique following resection of giant pituitary adenoma, meningioma, and craniopharyngioma.[86] An updated report described the use of a Janus flap in 16 cases of varying pathology, all of which entailed a large intraoperative CSF leak. There were no postoperative leaks in that series and no significant donor-site complications, though all but one case utilized a lumbar drain concurrently.[83] Outcomes from large series of turbinate flaps or other vascularized flaps have yet to be published.

The effect of reconstruction technique on patient-reported quality of life (QOL) is an important consideration that has been the subject of limited study. Studies by McCoul et al. analyzed series of endoscopic skull base reconstructions in which outcomes were assessed using two separate, validated, disease-specific QOL instruments. They found that the use of autologous fat or fascia lata for reconstruction was associated with significantly better postoperative QOL compared to cases where autologous tissue was not utilized. This suggests that autologous grafting may promote favorable tissue healing at the reconstruction site, and fewer postoperative symptoms, despite requiring a second surgical site. They also found that the use of a gasket seal closure or a nasoseptal flap was not associated with a difference in postoperative QOL.[87,88] This contrasts with another study that showed worse QOL in cases where a nasoseptal flap was utilized.[89] This disparity may reflect variability in surgical technique or postoperative care, and indicates the need for further study.

SUMMARY

Successful management of CSF leaks, meningoencephaloceles, and anterior skull base defects requires judicious use of diagnostic studies and expertise in the various available reconstructive options. An individualized approach is indicated given the variety of etiologies, patient-related factors, and defect dimensions that may occur. The primary goals are to create a watertight separation between the intracranial and sinonasal cavities, promote rapid healing, and minimize patient morbidity. A detailed understanding of the nuanced differences in the pathophysiology of the defect is critical, especially in patients with increased ICP and following endoscopic skull base tumor resection. The past decade has witnessed the rapid adoption of vascularized flaps to complement free-tissue grafts as an important advance in the management of complex defects. Well-designed clinical studies continue to be needed to define optimal repair techniques and materials, use of adjuncts including lumbar drain and shunt procedures, and long-term outcomes.

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SECTION 11

Endoscopic Surgery of the Orbit

CHAPTER

62 Orbital Decompression

Eugenie Du, Robert Schwarcz, Bradley A Schiff

INTRODUCTION

Graves' disease is a syndrome composed of diffused thyroid enlargement, palpitations, and exophthalmos first described by Robert Graves in 1835. It is now known that Graves' disease results from autoimmune hyperstimulation of the thyroid-stimulating hormone (TSH) receptor in the thyroid gland. In addition to activation of the thyrotropin receptor, the autoimmune process also affects the eyes (and other organ systems), leading to Graves' ophthalmopathy.

EPIDEMIOLOGY

The annual incidence of Graves' is estimated at 3 men and 16 women per 100,000.[1] Onset occurs most often between the ages of 40 and 60 and presentation in childhood is unusual. Among patients with hyperthyroidism, approximately 60–80% will have Graves' disease.[2] The prevalence of Graves' disease is similar among Caucasians and Asians, but lower in African Americans. Estimating the prevalence of Graves' ophthalmopathy depends on the diagnostic criteria used to define ophthalmopathy. Burch and Wartofsky found a 10–25% incidence of ophthalmopathy in Graves' disease patients if nonspecific signs such as "lid lag" and "stare" were excluded. The incidence increases to 30–45% if these signs were included. Severe forms with optic nerve involvement and visual impairment were only found in 2–5% on patients with Graves' disease.[3]

PATHOPHYSIOLOGY

IgG antibodies against thyroglobulin, thyroid peroxidase, and possibly a sodium iodine cotransporter in the thyroid tissue stimulate thyroid hypersecretion and lead to hypertrophy and hyperplasia of the thyroid follicles.[4] This results in overactivity and enlargement of the thyroid. There are complex cross-interactions between the various antibodies that modify their respective stimulatory effects such that there is no direct correlation between serum concentration of the antibodies and the thyroid hormones. In some patients, the concentration of serum antibodies can be so low that they are undetectable.[4] Intrathyroidal autoimmunity also plays an important role in the pathogenesis of Graves' disease.

In the past, it was theorized that cross-reactivity of thyroid antibodies against extraocular eye muscle fibers resulting in a local autoimmune reaction was responsible for the spectrum of pathology seen with Graves' ophthalmopathy. More recently however attention has focused on retrobulbar fibroblasts as a key mediator of the disease. Autoantibodies to fibroblast antigens appear to share some similarity to regions within the TSH receptor. Once stimulated, the fibroblasts secrete a range of glycosaminoglycans, which are hydrophilic and thus cause pronounced interstitial edema.[5] Similarly, there are pretibial fibroblasts possessing similar antigenic qualities thought to be responsible for the pretibial myxedema.[6] In addition to edema, Graves' ophthalmopathy is characterized by an intense local lymphocytic reaction. CD4+ and CD8+ T cells release cytokines that induce further fibroblast activity leading to proliferation of collagen, glycosaminoglycans, and ultimately fibrosis. Eventually, the deposition of glycosaminoglycans and ensuing edema leads to enlargement of orbital fat and extraocular muscles. The resultant increase in retrobulbar pressure can compress the optic

nerve, leading to vision change and loss. The increased intraorbital volume can also result in severe proptosis, exposure keratitis, chemosis, and even globe subluxation.

PREDISPOSING FACTORS

There is no single causative agent or factor that leads to the development of Graves' disease. Genetic predisposition and the role of HLA antigen susceptibility have been studied extensively but no clear conclusions can be drawn. The rate of concordant Graves' disease in monozygotic twins is 20%.[7] Ethnicity appears to also play a role as European patients with Graves' disease develop ophthalmopathy six times more frequently than Asian patients with Graves'.[8] In Caucasians, HLA-DR3 and HLA-DQA1*0501 appear to have a positive association with Graves' disease, whereas HLA-DRB1*0701 appears to confer some protection against the disease.

Graves' disease is much more common in females, with a strong 3:1 female-to-male ratio. Both genders show a bimodal peak in the fifth and seventh decade of life with mean age of onset slightly higher in men.[1] Male patient have a higher incidence of ophthalmopathy that also tends to be more severe. In a study of 101 patients with Graves' ophthalmopathy patients, the female-to-male ratio was noted to be 9.3:1 in patients with mild ophthalmopathy, 3.2:1 in those with moderate ophthalmopathy, and 1.4:1 in those with severe ophthalmopathy.[9] Several lines of thought have been proposed to explain this gender bias. Some believe that it is a result of the modulatory effects that estrogen has on the autoimmune system. For example, the onset of Graves' disease can be preceded by stressful life events suggesting that neuroendocrine pathways are involved in triggering the onset of disease. Others argue that the gender imbalance is secondary to the confounding relationship between higher smoking rates and the male gender.

Studies have shown a correlation between tobacco exposure and Graves' disease. Smoking is associated with many immunologic disorders and is thought to be a result of nonspecific suppression of T-cell activation and impairment of humoral and cell-mediated immunity.[10] The association between smoking and Graves' is much higher than that found in any other forms of thyroid disease, even autoimmune forms.[11] Once in remission, patients who smoke also have a significantly higher risk of relapsing Graves' hyperthyroidism.[12,13] There is also a strong association between tobacco and the development of ophthalmopathy, with an odds ratio among smokers versus nonsmokers of 7.7:1.[10] Some have questioned if this is a true association or if it simply reflects the confounding effects of males having both a higher incidence of smoking and of developing ophthalmopathy. However, the finding that the association between smoking and ophthalmopathy is dose dependent with the risk being proportional to the number of cigarettes smoked suggests that smoking is an independent risk factor. Finally, the response rate to radioiodine and prednisone treatment for Graves' ophthalmopathy is more favorable in nonsmokers than in smokers (94% vs. 68% showed improvement, 6% vs. 23% showed progression, respectively).[14] Taken together, the multitude of studies evaluating the relationship between smoking and Graves' disease and ophthalmopathy shows that smoking is the single risk factor that most impacts both the development of Graves' ophthalmopathy and the course of the disease, treated or not.

CLINICAL FEATURES

Many of the clinical features of Graves' disease simply reflect the hyperthyroid hypermetabolic state and are common to any form of hyperthyroidism. The most common symptoms include fatigue, palpitations, heat intolerance, weight loss, irritability, and nervousness. Atrial fibrillation, less common in younger patients, can be seen in up to 20% of patients over the age of 50. On physical examination, approximately 90% of patients under the age of 50 will have a palpable diffuse goiter.[15]

The most common symptoms of Graves' ophthalmopathy include eyelid retraction and periorbital edema. A small degree (1–2 mm) of lid lag can be seen in patients with all forms of hyperthyroidism and therefore is not considered specific to Graves' ophthalmopathy. Other findings include exophthalmos/proptosis and diplopia. Rare but severe manifestations include optic neuropathy and vision loss. The clinical presentation of Graves' ophthalmopathy can occur before, after, or simultaneously with the manifestations of hyperthyroidism. In their review, Burch and Wartofsky found that 20% of patients initially presented with eye findings alone, 39% presented with eye and systemic hyperthyroidism findings concurrently, and 41% presented initially with systemic hyperthyroidism alone. Most patients that first present with just eye or hyperthyroid symptoms will manifest the other symptoms within 1–2 years.[3] Evidence also suggests that a large percentage of Graves' hyperthyroidism patients have subclinical ophthalmic involvement that is only apparent on orbital US or CT imaging.[1,16] Graves' patients who have

Graves' ophthalmopathy are more likely to also have Graves' dermopathy, or pretibial myxedema. Myxedema presents as shiny red to brown plaques or nonpitting edema, usually in the pretibial region. Approximately 12–15% of patients with ophthalmopathy will also have pretibial myxedema.[6] Conversely almost all patients with pretibial myxedema will have ophthalmopathy.

NATURAL COURSE OF DISEASE

The natural history of Graves' ophthalmopathy can be divided into an acute and a chronic phase. The acute phase, usually lasting 6–24 months, is characterized by inflammation and increased intraorbital pressures. The initial rapid progression is often followed by a prolonged plateau phase with slow regression of disease.[3] Perros et al. followed 59 patients longitudinally for a median of 12 months and found that a significant proportion of patients improved spontaneously with no medical or surgical therapy (22% substantially, 42.2% moderately). Twenty-two percent of patients showed no change and 14% worsened to the extent of requiring therapy.[17] Lid retraction, chemosis, and eyelid edema tend to improve most consistently over the course of 1–5 years. About 30–40% of patients have some improvement in ophthalmoplegia. Ptosis appears to be the most persistent symptom, with only 10% of patients experiencing improvement without intervention.[3] If patients with optic neuropathy are left untreated, a significant proportion will be left with very poor visual acuity. In a review of 32 patients with untreated Graves' optic neuropathy, Trobe found that 21% had a visual acuity of 20/100 or worse with 16% progressing to near blindness.[18]

The chronic phase can occur up to 3 years after the onset of the disease. In this stage, which some refer to as the "burnt-out" stage, there is permanent enlargement or fibrosis of the extraocular muscles, which is often accompanied by an increase in orbital fat. Surgery usually is considered rehabilitative in this phase and aimed to correct persistent exophthalmos, strabismus, lid retraction, or a combination thereof.[19]

It is not clear what the impact of the patient's thyroid status has on the natural course of the associated eye disease. There is no consistent correlation between the thyroid status and severity of ophthalmopathy or ocular improvement.[20,21] Restoration of the euthyroid state, either medically or surgically, does not appear to alter the course of the eye disease. In a randomized prospective study of patients treated with methimazole, 4% with preexisting ophthalmopathy experienced improvement. Three percent of the entire cohort developed or had progression of eye disease.[22] Similar results were shown in a cohort of patients undergoing near-total thyroidectomies with worsening of eye disease in 3.3% of patients.[23] Interestingly, there is a small but defined risk of ophthalmopathy progression in patients treated with radioactive iodine; a risk that is appears to be ameliorated if prednisone is given concomitantly with radioiodine therapy.[22,24]

OPHTHALMOPATHY CLASSIFICATION

A clinical classification system for Graves' ophthalmopathy was proposed by Werner in 1969 and modified in 1977.[25,26] The classification system, approved by the American Thyroid Association, is also known as the NOSPECS classification system (Table 62.1).

Table 62.1: Clinical classification for Graves' ophthalmopathy

Class	*Grade*	*Symptom and signs*
0	No signs or symptoms	
I	Only signs (e.g. upper lid retraction and stare)	
II	Soft tissue involvement	
	0	Absent
	A	Minimal
	B	Moderate
	C	Marked
III	Proptosis ≥3 mm above upper normal limit	
	0	Absent
	A	3–4 mm above upper normal limit
	B	5–7 mm above upper normal limit
	C	>8 mm above upper normal limit
IV	Extraocular muscle involvement	
	0	Absent
	A	Limit of motion at extremes of gaze
	B	Evident restriction of motion
	C	Fixation
V	Corneal involvement as a result of lagophthalmos	
	0	Absent
	A	Stippling of cornea
	B	Ulceration
	C	Clouding, necrosis, perforation
VI	Sight loss (optic nerve involvement	
	0	Absent
	A	Disk pallor/choking, visual field defect, vision 20/20-20/60
	B	Disk pallor/choking, visual field defect, vision 20/70-20/200
	C	Blindness, vision <20/200

In the mildest form of optic involvement (Class I), there are nonspecific signs of lid lag and stare. These symptoms are thought to be a result of sympathetic overdrive and can be seen in patients with all forms of hyperthyroidism. As the disease progresses and the lymphocytic inflammatory process begins to involve the extraocular muscles and orbital fat, fibroblastic proliferation and glycosaminoglycan deposition lead to interstitial edema, increased intraocular pressure. The initial manifestation of increased intraocular pressure includes conjunctival chemosis, periorbital edema, photophobia, and increased lacrimation (Class II). The total orbital volume is fixed by the bony confines of the four orbital walls. As the expansion of extraocular muscle and orbital fat volume reaches and subsequently surpasses this volume, the increased pressure on the globe displaces it forward, leading to proptosis (Class III). As fibroblastic hyperactivity continues, deposition of glycosaminoglycans and collagen begin to limit the elasticity of the extraocular muscles leading to restriction of gaze and ophthalmoplegia (Class IV). With progressive proptosis, overexposure leads to corneal damage (Class V). Within the globe, progressive intraocular pressure beings to compress the optic nerve leading to gradual loss of visual acuity or visual fields (Class VI). Usually, this change is gradual and painless, but in some it can abruptly over days to weeks. The most sensitive indicators of optic nerve dysfunction are visual-evoked potentials and color vision[27] and the most common visual field deficits are inferior scotomata and cecocentral scotomata.[28] Evaluation of CT studies suggests that crowding at the orbital apex is most responsible of the resultant neuropathy.[27] Though the classification implies a sequence throughout the classes and grades, the disease itself does not necessarily progress systematically. Patients may not exhibit one more classes of symptoms. The NOSPECS classification has also been criticized for not taking into account whether the disease is stable or progressing, which is important for decisions regarding treatment.[29] As such, the classification system is largely considered a purely descriptive tool. Despite its limitations, the NOSPECS system is often used as a marker of disease severity, especially in assessing treatment efficacy for research purposes.

In 1992, an 18-member ad hoc committee representing the European, Latin-American, Japanese/Asia-Oceanic and American thyroid associations reached a consensus classification system.[30] They set forth seven categories of disease to take into consideration: maximal lid fissure distance, corneal pathology, extraocular muscle function, proptosis, optic nerve involvement, activity score, and patient self-assessment. The clinical utility of the newer classification system has not been fully evaluated.

MANAGEMENT

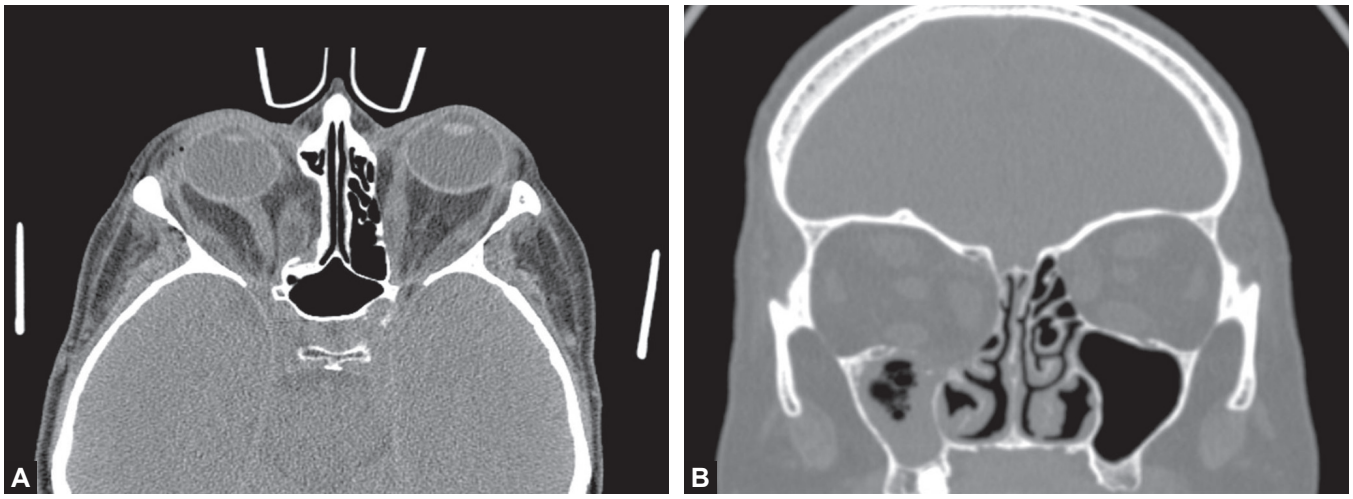
Evaluation

The diagnosis of Graves' hyperthyroidism hinges on both the physical examination and biochemical findings associated with the disease. Hyperthyroidism is suspected in patients reporting nervousness, fatigue, palpitations/rapid heartbeat, heat intolerance, and unintentional weight loss. On physical examination, younger patients (younger than 50 years old) often have a firm, diffuse goiter palpable on exam.[15]

Upon diagnosis of thyroid disease, a baseline ophthalmologic examination is warranted. Initial examination should include visual acuity, intraocular pressure, and pupillary examination including evaluation of afferent pupillary defect. Evaluation of optic nerve, visual fields, corneal and anterior segment examination includes accurate measurements with Hertel exophthalmometer. Signs of active disease should be noted including, but not limited to, caruncular hypertrophy, injection over rectus muscle insertion points, chemosis, and eyelid festooning. Of note there should also observation for lid lag, lagophthalmos with possibility for exposure keratitis, and eyelid retraction that would include margin reflex distance (MRD1 and 2).

A full endocrinology workup is central to the diagnosis and management of Graves' disease. Measurement of serum thyrotropin (TSH) is useful to screen for the presence of hyperthyroidism. Measurement of free thyroxine (T_4) then confirms the diagnosis. In early Graves' hyperthyroidism, patients may only show a mild increase in triiodothyronine (T_3) levels, as such, TSH, T_3 and T_4 are routinely measured. Serologic evaluation of thyroid autoimmunity is often performed. High serum concentrations of thyroid peroxidase antibody are present in approximately 80% of patients with Graves' disease[4] other autoimmune studies include microsomal antibody and TRAb assays. Occasionally, thyroid radionuclide studies may be helpful in distinguishing between Graves' hyperthyroidism and a painless, autoimmune thyroiditis.

CT is often used in Graves' ophthalmopathy both for diagnostic and surgical planning purposes. Typical CT finding shows enlargement of the extraocular muscle bodies with apical crowding (Figs. 62.1A and B). Ocular involvement is almost always asymmetric but some degree of



Figs. 62.1A and B: Axial (A) and coronal (B) CT scan through the orbits of a patient with Graves' ophthalmopathy showing medial and lateral rectus muscle enlargement. Left side is preoperative and right side is post medial and inferior endoscopic orbital decompression. In each case, the orbital fat can be seen filling the ethmoid sinus cavity. In (B), the removal of the inferior orbital wall laterally to the infraorbital nerve can be seen.

bilateral change is seen in 90% of patients on CT scans.[31,32] CT imaging can also be used to estimate orbital and extraocular muscle volumes.[16] Ultrasonography can also be used to evaluate extraocular muscle size. While not helpful for surgical purposes, serial orbital US has been proposed as an inexpensive and safe mechanism for evaluating treatment responses.[33] MRI also provides good visualization of the orbit soft tissue and allows for estimations of the orbit and extraocular muscle volumes. Recent studies suggest that elevated T2 relaxation times on MRI likely represent acute inflammatory changes and can provide a quantitative measure of disease activity.[34] Nuclear studies, such as SPECT using 99mTc-DTPA (diethylenetriaminepentaacetic acid) and gallium-67 citrate, have also been looked at as possible modalities for evaluating disease activity to aid in therapeutic planning.[35,36]

Medical Therapy

Mild ophthalmopathy is usually a self-limited disease requiring only local measures to provide symptom relief. Artificial tears, lubricants, and taping the eyelids at night can decrease irritation resulting from mild corneal exposure and dry eyes. Other measures include sunglasses for photophobia and prisms for mild strabismus. Recently, selenium has been shown to provide significant improvement in terms of Clinical Activity Score as well as quality of life in patients with mild ophthalmopathy.[37] In a randomized, double-blind, placebo control trial involving 159 patients, selenium therapy was shown to decrease ophthalmic symptoms in 61% of treated patients (vs. 36% improvement in the placebo group). Treatment was only given for 6 months, but the improvement in symptoms persisted at least an additional 6 months after therapy was discontinued. Selenium was also shown to decrease progression of disease as well as significantly improved quality of life. The researchers of the trial hypothesized the selenium works by improving the antioxidant–oxidant balance in hyperthyroid and Graves' patients.[37]

The most commonly used first-line treatment for Graves' optic neuropathy is high-dose corticosteroid therapy. Prednisone (80–100 mg/day) for 2 months followed by a slow taper is standard with a success rate of 48% after 2 months. There was rapid onset of improvement, usually within 72 hours with the maximal benefit seen after 6–8 weeks.[38] However, there are numerous and serious side effects from prolonged steroid therapy and symptoms can recur with tapering of treatment. Steroid treatment can also decrease proptosis and ophthalmoplegia but the effects often recur upon taper.

Immunosuppression, e.g. cyclosporine, has also been used. As the interaction between orbital fibroblasts and the autoimmune process that leads to the ocular changes seen in Graves' disease becomes better elucidated, more and more potential therapeutic targets are identified.[39]

Radiation Therapy

Radiation therapy has been used to treat orbital ophthalmopathy for well over 60 years. Treatment is done on

an outpatient basis; typically a 20 Gy dose is giving in divided 2 Gy fractions in 10 visits over a 2–2.5 week period. The rationale behind radiation is the thought that radiation decreases inflammation via inhibiting lymphocyte proliferation. In addition, it is thought to downregulate orbital macrophage activation as well as production of hydrophilic molecules such as glycosaminoglycans.[40] Initial reviews of radiation therapy reported excellent response rates, up to 90% in some studies.[41] However, the early evidence was largely based on retrospective experiences and uncontrolled studies. Given the lack of a control, it was difficult to tease out whether the improvement was a direct result of radiation therapy or simply a reflection of natural clinical regression of disease. There have been three published randomized control trials comparing radiation therapy to sham radiation. In 2000, Mourits et al. published a study involving 60 patients with moderate-to-severe ophthalmopathy. The patients were randomized to receive either standard radiation therapy (20 Gy divided into 10 2 Gy doses) or sham radiation (10 0 Gy doses). At 24 weeks, 60% of irradiated patients compared to 31% of sham-irradiated patients showed improvement.[42] A year later, a study published by Gorman et al. from the Mayo Clinic looked at 42 patients with mild-to-moderate ophthalmopathy. One orbit was randomly assigned to receive radiation and the other to serve as a control with sham irradiation. After 6 months, the treatments were reversed. At 6 months, there was no difference between the two groups in terms of outcomes; however at 12 months, there was an improvement in extraocular muscle volume and a slight improvement in exophthalmos in globes treated with radiation.[43] The third trial, by Prummel et al. looked at 88 patients with mild ophthalmopathy randomized to either radiation or sham. Fifty-two percent of radiated patients, as compared to 27% of sham-irradiated patients, had significant improvement in their designated major and minor criteria.[44] The study also used a disease-specific quality of life assessment, which did not show a significant difference between the two groups. A Cochrane Review published in 2012 combined the trials by Mouritis and Prummel to produce a composite risk ratio of success of 1.92 (95% CI 1.27–2.91).[45] The Cochrane Review chose to exclude the Gorman study. The authors felt that the radiotherapy could have had an effect on the control eye either by direct inadvertent radiation via radiation to the contralateral eye or by radiation effect on lymphocytes that could circulate from the contralateral eye. Either way, the authors did not feel that the orbit receiving sham radiation served as adequately independent controls. The authors concluded that though small their systematic review supported the use of radiotherapy for the treatment of moderate Graves' orbital disease.

The timing of radiotherapy appears to have an impact on its efficacy. In the randomized control trial by Prummel, the difference between radiated and sham-radiated patients widened when patients with early disease were analyzed separately. Fifty-eight percent of patients with a duration of disease < 18 months treated with radiation showed improvement versus 20% of sham irradiated (52% vs. 27%, respectively, when all patients were analyzed together).[44] Interestingly, the Mayo Clinic trial included patients with long duration of ophthalmopathy (up to 16 years). Some reviewers have speculated that inclusion of radiotherapy in late stages of the disease may have contributed to the lack of any significant difference between treated and control orbits in this study. All three randomized control trials noted that ocular motility and extraocular muscle volume were primarily the criterion that improved with radiotherapy. Exophthalmos appears to be fairly unresponsive to radiation. Furthermore, it does not appear that radiation therapy prevents the progression of disease. Radiotherapy has many potential long-term adverse effects. In several large retrospective series, the most common long-term complications appear to be the development of cataracts (~10%) and mild retinopathy.[46,47] No increases in mortality or cancer rates have been reported. So far, there has only been a single case report of the development of a malignancy (basal cell carcinoma) within the radiation field, and therefore possibly attributable to the irradiation.[48] The average follow-up for the large studies looking at long-term complications following radiation therapy is 11 years. One caveat is that studies assessing long-term complications are often limited by potentially long latency periods between exposure and subsequent development of said complication.

Surgical Indications

In the active inflammatory phase of thyroid ophthalmopathy, medical management with corticosteroids and immunosuppressants as well as radiation therapy can be used to offer symptomatic treatment. However, should these measures prove inadequate for control, then surgical interventions ought to be considered to decrease symptoms, especially in the setting of optic nerve neuropathy. In the later, burnt-out phase, orbital decompression, as well as a range of eyelid and strabismus procedures, can be considered for cosmesis and rehabilitation of the patient.

In a review of 56 articles over the past two decades discussing surgical techniques for decompression of thyroid ophthalmopathy, Leong et al. found that the most common indication for surgery was cosmesis (42.4%), followed by compressive optic neuropathy (40.6%), exposure keratitis (7.9%), and as an adjunct to an additional ophthalmic procedure (3%).[49] In a retrospective review of 125 patients, Baldeschi et al. found that there was no significant difference in surgical outcomes in terms of reduction in exophthalmos, symmetry, persistent postoperative swelling, and improvement in lid retraction between patients who underwent surgery early (<4 years after onset of disease) and those who underwent surgery late (>4 years).[50] They did, however, find that there was a statistically significant increase in the development of postoperative diplopia (29% in the early group versus 13% in the late group, $p = 0.033$.) It is important to note, however, that all patients in this series underwent bilateral, coronal approaches for aesthetic indications and were without preoperative diplopia. The indication for patients undergoing surgical intervention in the acute inflammatory phase would more often be optic nerve compression unresponsive to immunosuppression or radiation therapy.

Surgical Approaches

There are a myriad of techniques utilized by otolaryngologists, ophthalmologists, and neurosurgeons to decompress the orbit via alteration of one, or multiple orbital walls. Though there is a trend in the literature to move away from external approaches toward more endoscopic and minimally invasive techniques, the open approaches still feature prominently in the reserve of surgical options.[49] The wide variety of approaches in part speaks to the lack of a single superior method with consistently good outcomes and low complication rates and in part speaks to the differing skill sets among surgeons performing Graves' decompressions.

The severity of symptoms largely depends on an individual's anatomy and the compliance of the orbital architecture. The orbit is composed of four fixed bony walls with an average volume of 26 mL.[51] Within the orbital cavity, approximately 30% of the volume is taken up by the globe; the remainder is filled by retrobulbar and peribulbar soft tissue. With limited capacity for expansion, small changes in the volume of extraocular muscle or orbital fat can produce significant proptosis or compression on the optic nerve. An increase of 4 mL in orbital volume can result in 6 mm of proptosis.[51] Because of variation in orbital compliance, the degree of proptosis does not directly correlate with the severity of optic nerve compression,[28] thus close observation of optic nerve function is of importance. Maximal decompression is not the ultimate aim of surgery; rather the creation of sufficient space to allow for expansion of orbital contents and relief of optic neuropathy or keratosis must be balanced with the risk of postoperative diplopia. With improved understanding of orbital anatomy, perhaps there will be a trend toward a more individually tailored surgical approach.

Lateral Wall

Lateral wall approaches generally offer moderate reduction in proptosis (2–3 mm) with minimal diplopia. The morbidity from these approaches generally comes from the cosmetic changes associated with the incision. Later wall decompression was first described by Dollinger in 1911. Using Kronlein's approach, or a lateral orbitotomy approach, the lateral orbital wall was removed allowing for decompression into the temporal fossa. There are a number of different ways the lateral wall can be addressed in the treatment of patients with Graves' disease.

Lateral Canthotomy

A transconjunctival approach to the orbit can be used to access the orbital floor and the lateral and medial walls if necessary. A standard postseptal transconjunctival incision is made with dissection in the subperiosteal plane. After outfracturing the orbital floor a substantial decompression could be achieved with care to not injure the infraorbital nerve complex and the inferior oblique muscle as it originates from the maxillary bone. Removing a significant amount of orbital floor could result in permanent dystopia. The medial wall of the orbit can also be accessed through this incision with retraction of the globe and periorbita, as can the lateral wall. The transconjunctival incision can be closed with a few interrupted fast gut sutures or not closed and left to heal by secondary intention.

A transpalpebral approach is most commonly used to access the deep lateral wall of the orbit. A lateral upper eyelid crease incision is made and, using a Desmarres retractor, the skin and orbicularis oris are retracted to the level of the superolateral orbital rim. An incision is made through the periosteum and a subperiosteal dissection is carried down to the level of the superior orbital fissure past the greater wing of the sphenoid, and inferiorly to the inferolateral orbit. The lateral orbital rim could be

removed and replaced at the end of the case or a lacrimal keyhole could be fashioned, but would provide improved visualization for the deep lateral orbit. A high-speed neurosurgical drill is used to decompress the bone in this location. The decompression should include the greater and lesser wings of the sphenoid. Once the outer table cortical bone is removed the diploic bone is carefully burred down to the level of the inner cortical table. Similar to the medial wall, a periosteotomy is performed allowing the periorbital contents to occupy the newly created space. At this point extra and intraconal orbital fat could be removed from this location. After hemostasis is achieved, the upper eyelid crease incision is closed in a running type fashion.

The transcaruncular approach can be used to access the medial wall and floor of the orbit. The caruncle is incised and approximately 5 mm superior and inferior to it in a semilunar fashion an incision is made medial to the plica. After the lacrimal crest is palpated, an incision is made in the periosteum with tenotomy scissors at the level of the posterior lacrimal crest. A subperiosteal dissection is carried down to the posterior orbit. A strong understanding of the medial orbital anatomy is crucial. Attention must be given to the anterior and posterior ethmoidal arteries as well as depth in the orbit in relation to the optic canal. Utilizing a Kerrison rongeur the lamina may be decompressed. Via this approach the anterior ethmoidal air cells and as well as the maxillary bone and the palatine bone can be accessed but care must be taken not to disrupt the anterior orbital strut to prevent dystopia and increased risk of diplopia.[52] After adequate bone decompression has been performed, a periosteotomy is performed to allow the medial orbital contents to occupy the newly created orbital space. At this point medially accessed intra- and extraconal fat can be removed for a further fat decompression. After hemostasis is achieved, the caruncle is reapproximated and sutured with a 6-0 fast absorbing gut suture in an interrupted fashion.

Medial/Inferior Wall

Medial and inferior endoscopic approaches generally offer a larger reduction in proptosis (4–5 mm) and avoid the scarring associated with purely lateral approaches but have an increased incidence of diplopia.

In 1929, Hirsch published a single report of a patient who was operated on by decompressing the orbit into the maxillary sinus via a canine fossa approach. A few years later, in 1936, Sewall published a description of decompression into the ethmoid sinus via an external approach. In 1957, Walsh and Ogura described the transantral approach for decompression via the medial and inferior orbital wall, which essentially combined two prior decompression techniques reported.[53] The 8 initial cases they reported showed reductions of 4–7 mm (average 5.7). This compared favorably with the Naffzinger transcranial approach, which was, at that time, the most popular procedure.

The advent of endoscopic instruments and techniques for transnasal endoscopic sinus surgery introduced new approaches to the medial wall and orbital floor and was quickly adapted for orbital decompression replacing the transantral approach. The technique, first described by Kennedy et al. in 1990, produced equivalent results with decreased morbidity when compared to the traditional transantral approach.[54] With the patient supine on the operating table, under general anesthesia, an endoscopic wide maxillary antrostomy is performed in the standard fashion. The antrostomy is often widened anteriorly to the posterior border of the nasolacrimal dunce, inferiorly to the root of the inferior turbinate and posteriorly to the posterior limit of the sinus. This helps prevent postoperative maxillary sinusitis secondary to obstruction from the prolapsing fat. A total ethmoidectomy is then performed. Care is taken to remove every air cell superiorly to the skull base, and laterally to the lamina papyracea that should be completely skeletonized. Once the lamina is widely exposed it should be removed. This can be done using either a curette or a blunt edged freer. In rare cases, with extremely thick bone, a drill may be needed. Care must be taken when removing the lamina to ensure that the periorbita is not violated as the prolapse of fat through the periorbita makes the subsequent dissection more difficult. Once the lamina is completely removed (superiorly to the skull base, posteriorly to the apex and anteriorly to the lacrimal duct) the maxillary buttress must be removed. Sometimes this can be performed with downward pressure using a curette, but in case with thick bone a Kerrison or a drill might be needed. The medial orbital floor is then gently removed close to the infraorbital nerve. The bony extent removed is illustrated in Figure 62.2. This exposes the medial and inferior aspects of the periorbita. Once the periorbita is fully exposed, it should be removed. This can be done by making the superior and inferior incisions with a sickle knife. A beaver blade may also be used for the posterior incision. Great care must be taken when incising the periorbita so as to not damage the deeper structures of the orbit. The authors have found it easiest to first make the superior and inferior cuts through the lamina in a

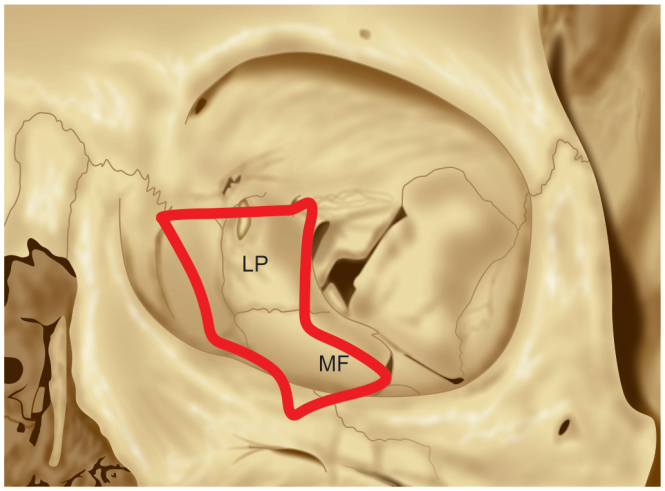


Fig. 62.2: The red outline demonstrates the margins of the bony contents removed during a medial and inferior wall decompression. The lamina paprycia (LP) is completely removed and the medial orbital floor (MF) removed laterally to the infraorbital nerve.

v-shape and then to peel the periorbita free from posterior to anterior. Once the periorbita is removed, the globe can be massaged and the periorbital fat simultaneously teased free using a ball probe or similar instrument.

Superior Wall

The orbital roof can be approached via a coronal incision made behind the hairline. Given the need for a craniotomy, decompression of the orbital contents superiorly into the anterior cranial fossa exposes the patients to significant complications, including meningitis, cerebrospinal fluid leak and pulsatile proptosis. As such, this approach is rarely utilized in clinical practice currently.

Combined Approaches

Khan et al. described a combined transconjunctival-endoscopic approach to more precisely address the orbital apex. The authors felt that a purely external approach was limited in its ability to access and address the apex while a purely endoscopic decompression has limited access to the anterior and lateral aspects of the orbital floor.[55] A small medial external skin incision is made to aid the retraction of the orbital contents so as to allow for a more complete dissection of the medial wall beyond the posterior ethmoidal neurovascular bundle up to the optic canal. The globe is released and pupillary checks are performed every 2–3 minutes to prevent central retinal artery occlusion.[56] A similar combined approach with endoscopic and subciliary decompression has also been described.[57]

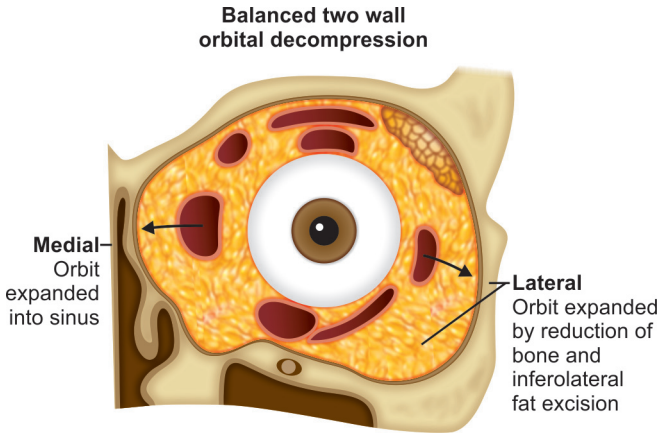


Fig. 62.3: Balanced decompression. The medial and lateral orbital walls are removed but the orbital floor is left intact.

The endoscopic approach has also been combined with a concurrent lateral decompression performed via an external incision.[58] Metson et al. have also reported performing the combined endoscopic and lateral decompression under local anesthetic techniques as an added safety measure to guard against intraoperative optic nerve damage.[59] The lateral approach can also be combined with the traditional transantral approach.

"Balanced" Decompression

Many surgeons have sought modifications to decrease the rate of new onset postoperative diplopia. One surgical variant is the preservation of an orbital strut at the maxillary–ethmoid junction to provide a medial ledge to reduce inferomedial displacement of the orbital contents.[52] While this may decrease diplopia, it also decreases the amount of decompression achieved. Other modifications are aimed at altering the manipulation of the periorbita via a single periorbital sling or leaving an anterior periorbital band.[60,61]

Several authors in recent literature have advocated a "balanced" approach to decompression, removing only the medial and lateral walls of the orbit and leaving the orbital floor intact (Fig. 62.3). Proponents of the balanced argue that the "unbalanced" 2-wall approach decompresses the orbital contents inferomedially and can cause a muscular shift that results in diplopia. Theoretically, this approach is thought to give inferior support to the orbital soft tissue and prevent unequal displacement in any direction. The medial wall can be approached endoscopically or via a transcaruncular approach; similarly, numerous external and minimally invasive approaches can be used to access

the lateral wall. Several case series have shown a lower rate of new postoperative diplopia with similar degrees of decompression when compared to three-walled approaches.[62-64]

Orbital Fat Decompression

Orbital fat decompression or removal can be used either in isolation, or in conjunction with other bony decompression procedures. It was first described by Trokel in 1993.[65] This procedure involves opening the periosteum using an extended transconjunctival approach and then, under direct visualization, using the bipolar cautery to dissolve the fat between and around the extraocular muscles. Some studies suggest a 2–3 mm decrease in proptosis can be expected.[65-66] The largest study in the literature, looking at over 3000 cases, reports almost 6 mm reduction in proptosis using this technique. The authors also report a significant reduction in diplopia and an improvement in visual acuity. While this procedure is performed by fewer surgeons that most of the other approaches discussed above, the results reported by Oliveri et al. are impressive and deserve further study.

SURGICAL OUTCOMES

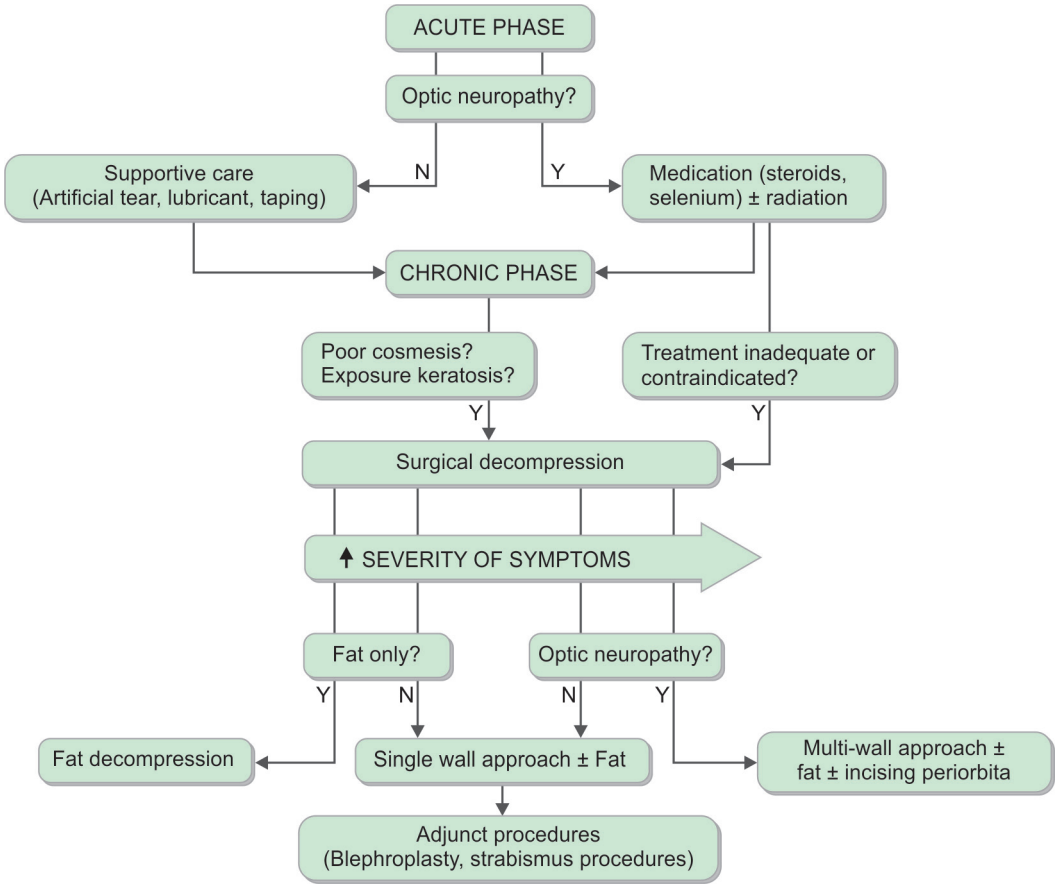
In general, the amount of orbital volume expansion, and thus proptosis reduction, correlates with the number and extent of walls removed. One can expect roughly 4–5 mm reduction in proptosis from the inferior and medial 2 wall decompression with an additional 3–4 mm of reduction from removal of the lateral wall. Removal of orbital fat can result in anywhere from 3–8 mm of reduction. The decision to perform a 1, 2, or 3 wall decompression is largely based on individual surgical experience and preference.

The measure of surgical success depends on the indication for the operation. For those undergoing decompression for optic neuropathy, the standard transantral two-walled approach has a high rate of success. The experience of the University of Washington with 36 orbits showed an improvement in visual acuity in 92% of eyes. Patients with very poor visual function (hand motion or light perception only) were the least likely to regain useful vision.[28] Color vision and visual fields also improved substantially (86% and 91%, respectively.) A large series review of 428 patients undergoing transantral orbital decompression showed similarly high success rates for improvement in visual acuity (89%) and visual field deficits (91%).[67] However, while not as extensively studied for optic decompression endoscopic or balanced approaches may offer the same success rate while limiting the morbidity of the transantral approach.

Using the standard Walsh and Ogura transantral approach, Calcaterra and Thompson reported an average recession of 4–5 mm with a range between 2–9 mm.[68] They noted that in patients who had long-standing disease or prior radiation the periorbital fat was gelatinous, which limited its ability to herniate through the periorbital incisions. Thirty percent of their patients had permanent postoperative diplopia and eventually underwent strabismus surgery. Numerous other case series report comparable average reductions in using the transantral approach.[69] The subciliary transorbital approach to the medial and orbital floor approach averaged similar reductions in proptosis with an average of 5 mm (range 0–10.5 mm).[70] The transconjunctival approach to medial wall and floor results in a smaller degree of decompression (average 3.6 mm, range 2–5 mm).[69] The restriction in the degree of decompression is thought to be secondary to limited exposure to the medial orbit and access to the orbital apex. Khan et al. suggest that this can be addressed using a combined endoscopic–transconjunctival approach to maximize access to the apex.[55] A subsequent case series of 72 decompressions on 41 patients using the combined endoscopic–transconjunctival decompression showed good visual acuity improvement (89.3%) and an average reduction in proptosis by 3.65 mm.[71] With the transnasal approach alone, Kennedy reported a postdecompression improvement of 4.7 mm on average. With the addition of a lateral orbitotomy approach, there was an additional 1 mm gained, resulting in an average improvement of 5.7 mm.[54,58] Case series with balanced medial and lateral wall decompression report average reductions between 4.1–5.9 mm[63-64]; even greater reduction can be achieved when fat excision is also performed (6.5 mm average).[72] A three-walled approach appears to most consistently achieve maximal decompression. However, modifications such as the addition of fat removal to "balanced" decompression can achieve comparable results.

Ophthalmoplegia and preoperative diplopia are less responsive to surgical decompression. In the University of Washington experience, only one-third of patients with preoperative impairment of extraocular motility showed any improvement; 9% actually reported worsening motility.[28] This is not surprising given that surgical decompression does not alter the pathologic deposition of glycosaminoglycans and collagen that stiffen and impair extraocular motility.

Flowchart 62.1: Algorithm for determining surgical approaches to orbital decompression. Surgery is indicated in the acute phase when medical management is inadequate or contraindicated or in the chronic phase for cosmesis or exposure keratosis. The extent of decompression needed corresponds to the severity of symptoms with consideration of the risk of postoperative complications. Adjunct procedures can be used following decompression to further enhance functional and cosmetic restoration. Adapted from Kacker et al. (2003).



In a large retrospective review of 428 patients undergoing transantral orbital decompression at the Mayo Clinic, Fatourechi et al. found that young age, male sex and long duration of eye symptoms were predictors of initial severity.[73] The only predictors of postoperative improvement in proptosis were severity of initial proptosis and time between operation and postoperative examination. Reduction in proptosis positively correlated with improvement in visual acuity, but these patients also had an increased rate of persistent postoperative proptosis. The only predictor of patient satisfaction with postoperative appearance was operations performed for cosmetic purposes.

SURGICAL ALGORITHM

The selection of surgical technique is currently largely based on surgeon comfort or institutional preferences rather than patient specific characteristics. In recent literature, there have been numerous proponents of a more a rationale approach for optimal management. Using their experience of both bony and fat decompression performed in 85 orbits, researchers at New York Presbyterian Hospital suggested a treatment algorithm for surgical decision making.[64] Looking at degree of fat hypertrophy, extraocular muscle hypertrophy, degree of proptosis and presence of optic neuropathy, the algorithm then recommends either a fat decompression, lateral versus medial approach with fat decompression or a combined lateral and medial decompression with possible opening of the periorbita (Flowchart 62.1). As previously stated, the measure of surgical success is dependent on the indication for surgery. Similarly, the risk of postoperative complications much be balanced with the urgency or extent of decompression needed. In cases of severe or rapidly worsening optic neuropathy, earlier and more aggressive surgical intervention is needed. In these cases, a degree of new-onset diplopia is acceptable, and perhaps even expected. When

the indication is purely cosmesis, however, then a more cautious, limited approach would be appropriate.

ADJUNCT SURGICAL PROCEDURES

In addition to orbital decompression, numerous surgical procedures have been described to aid in functional and cosmetic restoration in Graves' ophthalmopathy. Upper and lower eyelid retraction causing lid lag and ocular exposure can result in increased sympathetic stimulation of Müller's muscle and fibrosis of the levator and retractor muscles. Lysis of the fibrotic adhesions and insertion of a graft to act as a spacer can be used to address clinically significant retractions. Blepharoplasty can be used remove fat that has herniated in the upper and lower eyelids but should only be undertaken after the presence of eyelid retraction has been ruled out and the patient has reached a euthyroid state. Strabismus surgery can be offered to patients with clinically significant and persistent diplopia. It can be used to address both diplopia resulting directly from the thyroid eye disease and that resulted from orbital decompression. In patients with significant exophthalmos, orbital decompression should occur prior to any strabismus procedures. It is very important to be aware of the fact that strabismus surgery on Graves' ophthalmopathy can worsen proptosis and exposure keratosis, with an average postoperative increase of 0.9 mm in patients.[74] In approximately one-fourth of patient, the increase can be >2 mm. This represents a significant change, especially when considering the fact that most orbital decompression techniques only average a 3–6 mm decrease in exophthalmos.

COMPLICATIONS

The most discussed complication of orbital decompression is postoperative, new-onset diplopia. New-onset strabismus after decompression occurs in as many as 30–60% of patients following orbital decompression.[67,75] The reported range is quite wide as some case series report postoperative diplopia rates as little as 7%.[69] Diplopia exists in a large percentage of Graves' patients preoperatively; in some series as many as 67–85% of patients will report some degree before surgery.[28,67,69] Surgical decompression is unlikely to improve preoperative diplopia, although some patients report a difference in their existing diplopia postoperatively (e.g. objects now displaced to a different location).[69] The rate of diplopia associated with medial and inferior decompression approaches 66% in some series and is higher than the rate associated with other approaches. "Balanced" decompression was mainly developed to decrease the risk of postoperative diplopia; most case series report a new-onset rate of 0–15%.[63,64,72]

In analyzing 125 patients who underwent three-walled orbital decompression for cosmesis, Baldeschi et al. found a higher frequency of new-onset diplopia in patients who underwent early surgery as compared to those who underwent surgery late.[50] In looking at preoperative characteristics of the patients, they found that the degree of extraocular muscle enlargement was significantly higher in patients who underwent surgery early. Notably, these patients did not differ in their preoperative Hertel measurements, nor did they differ in the degree of postoperative reduction in exophthalmos. From this, the authors attributed the increased frequency of postdecompression diplopia in the early group to a larger contribution of extraocular muscle herniation into the newly created spaces created by decompression. In comparison, orbits that are operated on after many years of Graves' disease are more fibrotic, with decreased orbital distensibility and plasticity and therefore are less apt to prolapse after decompression.

Nearly all patients following the transantral approach report some degree of upper lip and cheek numbness in the immediate postoperative period (95%).[68] In a substantial number of patients, infraorbital nerve injury persists (40% in Calcaterra's study reported some numbness lasting > 2 years). Other reported complications from surgical decompression include epiphora, excessive eyelid skin, facial pain, sinusitis, cerebrospinal fluid leak, and epistaxis.[67,68,71]

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CHAPTER

Endoscopic Dacryocystorhinostomy

63

Nipun Chhabra, Giant Lin, Ralph Metson

INTRODUCTION

The endonasal approach for the treatment of lacrimal obstruction was first described by Caldwell[1] in 1893. Despite initial reports regarding the success of this procedure,[2,3] it fell out of favor because of difficulties with visualization and access in the narrow confines of the superior nasal cavity. Over the next century, external dacryocystorhinostomy (DCR)[4] became the treatment of choice for patients with epiphora and dacryocystitis. The obstructed lacrimal sac was identified and drained into the nasal cavity through a skin incision in the medial canthal region, providing satisfactory visualization with minimal risks.

The introduction of endoscopic instrumentation for sinonasal surgery prompted renewed interest in intranasal DCR in the 1990s. Small-diameter endoscopes provided excellent visualization of nasal anatomy, enabling the modern surgeon to open the obstructed lacrimal sac in a safe and effective manner through an entirely endonasal approach. In addition to avoiding the need for a facial incision, endoscopic DCR allowed the surgeon to identify and correct common intranasal causes of external DCR failure, including adhesions, septal deviation, and ethmoid sinusitis.[5,6] These advantages have led to widespread acceptance of endoscopic DCR as an excellent technique for the treatment of patients with nasolacrimal obstruction.

PREOPERATIVE EVALUATION

Indications

The most common presenting symptom of nasolacrimal duct obstruction is epiphora, or excessive tearing. Such tearing may interfere with vision and can have a significant negative impact on quality of life. Persistent blockage of the lacrimal sac can also lead to infection, which manifests as acute or chronic dacryocystitis. Purulent drainage may emanate from the canaliculi and cause inflammation of the skin near the medial canthus. In severe cases, incision and drainage of an abscess are necessary. Over time, inflammation, swelling, and recurrent infection lead to fibrosis, scarring, and subsequent stenosis of the lacrimal system with either partial or complete blockage.

Endoscopic DCR is most effective when the level of obstruction is located at the lacrimal sac–duct junction, leading to a dilated lacrimal sac. More proximally based pathology is amenable to an endoscopic approach, but may prove more technically difficult. Certain systemic conditions or inflammatory disorders, such as granulomatosis with polyangiitis (previously Wegener's granulomatosis) or sarcoidosis, may contribute to nasolacrimal duct obstruction. Infiltrative disorders such as neoplasms may cause epiphora and require DCR as part of the treatment plan after definitive management of the primary disease. Congenital nasolacrimal duct obstruction and traumatic disruption of the lacrimal drainage system are also common indications for surgery.[7] Within the realm of iatrogenic causes, injury of the lacrimal drainage system can be a complication of endoscopic sinus surgery,[8] and different types of maxillectomies can result in nasolacrimal duct transections. Head and neck radiation may also cause osteitis and mucosal scarring with subsequent epiphora. While experience with endoscopic DCR for the treatment of acute dacryocystitis is more limited, some authors have used this procedure with success.[9,10]

Contraindications

Endoscopic DCR is contraindicated in patients with malignancy involving the lacrimal system. Definitive treatment of the tumor, such as radiation or open resection, must take precedence. Patients with scarring of the puncta or canaliculi from prior orbital infection or trauma may also be poor candidates for DCR through an endoscopic approach. Pseudoepiphora, a condition of reflex tearing caused most commonly by dry eyes, is a contraindication to any DCR surgery.

Ophthalmologic Examination

Patients who are considered candidates for endoscopic DCR require a preoperative ophthalmologic assessment. Visual acuity, field testing, and slit lamp examination should be performed and documented. The external eyelid, ocular surface, and puncta should be inspected for abnormalities, such as scarring or strictures. In cases of chronic dacryocystitis, manual pressure over the region of the lacrimal sac may produce reflux of discolored drainage or debris, which suggests lower sac obstruction.

Nasal Endoscopy

Preoperative evaluation for endoscopic DCR includes nasal endoscopy to look for intranasal causes of lacrimal obstruction. A 3 or 4 mm diameter nasal endoscope with either a 0° or 30° viewing angle is used to examine the nasal cavity. Installation of a topical decongestant and anesthetic, such as 0.5% phenylephrine HCl and 4% lidocaine HCl, is recommended prior to endoscopy to enhance patient comfort. The initial assessment should include the inferior turbinate and inferior meatus. The nasolacrimal duct orifice is sometimes visible in the inferior meatus, and any masses or obstructing polyps that may impinge on the nasolacrimal duct orifice should be noted. Manual pressure over the medial canthus may produce fluid or air bubbles at the ductal orifice to confirm its location. Assessment should be made of any intranasal pathology that may affect access to the lacrimal sac, including septal deviation, middle turbinate hypertrophy or concha bullosa, ethmoid sinusitis, nasal polyps, or middle meatal scarring.

Assessment of Nasolacrimal Patency

The patency of the upper and lower canaliculi may be assessed with a lacrimal probe that is passed through the punctal openings. In some cases, dilation with successively larger-diameter probes may be necessary. Anesthetic drops such as proparacaine HCl 0.5% reduce patient discomfort during this procedure. Any resistance during passage of the lacrimal probe should be noted. It is important to document the approximate point of resistance as this may help differentiate proximal from distal nasolacrimal obstruction.

Another useful test for assessing the patency of the lacrimal system is the Jones dye test.[11] The Jones I and Jones II test are both used to determine the extent of nasolacrimal duct obstruction. The differentiating feature between these two modifications of the test is passive versus active assessment. In the Jones I test, a drop of fluorescein dye is placed into the subject's eye and a functional measure of tear drainage is determined. If the dye is recovered with a cotton-tipped applicator in the inferior meatus or visualized with a nasal endoscope, physiologic patency is confirmed. A variation in this test requires the patient to blow their nose to determine whether fluorescein is visible on tissue paper. Although false negatives may occur in nearly 50% of patients,[7] the use of rigid endoscopy allows direct visualization of the inferior meatus, which may improve the accuracy of testing.

If the Jones I test is abnormal or inconclusive, the Jones II test may be used to determine patency of the lacrimal system in the presence of active, manual hydrostatic pressure. A blunt-tipped 26- or 28-gauge cannula is used to irrigate the canaliculus with clear saline. If saline or dye is recovered in the nose or pharynx, a partial obstruction at the lower sac or duct or canalicular stenosis is present since this obstruction is overcome by the manual pressure of irrigation. If dye or saline regurgitates through the canaliculi or through the other punctum, then complete nasolacrimal duct or common canalicular obstruction is likely,[12] and the patient is considered a candidate for DCR.

Radiologic Evaluation

Radiographic imaging of the paranasal sinuses can be helpful prior to endoscopic DCR to delineate sites of lacrimal obstruction and identify sinonasal pathology not recognized on physical examination. In the patient with persistent epiphora or recurrent dacryocystitis, computed tomography (CT) scan will often reveal a dilated lacrimal sac filled with radiodense material suggestive of thick mucus or pus. It is not unusual for patients who require DCR to have radiographic evidence of concurrent sinus

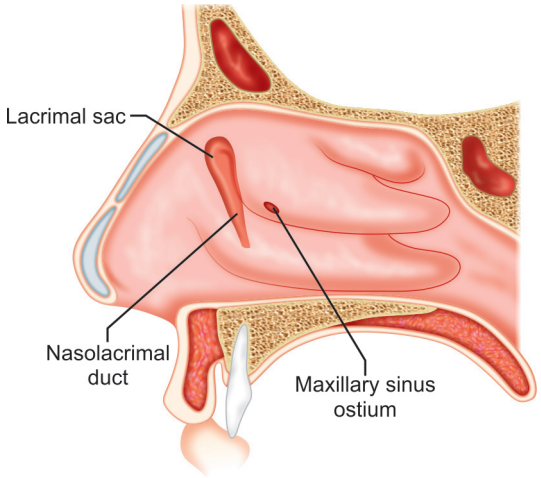

Fig. 63.1: The lacrimal sac along the lateral nasal wall. View of the right lateral nasal wall demonstrates the relationship of the lacrimal sac and nasolacrimal duct to the turbinates. The sac may extend beneath the middle turbinate, which may necessitate turbinate resection for adequate access.
Source: Redrawn with permission from Metson R. Dacryocystorhinostomy. In: Kennedy DW, Bolger WE, Zinreich SJ (Eds.). Diseases of the Sinuses: Diagnosis and Management. London: B.C. Decker; 2001.

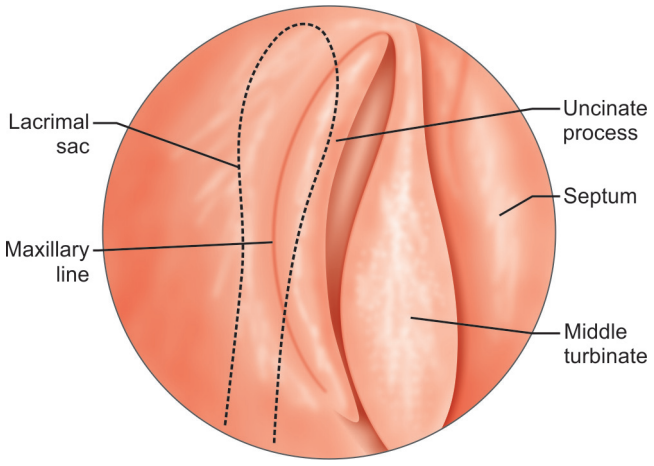

Fig. 63.2: The maxillary line. Endoscopic view of the right nasal cavity demonstrates location of the lacrimal sac (dotted line). The maxillary line is a bony eminence that corresponds to the suture line between the lacrimal and maxillary bones. It is a reliable landmark for the anatomic location of the lacrimal sac.
Source: Redrawn with permission from Sindwani and Metson.[24]

disease, particularly mucosal thickening or opacification of anterior ethmoid air cells overlying the lacrimal sac. Other radiologic findings that might also need to be addressed at time of surgery include the presence of a middle turbinate concha bullosa or superior septal deflection that may limit endoscopic access to the lacrimal sac. Magnetic resonance imaging (MRI) is generally not indicated in the preoperative workup for endoscopic DCR, unless an infiltrative neoplasm is suspected and further soft tissue imaging is deemed appropriate.

Dacryocystograms may also be ordered during the workup for nasolacrimal duct obstruction as a useful test to identify the precise location and degree of stenosis or blockage. In this test, radiopaque contrast media is injected into the canaliculi, while an X-ray or CT scan is performed. In many patients who require DCR, a dilated lacrimal sac filled with dye is observed, as the most common site of lacrimal obstruction is in the distal sac as it enters the bony canal to become the nasolacrimal duct. Although this test is not ordered routinely, it is particularly useful in cases of intermittent epiphora where lacrimal stones are suspected. These dacryoliths are visible as flow voids within the lacrimal sac. Dacryocystogram is also helpful in cases where irrigation of the lacrimal collecting system is inconclusive or cannot be satisfactorily interpreted to determine whether surgical intervention is necessary.

OPERATIVE TECHNIQUE

Surgical Anatomy

From an endoscopic perspective, the lacrimal sac can be found deep to the bone of the lateral nasal wall just anterior to the anterior attachment of the middle turbinate (Fig. 63.1). The superior border of the sac may extend above the level of the turbinate attachment. The maxillary line is an important landmark for endoscopic DCR. The maxillary line is a curvilinear eminence that extends along the lateral nasal wall from the anterior attachment of the middle turbinate to the root of the inferior turbinate (Fig. 63.2). It is also the site of attachment of the anterior portion of the uncinate process to the frontal process of the maxilla.[13] From an external perspective, the maxillary line corresponds to the suture line between the lacrimal bone and the maxilla, which runs in a vertical direction through the lacrimal fossa. To optimally expose the posterior aspect of the sac, the thin uncinate process and underlying lacrimal bone just behind the maxillary line must be removed. Anterior to the maxillary line is the much thicker bone of the frontal process of the maxilla, which must be removed to adequately expose the anterior portion of the lacrimal sac.

As the nasolacrimal duct courses in a posteroinferior direction, it passes an average of 10 mm (range 8–17 mm)

anterior to the natural ostium of the maxillary sinus. Overzealous bone removal in this location is the most common cause of iatrogenic nasolacrimal duct injury in endoscopic surgery for sinusitis.[14] Such injury can be avoided if the operator refrains from bone removal anterior to the maxillary line during the performance of maxillary antrostomy.

The bony nasolacrimal canal is formed by portions of the maxillary, lacrimal, and inferior turbinate bones. The lower aspect of the lacrimal sac tapers as it enters this rigid canal, where it becomes the nasolacrimal duct (Fig. 63.3). It is within this bony covering that the nasolacrimal duct runs for an approximate vertical distance of 10–12 mm. The osseous canal is approximately 1 mm in diameter and transitions to a membranous or meatal portion for about 5 mm after it passes the level of the inferior turbinate. It then terminates as an opening within the inferior meatus.[15,16] Approximately 8–10 mm behind the anterior head of the inferior turbinate and approximately 30 mm from the anterior nasal spine is the orifice of the nasolacrimal duct.[17] The ductal outlet is often covered by a small membranous flap of nasal and nasolacrimal epithelium, known as Hasner's valve, which serves to prevent retrograde reflux of nasal secretions through the nasolacrimal duct.

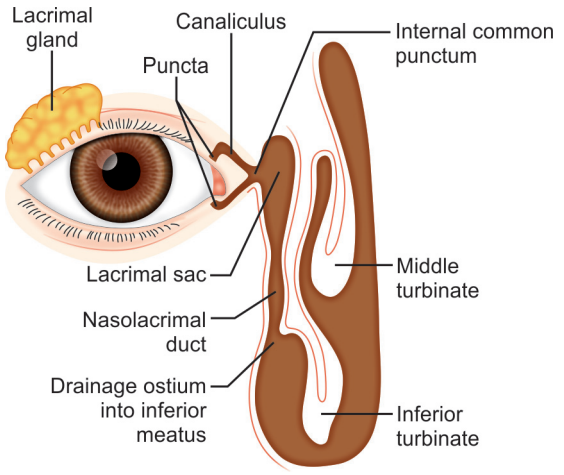

Fig. 63.3: Anatomy of the lacrimal drainage system.
Source: Redrawn with permission from Metson R. Dacryocystorhinostomy. In: Kennedy DW, Bolger WE, Zinreich SJ (Eds.). Diseases of the Sinuses: Diagnosis and Management. London: B.C. Decker; 2001.

Anesthesia

Depending on the patient's general condition and the surgeon's preference, endoscopic DCR may be performed under either local or general anesthesia. General anesthesia affords greater patient comfort and ease of operating in most cases. Additionally, a team approach utilizing skills of both the otolaryngologist and the ophthalmologist is favored. Prior to operative draping, oxymetazoline HCl 0.05% is sprayed into the bilateral nasal cavities to initiate vasoconstriction of the nasal mucosa.

The patient is positioned with the head slightly elevated to reduce venous pressure in the nose and paranasal sinuses. Submucosal injections of 1% lidocaine HCl with epinephrine 1:100,000 are placed under endoscopic visualization. The optimal sites for injection include the lateral nasal wall just anterior to the attachment of the middle turbinate in the region of the maxillary line and the inferior third of the middle turbinate itself. If concurrent septoplasty is to be performed to enhance access to the lacrimal sac, the septum is also injected. Following the injections, nasal packing in the form of pledgets soaked in either 0.5% oxymetazoline or 4% cocaine solution is placed to provide additional decongestion prior to the start of surgery.

Instrumentation

With a few additions, endoscopic DCR can be performed with the same array of instrumentation used for routine endoscopic sinus procedures. Additional instrumentation that is necessary includes a set of lacrimal dilators and probes, a drill or microdebrider for removal of the bone overlying the lacrimal sac, and a canaliculus intubation set. This set includes a pair of lacrimal probes (often referred to as Guibor or Crawford tubes) with an attached Silastic catheter that is used to stent the neo-ostium at the conclusion of surgery. Although intraoperative navigation is not routinely used for endoscopic DCR, it may be helpful if there is concern for altered anatomy, severe sinusitis, or large nasal polyps that may obscure anatomic landmarks.

Another optional tool for endoscopic DCR is a 20-gauge fiberoptic light probe that may be used to transilluminate the lateral wall. This probe is passed through a canaliculus into the lacrimal sac and provides confirmatory location of the sac. If a probe is used, it is important to bear in mind that the area of maximal brightness corresponds with the posterior aspect of the lacrimal sac.[18] In this region, the overlying bone is thinnest in contrast to the center or anterior portions of the sac, which is covered by the thicker maxillary bone.

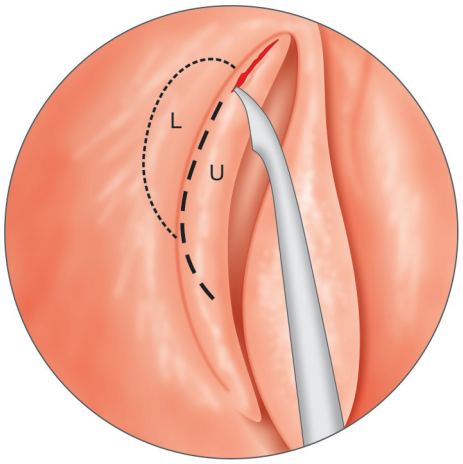

Fig. 63.4: Exposure of bone overlying the lacrimal sac. A semicircle of mucosa along the lateral nasal wall (L) is removed anterior to the maxillary line. The superior portion of the uncinate process (U) is also incised and removed.
Source: Reprinted with permission from Sindwani and Metson.[24]

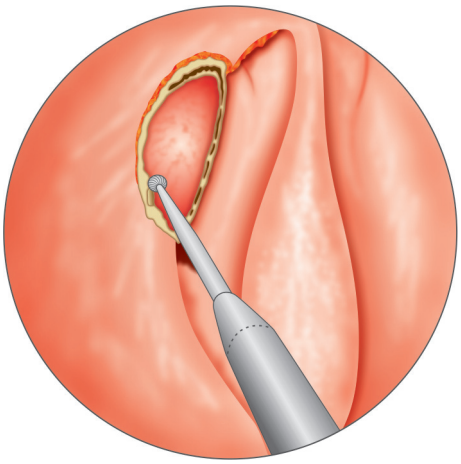

Fig. 63.5: Drilling of the bone to expose the lacrimal sac. A high-speed drill or microdebrider is used to remove the bone overlying the lacrimal sac.
Source: Reprinted with permission from Sindwani and Metson.[24]

Endoscopic DCR

A sickle knife is used to create a curvilinear mucosal incision along the lateral nasal wall overlying the lacrimal sac. This incision begins at the superior end of the maxillary line near the attachment of the middle turbinate and extends to the inferior end of the maxillary line at the root of the inferior turbinate (Fig. 63.4). The circumscribed flap of nasal mucosa measuring roughly 1 cm in diameter is then elevated and removed. The upper half of the uncinate process located posterior to the maxillary line is also incised and removed to expose the underlying lacrimal bone. If a maxillary antrostomy is planned to treat concurrent sinus disease, the lower half of the uncinate process is also resected.

Following uncinectomy, anterior ethmoid air cells overlying the lacrimal fossa may be encountered. These cells are opened and removed. If a large concha bullosa of the middle turbinate is present, the lateral lamella should be excised to enhance access to the lacrimal sac and decrease the likelihood of postoperative obstruction of the DCR ostium. Total or subtotal resection of the middle turbinate is rarely indicated during primary DCR. In cases where a significant septal deviation is present, septoplasty may be performed either with endoscopic assistance or through the surgeon's preferred technique.

Removal of the thin bone posterior to the maxillary line with a spoon curette will reveal the medial wall of the lacrimal sac. This landmark can be confirmed by gentle pressure on the medial canthal region near the lacrimal fossa that reveals movement as seen intranasally with the endoscope. To access the anterior aspect of the lacrimal sac, the hard bone of the frontal process of the maxilla must be removed. This portion of the procedure is generally the most technically difficult. Bone removal is typically performed with a drill bit attached to either a microdebrider or a long-handled otologic drill (Fig. 63.5). The microdebrider usually provides a self-irrigating tip and a protective sheath to reduce the likelihood of trauma to the adjacent septal mucosa. The otologic drill has the advantage of higher speed for more efficient removal of the hard maxillary bone. The use of the laser has also been described for bone removal during endoscopic DCR. The holmium:YAG laser, in particular, has superior bone cutting capabilities and fiberoptic delivery; however, difficulty in monitoring the depth of thermal penetration may result in bony sequestra and scar formation.[19,20]

Once the entire medial sac wall has been exposed, a lacrimal probe is passed through a canaliculus into the sac. This probe can tent the medial sac wall under tension. This maneuver isolates the medial sac and minimizes injury to underlying structures. In the event periorbital fat is visualized during the procedure, it should be left in place and not manipulated. Additionally, in rare cases, a branch of the angular artery or vein may be unroofed during removal of the bone overlying the lacrimal fossa. Hemostasis should be obtained with gentle bipolar or monopolar cautery or a few minutes of tamponade packing with nasal pledgets.

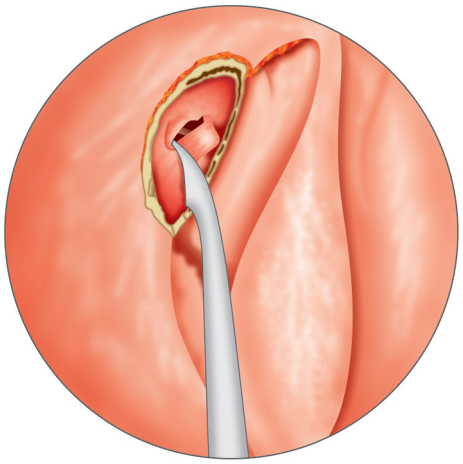

Fig. 63.6: Incision of the lacrimal sac. The lacrimal sac is entered with a sickle knife once bone removal is complete. This maneuver is facilitated by using a stent or probe passed through the canaliculus to provide countertraction of the medial sac.
Source: Reprinted with permission from Sindwani and Metson.[24]

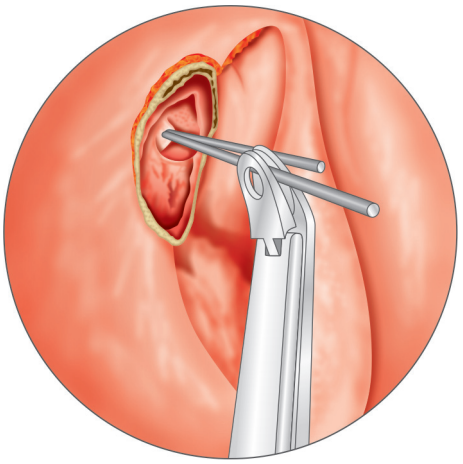

Fig. 63.7: Withdrawal of the lacrimal probes. A Blakesley forceps is used to grasp the lacrimal probes and withdraw them from the nasal cavity. The Silastic catheter threaded over the probes is trimmed and tied to serve as a stent during the healing period.
Source: Reprinted with permission from Sindwani and Metson.[24]

Once the entire medial sac wall has been exposed, it is entered with a sickle knife (Fig. 63.6). Medially directed tension from a lacrimal probe within the sac provides counter tension for the incision. The medial sac wall is removed with angled Blakesley forceps. Mucosal flaps are unnecessary and have no proven benefit. The inferior aspect of the opening should extend to the sac–duct junction. The neo-ostium is enlarged to a diameter of approximately 5–10 mm.

If purulence is encountered on opening the sac, a microbial culture may be obtained. Similarly, a portion of the sac wall should be sent for separate pathologic specimen to rule out occult neoplasm as a cause for the lacrimal obstruction. Once an adequate amount of the sac has been removed, the surgeon should be able to visualize the internal common punctum with a 30° endoscope. The location of this punctum is confirmed by passing metallic probes attached to Silastic tubing (Guibor or Crawford tubes) through the superior and inferior canaliculi. The distal ends of these stents are grasped intranasally under direct visualization with a Blakesley forceps (Fig. 63.7). They are then withdrawn from the nasal cavity and cut from the attached tubing. Lastly, the ends of the tubing are tied and trimmed within the nasal cavity in order to form a continuous loop around the canaliculi. Prior to securing the tubes in a knot, care is taken to ensure the tubing is neither too tight nor too loose by inspecting the tension of the tubing at the medial canthus. Nasal packing is generally not placed unless significant bleeding was encountered. The tubing serves to stent the surgical ostium during the postoperative healing process and is left in place for a period of 6 weeks in most patients. Certain conditions, such as autoimmune or inflammatory diseases, may mandate a longer period of stent placement, up to 6 months.

Revision Endoscopic DCR

Patients who develop recurrent symptoms caused by restenosis of the internal lacrimal ostium after either endoscopic or external DCR may be candidates for revision endoscopic DCR. Revision endoscopic DCR is usually less technically challenging than the primary operation because the bone overlying the lacrimal sac has already been removed.[5] The endoscopic approach offers the important advantage of correcting intranasal abnormalities that are common causes of primary DCR failure, including adhesions, concurrent sinusitis, septal deviation, hypertrophied middle turbinate, or the rare neoplasm.

Once the patient is prepared for surgery in the same manner as primary endoscopic DCR, the ophthalmologist passes a lacrimal probe through a canaliculus into the obstructed lacrimal sac and thereby places the medial sac wall under tension. This is a critical step in revision surgery since extensive fibrosis may obscure the normal lacrimal anatomy and caution should be exercised to avoid injury of the underlying orbital or periorbital structures. The otolaryngologist then uses a sickle knife in the same fashion as described to create a curvilinear incision in

the nasal mucosa approximately 1 cm anterior to the underlying tip of the lacrimal probe. There may be extensive submucosal fibrosis and scarring from prior surgery; therefore, this incision may need to be elevated sharply. Again, tissue removal over an area of approximately 10 mm in diameter is optimal. Through-biting Blakesley forceps are often useful for this maneuver. The assistant surgeon who directs the lacrimal probe can alert the otolaryngologist if the forceps appear to be encroaching on the medical canthus, which could injure the canaliculi. Angled endoscopic instrumentation with 30° or 45° views is helpful at this juncture to visualize the interior of the sac. Once the intranasal opening has been sufficiently enlarged, the lacrimal probes should pass freely without resistance from both the superior and inferior canaliculi. Guibor tubes (Guibor Canaliculus Intubation Set, Concept Inc, Largo, FL) may be used in place of the lacrimal probe since these instruments are fashioned with the Silastic stents already attached to the lacrimal probe apparatus. Threading and securing of the tubes is then completed in the same manner as primary endoscopic DCR.

Endoscopic Conjunctivodacryocystorhinostomy (CDCR)

When a patient fails repeated endoscopic or external DCR procedures, consideration must be given to proximal causes of lacrimal obstruction, such as punctal or canalicular stenosis.

In such cases, endoscopic CDCR may be necessary to bypass the blockage with a Jones tube. This procedure begins with resection of the caruncle, a fleshy mound of tissue at the medial canthus. A 14-gague angiocatheter or blunt needle is then directed through the conjunctiva at an angle of 45° into the nasal cavity using a single "poke-through" technique.[21] The catheter tip is identified intranasally with an endoscope as it penetrates through the lacrimal sac into the lateral nasal wall. It is important to direct the catheter anterior to the middle turbinate so that it does not become lodged against the turbinate surface. Once a conduit from the medial conjunctiva to the nasal cavity has been created, lacrimal dilators are usually necessary to enlarge the tract. The Jones tube can then be passed through the established tunnel so that its distal end protrudes at least 2 mm beyond the lateral nasal wall. These Pyrex glass tubes are available in a variety of diameters and lengths to suit variations in patient anatomy. A tube of sufficient length is very important, as undersized tubes will not completely stent the opening and an oversized tube may abutt the septal mucosa and become obstructed. At the completion of the procedure, fluorescein dye should freely flow from the eye, through the tube, and into the nasal cavity. The tube may be secured with a temporary suture around its proximal end through the skin of the medial canthus. While CDCR is effective in many patients, the Jones tube is prone to obstruction and may require replacement at regular intervals.[22]

The Role of Mitomycin C

Although it is not approved by the Food and Drug Administration for use in DCR, some surgeons elect to apply topical mitomycin C to the intranasal rhinostomy site at the time of revision cases. Mitomycin C is a chemotherapeutic alkylating agent that is isolated from the broth of *Streptomyces lavendulae* or *Streptomyces caespitosus*.[23] It has long been used for the systemic treatment of malignancies. Mitomycin C inhibits fibroblast and endothelial cell growth and replication. This agent is commonly used in eye surgery to improve the patency of shunts for the treatment of glaucoma. Since the most common cause of primary DCR failure is fibrosis or granulation tissue, mitomycin C may have a role in the prevention of recurrent scarring during revision cases. It is usually applied to the operative site at a concentration of 0.4 mg/mL on a cotton pledget for a period of 4 minutes,[24] followed by copious saline irrigation. Some variations in the amount and duration of topical treatment exist.[25-27] The reported outcomes and effect of mitomycin C on long-term patency of the DCR ostium are variable.[26,28-30] A recent randomized controlled trial investigating the efficacy of mitomycin C in revision endoscopic DCR versus without mitomycin showed no improvement.[31]

POSTOPERATIVE CARE

Patients are discharged with instructions to begin saline irrigations twice daily. Although there are no large series or controlled studies regarding the use of antibiotics following endoscopic DCR, prophylactic antibiotics may be prescribed per the surgeon's preference to reduce the possibility of secondary sinusitis or localized osteitis in the immediate postoperative period. The patient is also advised to avoid excessive nose blowing or strenuous activity for a period of 2 weeks to reduce the incidence of nasal bleeding.

Intranasal crust and debris, especially at the DCR site, are carefully removed under endoscopic guidance at the

first postoperative visit 1 week following surgery. Observed movement of the DCR tubes on endoscopic examination is a good prognostic indicator for long-term patency of the DCR ostium. Many patients report resolution of their preoperative epiphora within the first week.

The Silastic tubing used to stent the surgically created ostium is typically removed 6 weeks after surgery by cutting the exposed tubing at the medial canthus and withdrawing the tubes through the nose under direct visualization. If the tubes become dislodged prior to this time such that the patient experiences irritation against the conjunctiva or can see the tubes as they encroach on the cornea, the patient is instructed to wash their hands thoroughly and attempt to gently push the tubes toward the medial canthus. If this maneuver is unsuccessful, repositioning of the tubes should be performed under endoscopic guidance in the office. Occasionally, the tubes become repeatedly dislodged and are removed sooner than the recommended 6-week time period. The tubes may also be removed sooner if excessive granulation tissue formation is seen around the surgical ostium. In revision cases where postoperative scarring led to the initial surgical failure, stents may be left in place for 3–6 months. Similarly, for patients with a known autoimmune disorder, systemic inflammatory conditions, or a predilection for scar formation, the stents may be left in for an extended period of time.

Once the tubes are withdrawn, the patient's subjective report of symptom improvement and lack of epiphora is often adequate to confirm patency of the lacrimal drainage system. However, objective verification can be completed through the same tests detailed during the preoperative workup, such as irrigation of the canaliculi or the visualization of freely flowing fluorescein from the eye into the nose (Fig. 63.8). Although an attempt is made to make a generous opening into the lacrimal sac during endoscopic DCR, the final patency of the healed surgical ostium averages only 1–2 mm in greatest transverse dimension.[32]

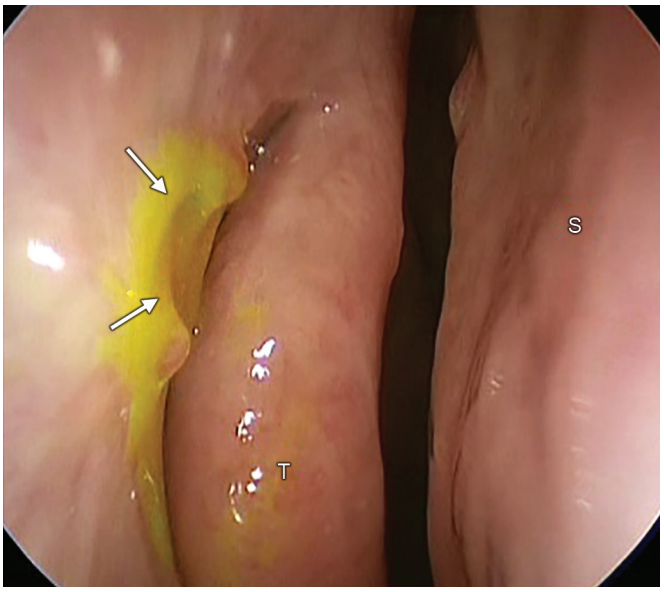

Fig. 63.8: Endoscopic view of right nasal cavity 6 weeks following endoscopic dacryocystorhinostomy (DCR). The healed lacrimal ostium (arrows) demonstrates free flow of fluorescein-stained tears draining through the lacrimal ostium into the nasal cavity. Septum (S) and middle turbinate (T).

SURGICAL RESULTS

Early reports of endoscopic DCR demonstrated success rates <90%, which is thought to reflect the learning curve associated with this procedure. Woog et al.[20] were the first to report on a large number of patients with follow-up for at least 1 year. In this study, the authors described a series of 40 consecutive endoscopic laser DCR procedures performed on 37 patients who were followed for an average of 12 months. The ostial patency was 82%. All surgical failures were evident within 4 months of the initial DCR and presented with recurrent nasolacrimal duct obstruction and epiphora. In a separate series of 46 endoscopic laser DCR procedures, Metson et al.[18] found that surgery relieved nasolacrimal duct obstruction in 85% of patients. Interestingly, serial endoscopic examinations in the postoperative period demonstrated a gradual stenosis and eventual closure of the surgical ostium in five of six patients who failed surgery. In one of these patients, a diverticulum of the lacrimal sac was found, which was not sufficiently drained during the initial endoscopic DCR.

Subsequent reports of endoscopic DCR using nonlaser technique have demonstrated even higher success rates. Ornerci et al.[33] reported 93% relief of epiphora in patients who underwent endoscopic DCR. A larger study of endoscopic DCR outcomes in 152 patients by Sprekelsen and Barberán[34] noted a "good" or "very good" result in 96% of surgical patients followed over a 12-month period. No significant complications were reported in either of these series. These results are comparable to the external DCR efficacy rate of 90–95%, with highest rates reported in dedicated oculoplastic centers.[35,36]

In the majority of patients, anatomic patency of the surgically created ostium correlates with symptomatic

improvement. Nonetheless, the success of the surgery may be influenced by the type of obstruction, whether anatomic or functional. In a recent report of 128 nonlaser endoscopic DCR procedures by Tsirbas and Wormald, anatomic patency of the surgical ostium was achieved in 96% of patients with a minimum follow-up of 12 months, whereas symptomatic relief occurred in 81% of patients.[37] The authors explain this discrepancy by the fact that a number of patients had functional nasolacrimal duct obstruction as opposed to a true anatomic blockage. This discrepancy may reflect a defect in the lacrimal pump mechanism thought to be necessary for normal tear drainage. It might also be caused by a "sump effect" in which tears collect in the lacrimal sac, but do not drain sufficiently into the nasal cavity because of a discrepancy between the location of the internal lacrimal ostium and internal common punctum.

COMPLICATIONS

Complications stemming from endoscopic DCR may occur during the intraoperative, early postoperative, or late postoperative periods. Most of the complications of endoscopic DCR are similar to those of endoscopic sinus surgery. Excessive bleeding during endoscopic DCR that cannot be controlled with temporary packing or cauterization should prompt termination of the procedure.

Occasionally, periorbital fat is exposed during endoscopic DCR. This fat should be left undisturbed to prevent injury to the underlying orbital structures. Injury to the medial rectus or superior oblique muscles, which lie deep to the periorbital fat, can result in diplopia. Blindness can result from direct injury to the optic nerve itself or from lacerations of periorbital vasculature with hemorrhage and resultant pressure ischemia at the orbital apex. Although very rare, if the globe is noted to be tense at any point during or immediately following surgery, a retroorbital hematoma may be present. This condition should be expeditiously managed with lateral canthotomy and cantholysis, as well as urgent ophthalmologic consultation.

Early postoperative complications occur up to 1 month following surgery and include bleeding, infection, and intranasal synechiae. Postoperative epistaxis severe enough to warrant nasal packing occurs in <5% of patients. Such hemorrhage usually occurs within 1 week of surgery and is most commonly caused by a branch of the sphenopalatine artery if the middle turbinate is resected at the time of surgery.

The most common late complication and the most common cause of failure for endoscopic DCR is the formation of postoperative adhesions.[6,38] These adhesions usually span the lateral nasal wall to the middle turbinate or septum, and thereby cause obstruction of the surgically created lacrimal ostium. For this reason, it is important to avoid trauma to the turbinate or septal mucosa during surgery. In the early postoperative period, intranasal adhesions can usually be divided with a suction or blunt probe. After 1 month, however, lysis of obstructing adhesions usually requires a local anesthetic. In cases of persistent lacrimal obstruction, the patient may need to return to the operating room for revision endoscopic DCR. Depending on intraoperative findings, concurrent middle turbinate reduction or septoplasty may be necessary to reduce the likelihood of recurrent adhesion formation.

CONCLUSION

Endoscopic DCR has proved to be an excellent alternative to external DCR for the treatment of nasolacrimal duct obstruction. In addition to avoiding a facial incision, the endoscopic approach allows the surgeon to address intranasal pathologies that may contribute to surgical failure. A team approach that utilizes the complementary skills of both an otolaryngologist and an ophthalmologist will maximize patient outcomes.

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SECTION 12

The Future of Rhinology: The Next Frontiers

CHAPTER

The Future of Rhinology: The Next Frontiers

64

Jeremy T Reed, David W Kennedy

INTRODUCTION

In recent years, rhinology has been the fastest growing field within otorhinolaryngology. This growth is evidenced by the rapid increase in publications within the field of chronic rhinosinusitis (CRS) from approximately 80 publications per year in 1985 to approximately 650 publications per year currently. Similarly, there has been a dramatic growth in publications on skull base surgery from approximately 35 per year up to approximately 550 per year in recent years. The introduction of rigid endoscopes in the latter part of the 20th century, combined with improved diagnostic techniques offered by endoscopy, computed tomography (CT), and magnetic resonance imaging (MRI), opened up new options in terms of minimally invasive surgical techniques, improved visualization, and reduced patient morbidity. The growth of rhinology is also demonstrated in the rapid growth of the number of subspecialty fellowships in rhinology from one in the 1988 to 28 today.[1] Over this time frame, we have significantly increased our knowledge with regard to the pathogenesis of CRS and, with improved instrumentation, significantly enhanced our ability to perform endoscopic surgical intervention while at the same time minimizing collateral damage.

However, despite our increased knowledge of the field and our improved surgical techniques, we have only begun to scratch the surface in our understanding of the broad syndrome encompassed by CRS. As we start to understand the microbiological revolution created by genetic identification of the microbiome, inflammatory pathways, and genetic predispositions to CRS, our ability to develop new medical therapies promises to dramatically increase. At the same time, surgical instrumentation continues to evolve and surgical training will likely continue to evolve toward simulation rather than early direct patient surgical intervention. Eventually, surgical robotic techniques will become miniaturized and applicable to transnasal skull base surgery, significantly enhancing the potential for transnasal intracranial surgical procedures. In this chapter, we have attempted to identify the areas that we believe are going to rapidly evolve within the field of rhinology in the coming years.

TOPICAL THERAPY

One in four adults worldwide is estimated to suffer from allergic rhinitis and there is an epidemic of atopic disease in westernized nations. First-line therapy for allergic rhinitis remains topical corticosteroid sprays and currently, over 16 different nasal steroid sprays are commercially available. While these are effective when used consistently, compliance is often poor. One study by Loh evaluated the compliance of 63 patients with allergic rhinitis who were prescribed intranasal steroids. When patients were >50%, compliant sneezing, rhinorrhea, and nasal itching decreased significantly.[2] Strict compliance, however, was only around 25%. The study also asserted that patient reported compliance differed significantly from actual compliance when the weight of medication consumed was evaluated. One must assume that topical medications with easier scheduling or automated reminders will increase patient compliance. Significant attention is also currently being directed toward improving topical therapy intranasal

delivery devices. Data suggest that low volume nasal corticosteroid sprays only treat nasal mucosa with almost no intrasinus distribution.[3] Clearly this limits intranasal steroid effectiveness at treating all affected tissues and reflects one of the challenges to topical treatment of other mucosal diseases such as CRS.

Numerous new drug delivery systems have been developed in an attempt to overcome the current problem of poor topical drug distribution within the nasal and parasinus cavities. These include large volume irrigation, aerosolizers, pulsating lavages, and nebulizers. While intranasal drug distribution is improved with these devices, delivery to the mucosa of unoperated sinuses is poor. Moller et al. showed that deposition of microparticles in the paranasal sinuses is significantly increased in nonoperated patients with pulsating nasal nebulizer use.[4] In surgically naïve patients suffering from CRS, however, swollen mucosa and blocked sinus ostia may prevent penetration of aerosols completely. The concept of potentially in the future restoring a more protective and healthy sinus microbiome makes the issue of providing appropriate intrasinus topical delivery even more important.

Two of the benefits of endoscopic sinus surgery are postoperative sinus debridement and drainage with better delivery of topical medications to diseased mucosa.[5] Due to the complex shape and orientation of the paranasal sinuses, topical liquid medications primarily reach gravity-dependent portions of the sinuses. This results in medication pooling (Fig. 64.1). Even with positioning maneuvers, medications delivered in irrigations are only in contact with affected tissues for a limited time. Eventually liquid therapies drain from targeted sinuses when patients stand up or bend forward. Emptying this reservoir is inconvenient and sometimes embarrassing. Nebulizers and aerosolized medications have aimed to address this problem. Aerosolized microparticles are more likely to coat the entire surface area of the sinuses with less residual to later drain from the nose. However, the current gold standard for topical anti-inflammatory therapy remains high-dose, high-volume nasal irrigation.

Even previously operated sinuses have natural barriers to drug delivery. These obstacles include the mucociliary blanket, mucociliary clearance, and gravity. Several novel topical drug therapies have been developed to overcome these problems. Mucociliary clearance occurs every 10–15 minutes in healthy sinuses. The gel and sol layers provide an anatomic barrier to diffusion of topical medications into diseased mucosa, while the mucociliary clearance limits the contact time, thus preventing maximal drug absorption. With this in mind, Nakamura et al. linked budesonide to copolymers of polymethacrylic acid and polyethylene glycol. When administered in powder form, this medication turns into a gel on nasal mucosa. In the gelatinous state, mucociliary clearance is decreased and mucosal contact time increased allowing for sustained release of budesonide with peak concentrations at 45 minutes after application.[6] Another interesting drug delivery strategy developed to overcome ciliary clearance is linking therapeutic medications to cell surface adhesive proteins. These work by attaching therapeutic medications to the epithelial cell (Figs. 64.2A to C), thereby decreasing physical drug clearance from the sinuses and the amount of medication required. It may also potentially decrease dosing rates.[7]

Intraoperatively, a pulsatile high-flow, high-volume irrigation as with the Hydrodebrider (Medtronic-Xomed,

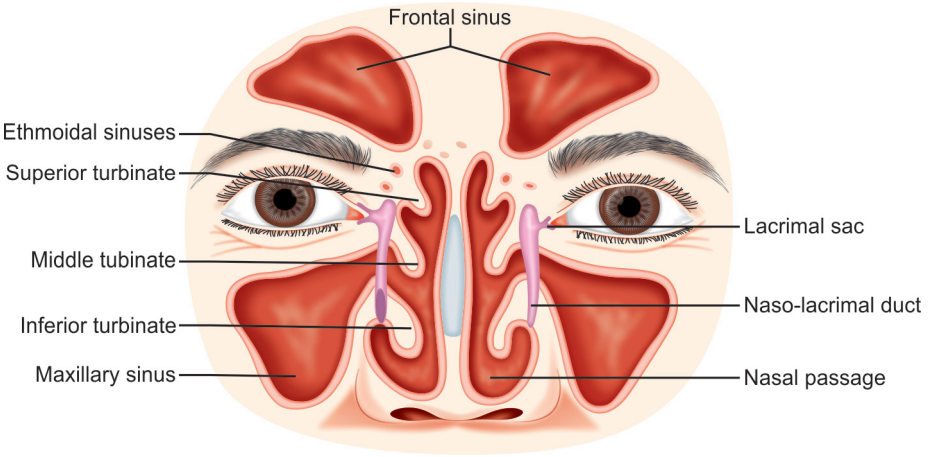
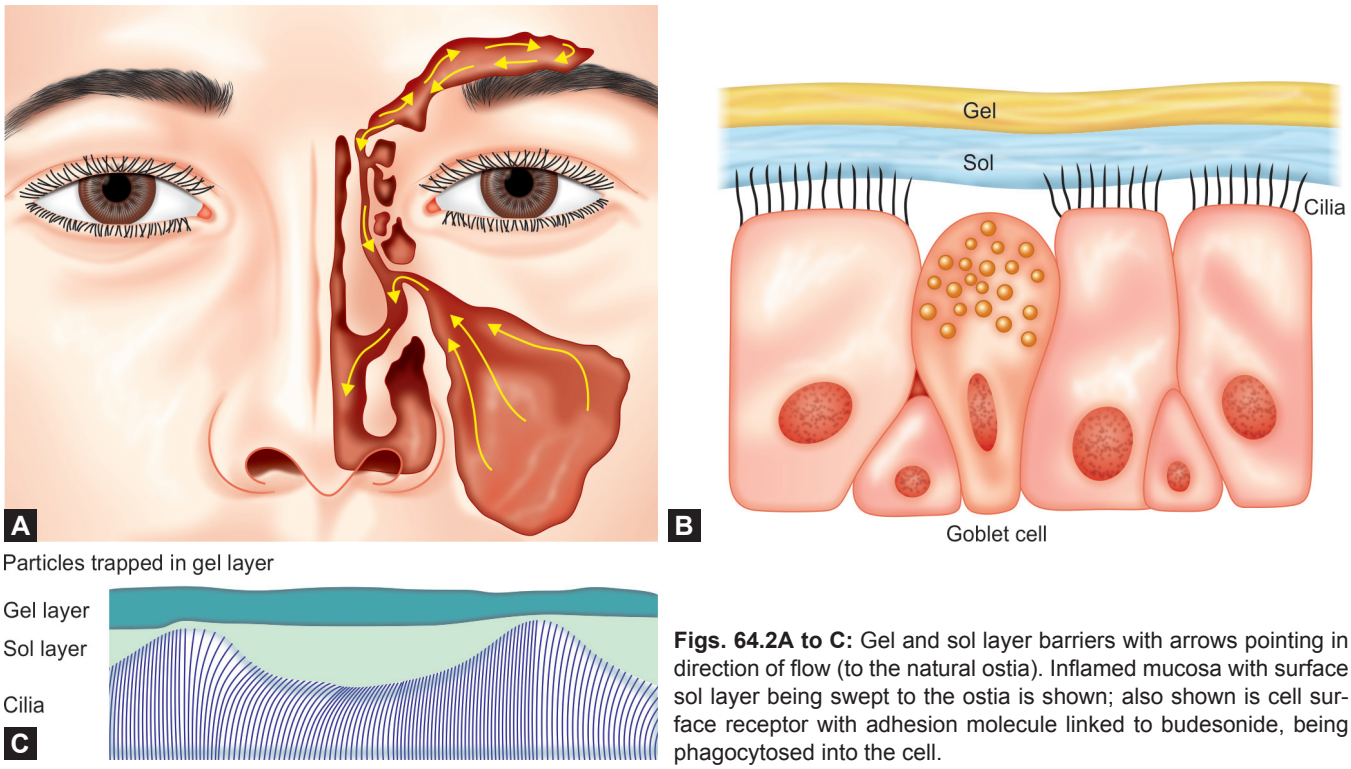


Fig. 64.1: Sinus irrigation pooling before and after irrigation.



Figs. 64.2A to C: Gel and sol layer barriers with arrows pointing in direction of flow (to the natural ostia). Inflamed mucosa with surface sol layer being swept to the ostia is shown; also shown is cell surface receptor with adhesion molecule linked to budesonide, being phagocytosed into the cell.

Jacksonville, FL) has been demonstrated to significantly reduce the bacterial biofilm. Intraoperative topical therapy for hemostasis also continues to evolve. The topical use of intraoperative 1–1000 epinephrine with thrombin has gained increased acceptance, and multiple very effective hemostatic agents are now available, but may increase postoperative scarring. However, the ideal postoperative hemostatic dressing, one that does not encourage adhesions and yet enhances wound healing, still remains to be identified. An ideal intraoperative topical therapy would be absorbable, hemostatic, and allow access to the sinuses for suction of bacterially and fungally contaminated secretions, and would prevent the formation of postoperative synechiae. Chitosan, a long chain polysaccharide found in the shell of crustaceans, fungus, and insects, may fill some of these needs.[8] A study by Athanasiadis et al. compared hemostasis, adhesion formation, and wound healing in sheep models after a mucosal injury was created that was similar to that caused during endoscopic sinus surgery. These sheep models were treated topically with polyethylene glycol, recombinant tissue factor, and chitosan–dextran. The authors found chitosan to be superior to the other topical agents studied at adhesion prevention. They also showed improved microscopic wound healing up to 2 months postoperatively.[9]

GENETIC TESTING AND INDIVIDUALIZED THERAPY PHARMACOGENETICS

As genetic testing and research advances, medical therapy will increasingly demonstrate greater individualization. With the continued identification of genetic predispositions to medical ailments such as asthma, nasal polyps, and obesity, it is reasonable to assume that physicians will screen for these conditions earlier in life.[10] Early screening may allow for prophylactic treatment of the "at risk" cohorts before symptoms occur. For instance, it is previously been identified that treating children with allergic rhinitis with sublingual immunotherapy (SLIT) decreases the risk of subsequent asthma. In the future, genetic testing should also help to determine patient responsiveness to specific medications and interventions. A current example, outside of the field of otolaryngology, is Vanderbilt University, where a DNA biobank has been developed that incorporates patients' DNA into their personalized electronic medical record (EMR). As specific genes are identified that predispose to disease or predispose responsiveness to specific medical treatment, patients' EMRs are flagged. When those patients returns to receive care, their treatments

are then individually tailored based on their genetic profile from their EMR.[11]

ALLERGY AND IMMUNOLOGY

SLIT will likely continue to gain in popularity as the epidemic of allergy continues in the westernized nations. It is estimated that one quarter of people in the developed world suffer from allergic rhinitis. Allergic rhinitis is responsible for 3.5 million missed workdays and 2 million missed school days per year, as well as a significant impact on sleep and presenteeism.[12] Clearly this has a substantial economic impact on society and quality of life. Allergic rhinitis patients are initially treated with systemic antihistamines or topical nasal corticosteroids. These medicines treat symptoms but do nothing to modify the underlying causes of the disease process. As previously noted, compliance with this medical therapy is often poor. Even in some compliant patients, medicines are only partially effective. In these cases, allergy skin or lab testing is appropriate. If atopy to specific allergens is discovered, subcutaneous immunotherapy (SCIT) may currently be recommended. Unfortunately, desensitization regimens are rigorous and require routine scheduled visits to the allergy clinic for injections and patient compliance is generally low. Several studies have identified that compliance with SCIT ranges from 33% to 89%.[13] One significant reason for the low compliance is patient inconvenience and therefore a convenient alternative to SCIT is of significant value.

SLIT has been shown to be effective at treating allergic rhinitis in adults and, following the initial dose, can be self-administered at home.[14] While somewhat less effective than SCIT, several studies have demonstrated the strong safety profile of SLIT and demonstrated long-lasting immunologic alteration.[15] This has significant implications on patient quality of life and should increase compliance, while decreasing overall treatment costs.

ANTIMICROBIAL PHOTODYNAMIC THERAPY (BIOFILMS)

Biofilms play a significant role in the manifestation of many otorhinolaryngologic illnesses. It has been shown that patients with biofilm compounded CRS do worse postoperatively than those without biofilms.[16] This relatively recent discovery offers a new angle for novel treatments. Mechanical cleansing had already proven efficacious, and a novel form of photodynamic therapy has recently been proposed.[17] Treating topically prepared nasal and paranasal sinus mucosa with selective laser light exposure effectively destroys biofilms while preserving normal tissue and reducing the need for antibiotics. Several studies have suggested that presensitization of biofilms with enzymes, plant extracts, hydrogen peroxide, dyes, or antibiotics may contribute to laser photo destruction while simultaneously decreasing the concentration of light required for treatment.[18] Krespi et al. even showed that *Pseudomonas aeruginosa* biofilms could be effectively disrupted and the indwelling bacteria exposed by using a Q-switched ND:YAG laser and specially designed probes that generated plasma and subsequent shock waves without damaging underlying tissue. This process made involved bacteria susceptible to ambient antibiotics.[19] Another photodynamic therapy approach entering clinical trials is the use of methylene blue as a photosensitizer, followed by the application of a diode laser. In laboratory trials, this approach resulted in reductions of 99.9% of biofilm bacterial colonies.[20]

DRUG ELUTING IMPLANTS

The introduction of FDA-approved biodegradable drug eluting implants is an extremely exciting advance in the topical therapy of CRS, and the utilization is likely to continue to grow. The currently available device (Propel implant, IntersectENT, Menlo Park, CA) holds the turbinate medially during the postoperative period and releases 370 μg of mometasone furoate over 30 days. The implant can be placed at the time of surgery or postoperatively. Wei and Kennedy reviewed three studies evaluating the efficacy of this stent and concluded that the Propel sinus implant reduced postoperative inflammation, polyposis, middle turbinate lateralization, and intranasal synechiae (Fig. 64.3). They also concluded that the need for postoperative steroids was reduced, and possibly even the need for postoperative debridement and lysis of adhesions.[21] A smaller stent (Propel Mini) that can also be placed in the frontal sinus is now also available. A significantly longer-lasting device (90 days of drug elution) for the medical treatment of recurrent nasal polyps is also in clinical trials for patients who would otherwise require revision surgical intervention. Early experience has demonstrated a significant reduction in polypoid mucosa and symptoms scores lasting 6 months post placement. However, it is likely that these devices just represent the beginning of

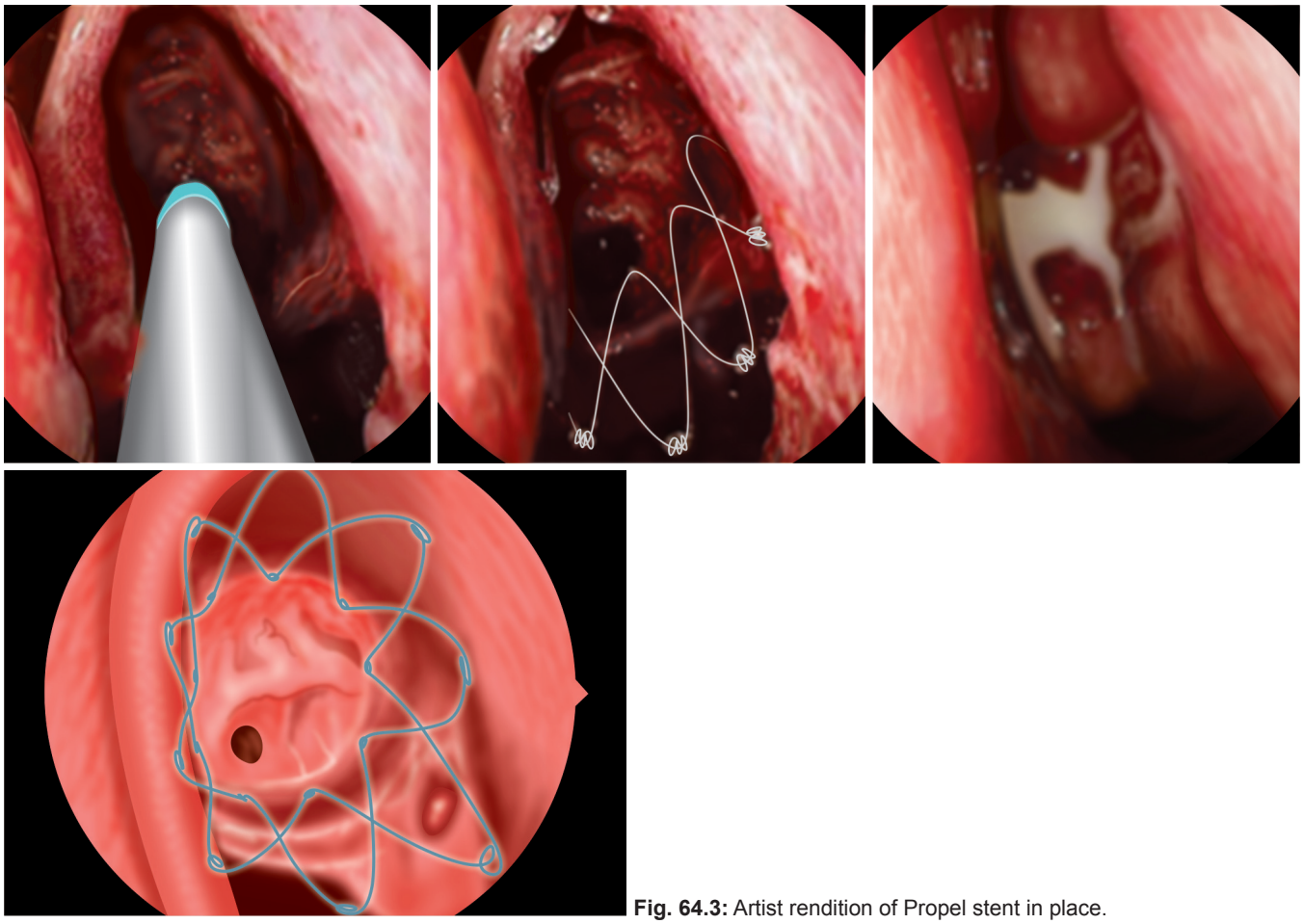


Fig. 64.3: Artist rendition of Propel stent in place.

a new era in topical therapy. Additional nonsteroidal anti-inflammatory agents or wound healing topical therapy could potentially be administered through search biodegradable implants. The combination of such topical therapy with a minimally invasive device such as balloon dilatation could usher in a new era in truly effective minimally invasive approaches.

SINUS MICROBIOME ALTERATION, MOLECULAR DIAGNOSTICS, AND WOUND HEALING

Genetic identification of bacteria is beginning to change our prior understanding of bacteriology and our concepts of the normal and abnormal bacterial microbiome. While, at the present time, it is difficult to identify the critical elements in all of the data which this new technology generates, in the future it is possible that identification and manipulation of sinus microbiomes will revolutionize how chronic sinusitis is treated. Recent research from Abreu et al. and other researchers has demonstrated that the paranasal sinuses support a local bacterial microbiome that consists of a population of different bacterial species, each in different concentrations. The diversity and density balance of this bacterial microbiome may determine which patients have healthy sinuses and which have CRS. Abreu et al. evaluated the microbiomes of seven healthy patients and compared them to seven CRS patients. Using a standardized phylogenetic microarray, they identified the presence and relative abundance of 8500 different bacterial species. They discovered that pathogenic strains were present in both healthy and diseased sinuses. This suggests that the mere presence of pathogenic bacteria is not solely responsible for CRS. It also brings into question the utility of sinus cultures that aim to isolate and identify pathogenic bacteria while

neglecting normal sinus flora. This study found that it was not the presence of pathogenic bacteria, but rather the relative concentration of pathogenic bacteria that differed between healthy and diseased sinuses. *Corynebacterium tuberculostearicum* was identified in significantly increased relative abundance in patients with CRS; while probiotic species such as *Lactobacillus sakei* were present in significantly reduced relative amounts, and that healthy sinuses appeared to have a more diverse sinus microbiome than CRS patients.[22] To further evaluate the role of this microbiome balance in the pathogenesis of sinusitis, Abreu manipulated the microbiome of murine models. Four groups of mice were evaluated: a control, an antibiotic-treated (microbiome depleted), a *C. tuberculostearicum*-inoculated, and an antibiotic-treated *C. tuberculostearicum*-inoculated groups. Histologic samples of sinus mucosa were then evaluated for goblet cell hyperplasia, a histologic marker for sinusitis. It was found that the control, antibiotic-treated, and *C. tuberculostearicum*-infused sinus mucosa were all similar; however, the antibiotic-depleted, *C. tuberculostearicum*-infused sinus mucosa showed significant goblet cell hyperplasia suggesting that opportunistic growth of pathogenic bacteria in a microbiome-depleted sinus contributes to sinusitis. Similarly, a mouse model was infused with equal numbers of *C. tuberculostearicum* and *L. sakei* to determine if the *Lactobacillus* was protective. It was discovered that the sinus mucosa in these mice were similar to that of mice infused with *L. sakei* alone. This suggests that the presence of *L. sakei* in higher microbiome concentrations may be protective for sinusitis.

It is certainly possible that manipulation of sinus microbiome may be an effective and minimally invasive treatment of CRS in the future. Several microbiology labs are able to profile the microbiomes of sinus samples with 48-hour turn-around times. Moving forwards, point of service genetic identification of bacteria at a cost lower than that of bacterial culture is likely. However, as noted previously, the wealth of data produced is difficult to interpret clinically. The goal, however, would be to prescribe appropriate antibiotics to deplete specific components of the microbiome. Additionally, following treatment, microbiome-depleted patients might be infused with probiotic-rich media in order to protect against recurrence.

To date, such molecular DNA-based polymerase chain reaction and sequencing have been utilized successfully in the management of chronic wounds, but not in sinusitis. Dowd et al. compared chronic wound healing in patients treated with systemic antibiotics based on traditional wound cultures to those treated with selective systemic or topical antibiotics based on molecular diagnostic evaluation. They found that the time to complete wound closure decreased 26% in patients treated with systemic antibiotics and 46% in patients treated with topical antibiotics based on molecular diagnosis of the wound microbiome.[23] Significant effort is currently being expended to try to identify appropriate bacterial targets and probiotics within the nose and paranasal sinuses.

SKULL BASE SURGERY

In the surgical field, endoscopic skull base surgery has increased dramatically. Utilizing juvenile nasal angiofibroma (JNA) as a relatively common example of a skull base tumor, there is a clear trend from open to endoscopic excision over the past 20 years. A literature search for case series and case reports from the last 20 years shows a near complete paradigm shift to endoscopic excision of JNAs from open approaches for almost all stages of tumor with the exception of intracranial extensions (Fig. 64.4). Additionally, there is clear evidence to show that the postoperative recovery, hospital stay, and blood loss are decreased with endoscopic approaches compared to open surgeries.

When one considers malignant skull base lesions, the trends are similar. Suh et al. reviewed all skull base malignancies resected with curative intent from 2002 to 2010 in a tertiary referral institution and found that exclusively endoscopically resected malignant tumor patients suffered from less surgical and medical complications postoperatively than those operated on through open and combination approaches.[24] A higher recurrence rate in the open cases was likely due to higher T stages of tumors selected for an open procedure. A study by Abergel et al. also showed that in most cases, patient quality of life after endoscopic skull base tumor resection is equal to or better than open approaches while providing for shorter hospital stays.[25] The potential complications of endoscopic skull base surgery, however, still remain catastrophic. Furthermore, it is absolutely essential that an identical margin of tissue is obtained endoscopically to that required for standard oncologic surgery. However, improved training, increased surgical familiarity, novel technology, and innovative methods of skull base reconstruction have continued to expand the indications for endoscopic resection. As technology and experience

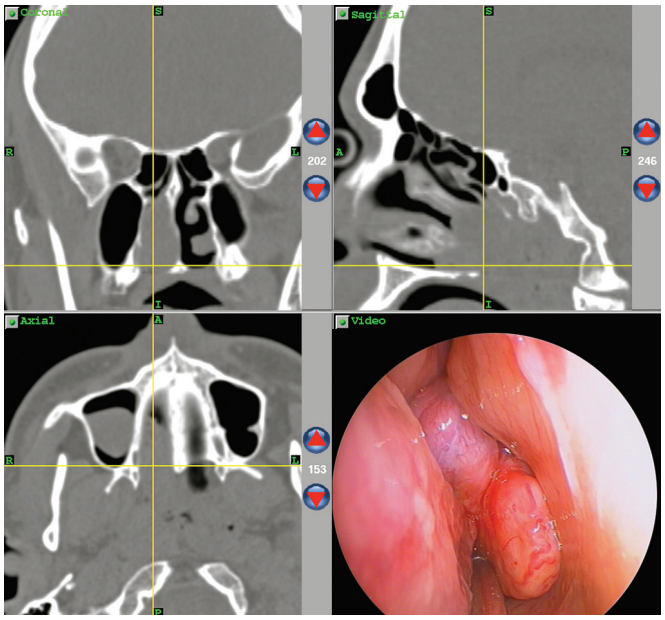


Fig. 64.4: Endoscopically visualized juvenile nasal angiofibroma using three-dimensional image guidance.

continue to mature, we anticipate that the role of endoscopic skull base approaches will continue to grow and further extend the variety of pathology and intracranial surgical reach of these narrow surgical corridor endoscopic options.

ROBOTIC SKULL BASE SURGERY

Robotic surgery will expand into the field of rhinology in the near future. Advantages of robotic surgery include three-dimensional visualization, tremor and fine motor scaling, and increased magnification. Robots, unlike humans, do not fatigue during long cases and robotic control consoles allow surgeons to function more comfortably for longer periods of time.[26] Robotic arms have the advantage that they mimic and even exceed the functional range of motion of human hands and robotic arms can offer 7° of motion.[27] The increased range of motion combined with steady instrument movements allows for very precise dissection at high magnification from a three-dimensional perspective.

Although the development of robotic sufficiently delicate instrumentation with sufficiently close ports for endoscopic transnasal endoscopic surgery has been slow in coming, there is some evidence that obstacles to the use of robots for skull base surgery are slowly being overcome. Shorter, less bulky robotic arm attachments are being designed to allow easier access to the skull base transnasally. Vanderbilt is currently developing a robot system that uses concentric tubing to provide tentacle-like movements from robotic arms. These arms are small enough that several instruments may be used through the same nostril simultaneously. Image guidance is being added to these robotic arms to allow for intraoperative navigation.[28]

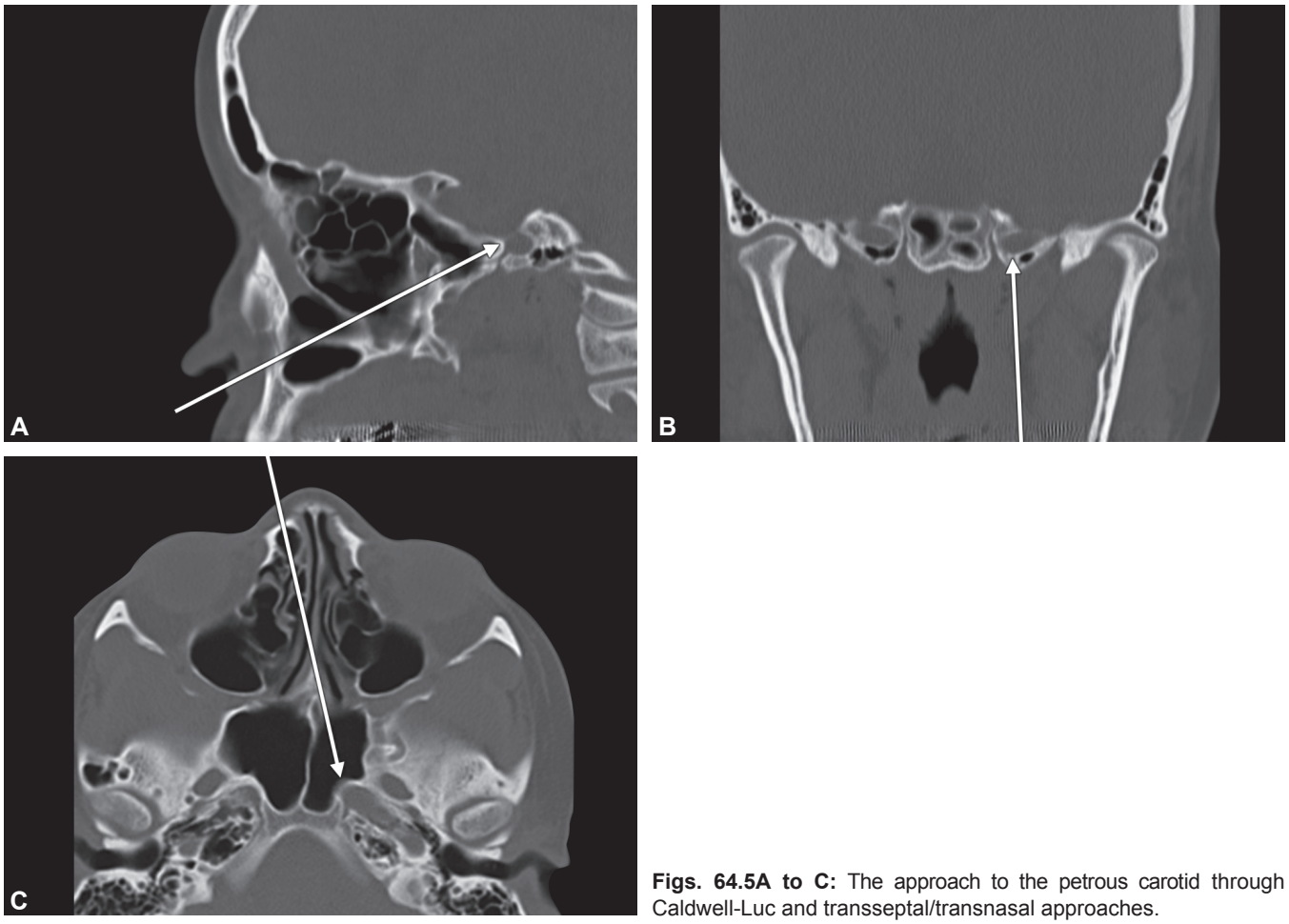
With the development of robotic arms that articulate in several dimensions, previously impossible surgical maneuvers will be achievable, including the suture closure of dural defects and delicate bipolar coagulation in areas where this is currently not possible. The addition of three-dimensional viewing should also impact tumor resection. One article published in 2009 using cadavers showed increased performance efficiency at simple tasks and decreased performance error at more complex tasks, when performed under three-dimensional visualization.[29]

An often overlooked advantage of robotic surgery is the potential for telesurgery. In 2001, Marescaux published an article detailing a laparoscopic cholecystectomy that was performed robotically in Strasbourg, France, by an operating surgeon located in New York City.[30] With increased strain on already limited medical resources, robotic surgery may offer surgical subspecialty care in locations where it has not previously been available. Such applications are of considerable interest to the military where robotic telesurgery may provide life-saving surgical interventions at forward deployed areas while avoiding evacuation time and unnecessary surgeon exposure.[31] In the event of polytrauma, it would be possible to have a neurosurgeon, general surgeon, and otolaryngologist all operating on the same patient at the same time from different locations globally.

In less emergent cases, robotic telesurgery could potentially allow more effective surgical resource allocation. It may be possible to perform complex surgical cases with multiple operating physicians operating from multiple institutions. For instance, it may be possible that one otolaryngologist performs a skull base tumor approach before a neurosurgeon resects the tumor robotically from another location. Likewise, emergency intraoperative consultations and interventions may be performed telerobotically saving the need for transfer of critically ill patients between institutions.

SKULL BASE RESECTION LIMITS

As instrumentation improves, so will the breadth of cranial base tumors that are amenable to endoscopic resection.

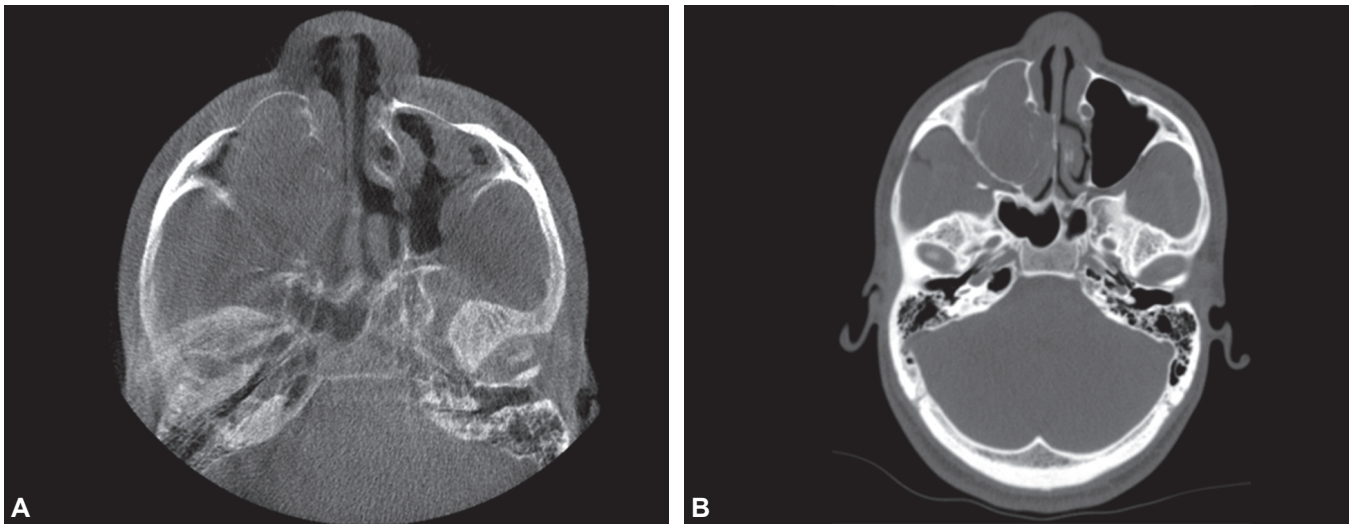


Figs. 64.5A to C: The approach to the petrous carotid through Caldwell-Luc and transseptal/transnasal approaches.

Several studies have recently attempted to identify the limits of transnasal endoscopic approaches to the skull base. One study defined the sagittal and coronal planes and described the surgical limitations to the use of these approaches respectively. Regarding skull base tumors in the sagittal plane, the transcribriform, transplanum, and transsellar routes were evaluated. The authors found that the limits of the median sagittal approach were lesions larger than 4 cm, those extending lateral to the optic canals, those encasing neurovascular structures, and those with invasion of brain tissue.[32] The lateral extent of exposure to the clivus was found to be limited by the Eustachian tubes unless a transpterygoid approach was incorporated.[33] Other studies evaluated the lateral extent of coronal approaches and found that transnasal combined with Caldwell-Luc approaches allowed dissection of the petrous carotid artery (Figs. 64.5A to C).[34,35] Harvey et al. examined the maxilla and infratemporal fossa to determine the extent of endoscopic resection that is possible and found that with a combination of unilateral endoscopic maxillary antrostomy, medial maxillectomy, and transseptal approaches nearly all of the maxilla and infratemporal fossa are accessible with occasional difficulty anteriorly in the maxillary antrum.[36] Surgeon training, experience, and skill continue to expand the willingness of surgeons to stretch the limits of transnasal skull base tumor resection, while improved instruments, endoscopes, and, in the future, robotic usage should allow them to do so.

BALLOON OSTIAL DILATION

Since its original introduction in 1993, a variety of different balloon ostial dilation tools have been introduced. Current data supports its use for adult and pediatric CRS, limited CRS, and frontal sinusitis.[37] However, it is important to remember that CRS is not just a plumbing problem and ostial dilation typically needs to be combined



Figs. 64.6A and B: Side-by-side comparison of conventional versus cone beam scanner. Axial cut of cone beam and conventional computed tomography (CT) scans of the same patient, showing mucosal thickening of left maxillary sinus (cone beam image) and right maxillary mass (both images). This demonstrates the ability of cone beam CT scanners to adequately resolve both infectious and neoplastic sinonasal pathology.

with anti-inflammatory therapy. The future combination of balloon dilation with drug eluting anti-inflammatory stents therefore does create a very viable potential therapy. One advantage of balloon catheter dilation is the ability to perform it with relative ease in clinic and in the ICU. Because it typically requires only minimal additional setup, overall costs of sinus surgery may decrease thereby saving valuable operating room time for more urgent cases.

Multiple balloon types, sizes, delivery instruments, suctions, and irrigation adaptors exist. Not surprisingly, some balloon catheters are also compatible with image guidance systems.[38] Physicians with limited endoscopic instruments may find balloon sinuplasty less challenging than traditional endoscopic sinus surgery with less risk of intraoperative complications and postoperative scarring. However, studies have shown that attempted balloon dilation of the maxillary sinus results in the creation of an accessory ostium rather than dilation of the natural ostium in the majority of cases.[39] Still, the technology has a good safety record, even in the hands of surgeons less skilled in advanced endoscopic techniques. One study retrospectively reviewed 1036 patients and reported only two cerebrospinal fluid leaks, neither of which were attributed to balloon use.[40]

CT IMAGING

Intraoperative CT scanning has demonstrated significant benefit in endoscopic surgical procedures and allows real-time updates to the computer navigation system. A study by Jackman showed that intraoperative CT scanning changed the surgical plan in 30% of sinus cases.[41] Accordingly, the real-time intraoperative results offered by these scanners should decrease the need for revision surgery, even in experienced hands. However, the difficulty of obtaining reimbursement for the time spent performing intraoperative scans has probably significantly inhibited its utilization, despite the availability of relatively low-cost, low-irradiation cone beam scanners.

In the office, the use of cone beam CT scanning allows for more efficient diagnosis, improved patient satisfaction, and may decrease antibiotic usage. Although the soft tissue resolution is significantly less with a cone beam scanner, it is clearly adequate for the diagnosis of sinus disease and provides good detail with regard to sinus anatomy (Figs. 64.6A and B). However, it has also been demonstrated that the presence of an in-office CT scanner significantly increases CT scan usage by at least two times.[42] However, the total per scan radiation dose for cone beam scanning is significantly reduced compared to conventional CT scanning. One conventional multidetector planar sinus CT scan is equivalent to the radiation dose received from approximately 100 chest X-rays. This is 3–10 times the amount of radiation exposure from one cone beam sinus CT scan; an important advantage in this era of increased CT usage.[43]

EVOLVING ENDOSCOPE TECHNOLOGY

Three-dimensional endoscopes may, over time, become increasingly utilized. However, over the years, numerous companies have attempted to commercialize three-dimensional endoscopes and none have yet demonstrated long-term success. Common hurdles to their practicality include the need to wear specialized shutter goggles, surgeon nausea and headache, large scope caliber, difficulty righting the picture with angled telescopes, and poor resolution.[44] Newer technology utilizes a microarray of lenses similar to an insect eye. Images from these lenses are computer processed in order to reconstruct a three-dimensional image. Operating surgeons wear polarized glasses, similar to three-dimensional movie glasses, when viewing the stereoscopic video.[45] This system has some advantages over previous systems and, at least to some extent, the picture can be righted when an angled telescope is rotated. The use of polarized glasses is more comfortable then shutter glasses or a heads-up display. Currently 0° and 30° endoscopes with this technology are available and being used in several tertiary care centers throughout the United States.

Distal chip endoscopes, rigid, malleable and flexible are being developed that will allow for smaller diameter scopes, reduced cost, and potentially greater durability. The potential also exists to add such miniature chips and light arrays to other surgical instrumentation in the future. Endoscopes with a distal rotating prism have also been developed, allowing for wide variation in angle of view. However, at this point in time they remain expensive and heavy for routine sinus surgery use.

EVOLVING TECHNIQUES IN PRECISION RADIATION DELIVERY

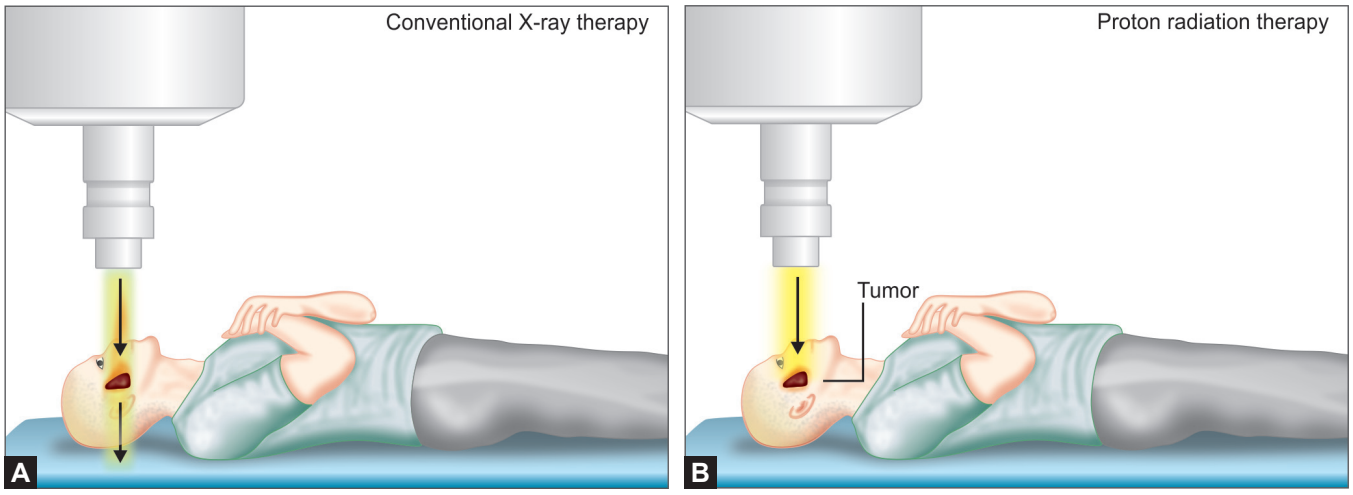
Although expensive, proton radiation has many advantages for head, neck, and skull base tumors. Conventional radiation treatments direct electrons at tumors with the intent of inducing cell death through DNA damage.[46] In order for radiation to reach tumors, it must pass through healthy, nonpathologic tissues. Additional collateral tissue damage is induced after it passes through targeted tumors. Added exposure of adjacent healthy tissues to unnecessary radiation results in side effects such as xerostomia, osteoradionecrosis, and cataracts. Intensity-modulated radiation therapy (IMRT) partially addresses this problem. Since radiation induced effects are additive, directing multiple radiation beams at a tumor from different directions reduces the cumulative dose to any one set of tissues. At the same time, this concentrates intersecting beams on the tumor. While IMRT reduces the incidence of radiation induced side effects, it does so at the cost of radiating a larger volume of healthy tissue unnecessarily. Additional radiation exposure of healthy tissue may cause radiation induced tumors later in life and is especially a concern in pediatric patients.

Proton beam radiation avoids many of the disadvantages of conventional radiation. Charged nuclear particles, like protons, have a spread-out Bragg peak followed by a very sharp drop-off, so that deeper tissues are spared almost any radiation. Using multiple beams at varying intensities, irregularly shaped tumors may be radiated with very specific radiation doses (Figs. 64.7A and B). Radiation oncologists can maximize proton radiation transfer to tumors and significantly reduce collateral tissue.[46] Obviously this is very applicable to the skull base region where vital structures can be spared. Similarly, decreasing the volume of radiated tissue may decrease radiation-induced tumors, especially in younger patients.

One study by Dvorak examined the potential economic advantage of proton radiation. The article asserted that all tumor patients would likely benefit from proton radiation over conventional radiation. In reviewing five other studies, the article found that proton beam radiation was being used on head and neck tumors between 9% and 40% of all the times radiation was used.[47] It is important to remember that reducing radiation side effects helps to offset the additional cost of proton radiation. Decreased need for dental visits, decreased need for medicines to treat xerostomia and radiation induced ulcers, decreased need for radiation induced tumor treatment, decreased risk of undergoing surgery, and improved patient quality of life will all play a role in increasing the use of proton beam radiation for head and neck tumors.

SURGICAL TRAINING AND COMPETENCY

Surgical subspecialty training continues to improve but will face many obstacles in the future. In July 2003 the Accreditation Council for Continuing Medical Education (ACGME) instituted the 80-hour workweek. Although data regarding changes in resident case load is mixed, it appears that cases with residents as first assistants are shifting toward upper level residents.[48,49] This creates a void in lower level surgical training that patient simulator training may fill. Obvious advantages to simulation training are that it involves minimal risk, does not require live



Figs. 64.7A and B: Artist rendition of conventional radiotherapy. (A) Irregularly shaped tumor on anterior skull base with conventional radiation from two directions, intersecting at the tumor, but also exposing the brain and eyes to undue radiation on entry and exit of the beam. (B) Irregularly shaped tumor irradiated with proton beam radiation showing the shape modulation minimizing the collateral damage upon entry with no exit damage.

patients, and can be standardized. Allowing residents to make mistakes on simulators provides documented background procedure experience and shortens learning curves for operative procedures on live patients.

Surgical simulators will allow comparison of the surgical skill of residents from the same year. With standardized, step-wise grading and objective competency evaluations, residency programs will be able to follow resident surgical progression through the duration of training. The Joint Commission on Accreditation of Health Care Organizations (JCAHCO) now includes competency requirements and assessments as part of its evaluation. Patient surgical simulators may help to accomplish this goal.

Several simulators are in use. One in particular that has been highly researched is the ES3 by Lockheed Martin. The ES3 uses three dimensionally reconstructed CT scans to generate a virtual image. Using a specialized virtual endoscope, operating surgeons navigate their way through different tasks at three different levels: novice, intermediate, and advanced. One study showed that these simulator-acquired skills transfer well to the operating room. It compared "simulator pre-trained" PGY 1 and 2 year residents with non-simulator trained residents of the same year. This study found that completion time, instrument manipulation, and the rate of surgical mistakes were all decreased in the simulator group.[50] A continuation study by Fried et al. demonstrated that surgical skills of all levels reached a plateau after ten cases on the simulator. Not surprisingly, this study showed that novice and intermediate level personnel stand to gain the most from simulation training.[51] However, these simulators are expensive and there is evidence that more basic endoscopic manual skills trainers, utilizing readily available materials, can also decrease the surgical learning curve.

In the future, surgical simulators should allow difficult cases to be practiced by operating surgeons and their operating teams before the surgery takes place. Eventually it will be possible to take a CT for a revision sinus or skull base tumor case, print out a three-dimensional model from material that is similar to tissue, and then rehearse the surgery prior to performing it. This would allow the surgeon to determine what instruments are needed and what approach is most advantageous. Terumichi et al. used virtual endoscopy images to visualize nine patients' CT scans. The authors found this useful in revision sinus cases and in those with sphenoethmoidal (Onodi) cells.[52] From an educational standpoint, practicing on a virtual simulator may reaffirm attending confidence in residents and increase resident participation in difficult cases.

Simulators have a role not only in teaching surgery, but also in team training and in teaching complication management. For obvious reasons, training in intraoperative complications is difficult to accomplish. In rhinology, neurovascular injuries can be debilitating and catastrophic. Training in how to manage these complications is needed. Wormald has developed a sheep model that allows simulation of intrasphenoid carotid injury.[53] With carotid injuries being one of the most feared complications

of endoscopic surgery, the value in simulating this event with residents and one's skull base team is immeasurable.

Simulation training will also become an increasing necessity as society becomes more litigious. The American Medical Association cites that 6 in 10 doctors older than 55 have had medical malpractice claims against them. Although this varies by specialty, the AMA reports that 57% of surgical subspecialists have been sued, and 36% have been sued twice.[54] Another article, however, suggests that 54% of these lawsuits are dismissed.[55] With an expected increase in doctor workload due to the implementation of the Patient Protection and Affordable Care Act, it is likely that this trend will continue.

Further contributing to this is the fact that many patients research their doctors online and an increasing number of patients are reluctant to allow residents to operate on them. The question "How many times have you done this procedure before?" is increasingly been asked. Surgical simulator training may allow physicians to better market their skills to patients with rare disease process requiring unique surgeries.

SUMMARY

The field of rhinology has grown rapidly since the introduction of the endoscope and detailed imaging in the latter part of the 20th century. We have learned that CRS is an inflammatory rather than primarily an infectious process and that there are strong environmental influences in many patients with this disease process. At the same time, there has been a marked increase in the incidence of airway atopic diseases in westernized countries. Although our medical and surgical therapies have improved, the very common syndrome of CRS still remains somewhat of an enigma even as we begin to unravel some of the inflammatory pathways involved in the associated disorders. We have yet to understand the influence of the sinus microbiome and need to further identify the genetic predispositions associated with this syndrome.

As we become armed with the rapidly evolving body of knowledge regarding the inflammatory pathways, genetic influence, and the effects of the local microbiome, our ability to develop new medical therapies promises to dramatically increase. At the same time, surgical instrumentation continues to evolve and, at some point, robotic technology should dramatically improve, but it is currently possible with skull base and transnasal intracranial surgery. The training itself for rhinologic surgical procedures will likely continue to evolve toward simulation rather than early direct patient surgical intervention. We look forward to the day when the syndrome can be better classified, recalcitrant disease can be more effectively managed, and topical therapies more effectively applied for inflammatory control and improved postoperative wound healing.

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