Algorithms *in* PEDIATRICS

Editors
Anand S Vasudev • Nitin K Shah

Foreword
Pramod Jog

JAYPEE

Algorithms in

PEDIATRICS

Algorithms in
PEDIATRICS

Editors

Anand S Vasudev DNB D Ped DCP MNAMS MICP (USA) FIAP FIMSA
Senior Consultant, Pediatric Nephrologist
Indraprastha Apollo and Max Hospital
New Delhi, India

Nitin K Shah MD DCH DNB
Professor and Consultant Pediatrician
PD Hinduja National Hospital and
Medical Research Centre
Honorary Hematoncologist
BJ Wadia Hospital for Children
Lions Hospital
Mumbai, Maharashtra, India

Foreword

Pramod Jog

The Health Sciences Publisher

New Delhi | London | Panama

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
Email: 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
Email: 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
Email: cservice@jphmedical.com

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

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

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

Algorithms in Pediatrics / Anand S Vasudev, Nitin K Shah

First Edition: **2017**

ISBN: 978-93-5152-160-0

Contributors

EDITORS

Anand S Vasudev DNB D Ped DCP MNAMS MICP (USA) FIAP FIMSA
Senior Consultant, Pediatric Nephrologist
Indraprastha Apollo and Max Hospital
New Delhi, India

Nitin K Shah MD DCH DNB
Professor and Consultant Pediatrician
PD Hinduja National Hospital and Medical Research Centre
Honorary Hematoncologist
BJ Wadia Hospital for Children
Lions Hospital
Mumbai, Maharashtra, India

SECTION EDITORS

Piyali Bhattacharya DCH MD FCCM PGDMLS
Specialist
Sanjay Gandhi Post Graduate Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Amar J Chitkara MD DNB
Head
Department of Pediatrics
Max Superspeciality Hospital
New Delhi, India

Rajesh R Chokhani MD DCH FRCPCH
Consultant
Mumbai, Maharashtra, India

Jaydeep Choudhury DNB MNAMS
Associate Professor
Department of Pediatrics
Institute of Child Health
Kolkata, West Bengal, India

Neelu A Desai MD DNB
Consultant
Department of Pediatric Neurology
PD Hinduja National Hospital and Medical Research Centre
Mumbai, Maharashtra, India

Pankaj V Deshpande MRCP MD DCH FCPS
Consultant
Department of Nephrology
PD Hinduja National Hospital and Medical Research Centre
Mumbai, Maharashtra, India

Anaita Udwadia Hegde MD MRCPCH
Consultant
Department of Pediatric Neurology
Jaslok Hospital and Research Center
Breach Candy Hospital Trust
Bai Jerbai Wadia Hospital for Children
Mumbai, Maharashtra, India

Vaman V Khadilkar MD DNB MRCP DCH
Pediatric Endocrinologist
Jehangir Hospital
Pune, Maharashtra, India
Bombay Hospital
Mumbai, Maharashtra, India

Praveen Khilnani MD FICCM FSICCM FAAP FCCM
Director
Pediatric Critical Care Services and Fellowship Program
BLK Superspeciality Hospital
New Delhi, India
PICU Mediclinic City Hospital
Dubai, UAE

Vikas Kohli MD FAAP FACC
Fetal, Neonatal, Pediatric Cardiologist
Director
Delhi Child Heart Center
New Delhi, India

Anurag Krishna MCh FAMS
Director
Department of Pediatrics and Pediatric Surgery
Max Institute of Pediatrics,
Max Healthcare
New Delhi, India

Shyam Kukreja
Head
Department of Pediatrics
Max Superspeciality Hospital
New Delhi, India

Anjali Kulkarni MD FRCPCH
Head
Department of Pediatrics and Neonatology
Sir HN Reliance Foundation Hospital
Mumbai, Maharashtra, India

Ashish Mehta MD DCH
Consultant and Director
Arpan Newborn Care Centre Pvt Ltd
Ahmedabad, Gujarat, India

Rujuta Mehta MS DNB
Consultant
Balabhai Nanavati Hospital
Jaslok Hospital and Research Centre
Shushrusha Hospital
Head
Department of Pediatric Orthopedics
Bai Jerbai Wadia Hospital for Children
Mumbai, Maharashtra, India

Vibhu Mendiratta MD
Consultant and Professor
Department of Dermatology and STD
Lady Hardinge Medical College and
Associated Hospitals
New Delhi, India

Taral V Nagda MS DNB DOrth
Consultant
Department of Pediatric Orthopedics
PD Hinduja National Hospital and
Medical Research Centre, Saifee
Hospital, Jupiter Hospital
Mumbai, Maharashtra, India

MKC Nair
Professor and Vice Chancellor
Kerala University of Health Sciences and
Founder Director
Child Development Centre
Thrissur, Kerala, India

Priyankar Pal MD
Associate Professor and Head
Department of Pediatrics
Institute of Child Health
Kolkata, West Bengal, India

Usha Pratap MD MRCP
Senior Consultant
Department of Pediatric Cardiology
Deenanath Mangeshkar Hospital
Pune, Maharashtra, India

Girish Raheja MS
Senior Consultant and Academic
Coordinator
Indraprastha Apollo Hospital
New Delhi, India

ATK Rau MD DHA
Professor and Incharge
Department of Pediatrics
MS Ramaiah Medical College
Bangalore, Karnataka, India

GR Sethi MD
Formerly Head
Department of Pediatrics
Maulana Azad Medical College
New Delhi, India

Rasik S Shah MCh
Section Incharge
Department of Pediatric Surgery
PD Hinduja National Hospital and
Medical Research Centre
Mumbai, Maharashtra, India

Anand K Shandilya MD DCH FRCPCH
Consultant
Department of Pediatrics
Dr Anand's Hospital For Children
Mumbai, Maharashtra, India

Anupam Sibal MD FIMSA FIAP FRCP FRCP
Senior Consultant
Department of Pediatric
Gastroenterology and Hepatology
Indraprastha Apollo Hospitals
New Delhi, India

Varinder Singh MD FRCPCH
Director Professor
Department of Pediatrics
Lady Hardinge Medical College and
Kalawati Saran Children's Hospital
New Delhi, India

Tanu Singhal MD MSc
Consultant, Department of Pediatrics
Kokilaben Dhirubhai Ambani Hospital
Mumbai, Maharashtra, India

Soonu Udani MD
Pediatric Intensivist
Section Head Pediatrics
PD Hinduja National Hospital and
Medical Research Centre
Mumbai, Maharashtra, India

Vrajesh Udani MD
Consultant
Department of Pediatric Neurology
PD Hinduja National Hospital and
Medical Research Centre
Mumbai, Maharashtra, India

Shashi Vashisht MS
Professor and Head
Department of Ophthalmology
Dr Ram Manohar Lohia Hospital
New Delhi, India

Anju Virmani MD DNB
Senior Consultant, Apollo, Max,
Pentamed and Sundar Lal Jain Hospital
New Delhi, India

Surender K Yachha MD DM
Professor and Head
Department of Pediatric Gastroenterology
Sanjay Gandhi Postgraduate Institute of
Medical Sciences
Lucknow, Uttar Pradesh, India

CONTRIBUTING AUTHORS

Kochurani Abraham DCH
Senior Registrar
Department of Pediatrics
Jehangir Hospital
Pune, Maharashtra, India

Mohan K Abraham MS MCh
Professor and Head
Department of Pediatric Surgery
Amrita Institute of Medical Sciences
Kochi, Kerala, India

Bharat Agarwal MD DCh
Head
Department of Hemato-Oncology
BJ Wadia Children Hospital
Mumbai, Maharashtra, India

Gautam S Agarwal MCh
Principal Consultant
Department of Pediatric Surgeon
Max Super Speciality Hospital
New Delhi, India

Manjari Agarwal MD
Attending Consultant
Department of Pediatric Rheumatology
Institute of Child Health
Sir Ganga Ram Hospital
New Delhi, India

Mridul Agarwal MD FNB
Consultant
Department of Pediatric Cardiac Sciences, Sir Ganga Ram Hospital
New Delhi, India

Mandar Agashe MS
Consultant, Centre for Pediatric Orthopedic Care, Dr Agashe's Hospital
Mumbai, Maharashtra, India

Anju Aggarwal MD FIAP
Associate Professor
Department of Pediatrics
University College of Medical Sciences and Guru Tegh Bahadur Hospital
New Delhi, India

Neeraj Aggarwal MD FNH
Consultant, Department of Pediatric Cardiac Sciences, Sir Ganga Ram Hospital
New Delhi, India

Satish K Aggarwal MS MCh
Senior Consultant
Department of Pediatric Surgery
Sir Ganga Ram Hospital
New Delhi, India

Atul Ahuja MS
Senior Consultant
Department of ENT and Head and Neck Surgery
Indraprastha Apollo Hospital
New Delhi, India

Ira E Almeida DCH MD DNB PG-DAP
Senior Pediatrician
Department of Pediatrics
Hospicio Hospital
Margao, Goa, India

Parmanand GK Andankar DCH DNB
Pediatric Intensivist
Wadia Children Hospital
Consultant Pediatric and Neonatal Intensivist
Jupiter and Bethany Hospital
Thane, Maharashtra, India

Alaric J Aroojis MS DNB FCPS
Consultant
Department of Pediatric Orthopedics
Kokilaben Dhirubhai Ambani Hospital and Bai Jerbai Wadia Hospital for Children
Mumbai, Maharashtra, India

Priyanka Arora MS
Assistant Professor
Department of Ophthalmology
Dayanand Medical College and Hospital
Ludhiana, Punjab, India

Shreedhara Avabratha K MD DNB
Professor
Department of Pediatrics
Father Muller Medical College
Mangalore, Karnataka, India

Sanjay M Bafna MD
Senior Consultant and Head
Department of Pediatrics
Jehangir Hospital
Pune, Maharashtra, India

Vibha S Bafna MD DCH
Senior Consultant
Department of Pediatrics
Jehangir Hospital
Pune, Maharashtra, India

Arvind S Bais MS FIMSA
Senior Consultant
Department of ENT
Indian Spinal Injury Hospital
New Delhi, India

Naveen Bajaj DM MD
Consultant, Department of Neonatology
Deep Hospital
Ludhiana, Punjab, India

Anurag Bajpai MD FRACP
Consultant, Department of Pediatric and Adolescent Endocrinology
Regency Hospital Limited
Kanpur, Uttar Pradesh, India

Minu Bajpai MS MCh PhD FRCS
Professor
Department of Pediatric Surgery
All India Institute of Medical Sciences
New Delhi, India

Chandra S Bal
Professor
Department of Nuclear Medicine
All India Institute of Medical Sciences
New Delhi, India

Padma Balaji MD
Junior Consultant
Kanchi Kamakoti Childs Trust and Childs Trust Medical Foundation
Chennai, Tamil Nadu, India

Suma Balan MD MRCP CH CCST
Consultant
Department of Pediatrics
Amrita Institute of Medical Sciences
Kochi, Kerala, India

Indira Banerjee MD DNB MRCPCH
Trainee, Department of Pediatric Cardiology, Rabindranath Tagore International Institute of Cardiac Sciences
Kolkata, West Bengal, India

Sushmita Banerjee DCH MSc MRCPI FRCPCH
Consultant
Department of Pediatric Nephrology
Calcutta Medical Research Institute
Kolkata, West Bengal, India

Rahul P Bhamkar DNB DCH MNAMS
Associate Consultant
Department of Pediatrics
Sir HN Reliance Foundation Hospital
Mumbai, Maharashtra, India

Vidyut Bhatia MD
Consultant
Department of Pediatric
Gastroenterology and Hepatology
Indraprastha Apollo Hospitals
New Delhi, India

Veereshwar Bhatnagar MS MCh
Professor
Department of Pediatric Surgery
All India Institute of Medical Sciences
New Delhi, India

Sagar Bhattad MD
Senior Resident
Department of Pediatrics
Postgraduate Institute of
Medical Education and Research
Chandigarh, India

Reeta Bora MD DM
Associate Professor and Incharge of
Neonatal Unit
Department of Pediatrics
Assam Medical College
Dibrugarh, Assam, India

Sudha R Chandrashekhar MD ESPE
Professor
Department of Pediatrics
Bai Jerbai Wadia Hospital for Children
and Seth GS Medical College
Mumbai, Maharashtra, India

Anirban Chatterjee MS DNB MNAMS
Senior Consultant
Department of Orthopedics
Medica Superspecialty Hospital
Kolkata, West Bengal, India

Jasodhara Chaudhuri MD MRCPCH
RMO-cum-Clinical Tutor
Department of Pediatric Medicine
Medical College
Kolkata, West Bengal, India

Hitesh B Chauhan MS
Pediatric Orthopedic Surgeon
Department of Pediatric Orthopedic
Rainbow Superspeciality Hospital and
Children's Orthopedic Centre
Ahmedabad, Gujarat, India

Deepak Chawla MD DM
Associate Professor
Department of Pediatrics
Government Medical College Hospital
Chandigarh, India

Harshika Chawla MBBS
Postgraduate Resident
Department of Ophthalmology
Postgraduate Institute of Medical
Education and Research and
Dr Ram Manohar Lohia Hospital
New Delhi, India

Dinesh K Chirla MD DM MRCPCH
Consultant
Department of Neonatology
Rainbow Children's Hospital
Hyderabad, Telangana, India

Sushma P Desai DCH MD PGDAP
Counseller
Gopi Children and Orthopedic Hospital
and Adolescent Speciality Clinic
Surat, Gujarat, India

Vaishali R Deshmukh DCH DNB PGD-AP
Consultant and In-Charge
Nine-to-Nineteen Clinic
Deenanath Mangeshkar Hospital and
Research Center
Pune, Maharashtra, India

Taru Dewan MS FRCSEd
Associate Professor
Department of Ophthalmology
Postgraduate Institute of Medical
Education and Research and
Dr Ram Manohar Lohia Hospital
New Delhi, India

Arjun A Dhawale MS DNB MRCSEd
Surgeon, Department of Orthopedics
and Spine Surgery
Sir HN Reliance Foundation Hospital and
BJ Wadia Hospital For Children
Mumbai, Maharashtra, India

Dhulika Dhingra MD
Assistant Professor
Department of Pediatrics
Chacha Nehru Bal Chikitsalaya
New Delhi, India

Vinod Gunasekaran MD FIAP
Clinical Assistant, Institute of Child Health
Sir Ganga Ram hospital
New Delhi, India

Vikram Gagneja DNB FNB FCCM
Consultant Pediatrician and Intensivist
Gagneja Speciality Clinic
New Delhi, India

Suma Ganesh MS DNBE
Consultant and Head
Department of Pediatric Ophthalmology
and Strabismus
Dr Shroff's Charity Eye Hospital
New Delhi, India

Niti Gaur MD
Senior Resident
Department of Dermatology
Lady Hardinge Medical College and
Associated Hospitals
New Delhi, India

Paula Goel MD PGDAP PGDMLS
Consultant and Director
Fayth Clinic
Mumbai, Maharashtra, India

Anju Gupta MD
Associate Professor
Department of Pediatrics
Postgraduate Institute of Medical
Education and Research
Chandigarh, India

Sailesh G Gupta MD DCH
Consultant
Department of Pediatrics and
Neonatology, Ashna Childrens Hospital
and Arushee Childcare Hospital
Mumbai, Maharashtra, India

Shalu Gupta MD
Professor, Department of Pediatrics
Lady Hardinge Medical College and
Kalawati Saran Children's Hospital
New Delhi, India

Supriya Phanse Gupte MD PDCC
Leeds Royal Infirmary
United Kingdom

Omkar P Hajirnis MD DNB MRCPCH
Pediatric Neurologist
Department of Pediatric Neurology
Bhaktivedanta Hospital and Research
Centre, Dr LH Hiranandani Hospital
Rajiv Gandhi Medical College and
CSM Hospital
Mumbai, Maharashtra, India

Manisha Halkar MD DNB
Consultant, Department of Neonatology
Meenakshi Hospitals
Bangalore, Karnataka, India

Aru C Handa
Senior Consultant
Department of ENT and Head Neck
Surgery Medanta Medicity
Gurgaon, Haryana, India

Kumud K Handa MS DNB MNAMS
Director and Head
Department of ENT and Head Neck
Surgery
Medanta Medicity
Gurgaon, Haryana, India

Rashna D Hazarika MD
Senior Consultant and Chief
Department of Pediatrics, Pediatric and
Neonatal Intensive Care
Midland Hospital and Rigpa Children's
Clinic
Guwahati, Assam, India

Ira J Holla MBBS
Junior Resident
Department of Pediatrics
Lok Nayak Jai Prakash Narayan Hospital
New Delhi, India

Ram G Holla MD DM
Senior Consultant
Department of Neonatology and
Pediatrics, Adiva Hospitals
New Delhi, India

Aspi J Irani MD DCH
Pediatrician, Department of Pediatrics
Nanavati Super Speciality Hospital
Mumbai, Maharashtra, India

Nurul Islam MD DNB
Consultant, Pediatric Cardiology
Mission Hospital
Durgapur, West Bengal, India

Barath Jagadisan MD PDCC
Associate Professor
Department of Pediatrics
Jawaharlal Institute of Postgraduate
Medical Education and Research
Pondicherry, India

Ashish Jain MD DNB DM
Assistant Professor
Department of Neonatology
Maulana Azad Medical College
New Delhi, India

Naveen Jain DM
Coordinator, Department of Neonatology
Kerala Institute of Medical Sciences
Trivandrum, Kerala, India

Shikha Jain MS
Medical Officer
Department of Ophthalmology
Dr Ram Manohar Lohia Hospital
New Delhi, India

Manisha Jana
Assistant Professor
Department of Radiodiagnosis
All India Institute of Medical Sciences
New Delhi, India

Kana R Jat MD FCCP MNAMS
Assistant Professor
Department of Pediatrics
All India Institute of Medical Sciences
New Delhi, India

Nameet Jerath MD
Senior Consultant, Department of
Pediatric Critical Care and Pulmonology,
Indraprastha Apollo Hospital
New Delhi, India

Ganesh S Jevalikar MD DNB PDCC
Consultant, Department of
Endocrinology and Diabetes
Medanta The Medicity
Gurgaon, Haryana, India

Nachiket M Joshi MBBS
Resident
Department of General Surgery
PD Hinduja National Hospital and
Medical Research Centre
Mumbai, Maharashtra, India

Nandkishor S Kabra DM MD DNB MSc
Director, Department of Neonatology
Surya Mother and Child Care
Mumbai, Maharashtra, India

Veena Kalra
Consultant
Department of Pediatric Neurology
All India Institute of Medical Sciences
New Delhi, India

Akshay Kapoor MD
Consultant
Department of Pediatric
Gastroenterology and Hepatology
Indraprastha Apollo Hospitals
New Delhi, India

Gauri Kapoor MD PhD
Director
Department of Pediatric Hematology
Oncology
Rajiv Gandhi Cancer Institute and
Research Centre
New Delhi, India

Dasmit S Khokar MS MCh FIAPS
Professor
Department of Pediatric Surgery
BJ Medical College and
Sassoon General Hospitals
Pune, Maharashtra, India

Vinayan KP MD DCH DNB DM
Professor and Head
Department of Neurology
Amrita Institute of Medical Sciences
Kochi, Kerala, India

Venkatadass Krishnamoorthy MS DNB
Consultant, Department of Orthopedics
Ganga Hospital
Coimbatore, Tamil Nadu, India

Rakesh Kumar
Professor
Department of Nuclear Medicine
All India Institute of Medical Sciences
New Delhi, India

Rashmi Kumar
Professor and Head
Department of Pediatrics
King George Hospital
Lucknow, Uttar Pradesh, India

Sathish Kumar MD DCH
Professor and Consultant
Department of Pediatrics
Christian Medical College
Vellore, Tamil Nadu, India

Ritabrata Kundu MD FIAP
Professor, Department of Pediatrics
Institute of Child Health
Kolkata, West Bengal, India

PA M Kunju MD DM
Professor and Head
Department of Pediatric Neurology
Government Medical College
Trivandrum, Kerala, India

Lokesh Lingappa MD DM MRCPCH
Consultant, Department of Pediatric
Neurology, Rainbow Children's Hospital
Hyderabad, Telangana, India

Gaurav Mandhan MD FIAP
Associate Consultant
Department of Neonatology
Max Super Specialty Hospital
New Delhi, India

Mamta V Manglani MD DCH
Professor and Head
Department of Pediatrics
Lokmanya Tilak Municipal Medical
College and General Hospital
Mumbai, Maharashtra, India

Mukta Mantan MD DNB
Professor, Department of Pediatrics
Maulana Azad Medical College
New Delhi, India

Manoj G Matnani MD PGDVES PGDMDPN
PGDVIH PGDCH
Consultant
Department of Pediatric Nephrology
KEM Hospital, Jehangir Hospital
Pune, Maharashtra, India
Bombay Hospital
Mumbai, Maharashtra, India

John Matthai DCH MD FAB FIAP
Professor and Head
Department of Pediatrics
PSG Institute of Medical Sciences
Coimbatore, Tamil Nadu, India

Puthezhath SN Menon MD MNAMS
FIAP FIMSA
Consultant and Head
Department of Pediatrics
Jaber Al-Ahmed Armed Forces Hospital
Kuwait, Kuwait

Bhavesh M Mithiya MD
Dip (Pediatrics)
Consultant
Department of Pediatrics
Jupiter Hospital
Kotagiri Medical Fellowship Hospital
Thane, Maharashtra, India

Aparajita Mitra MCh
Senior Resident
Department of Pediatric Surgery
All India Institute of Medical Sciences
New Delhi, India

Monjori Mitra DCH DNB FIAP
Associate Professor
Department of Pediatrics Medicine
Institute of Child Health
Kolkata, West Bengal, India

Rakesh Mondal MD DNB PDSR MNAMS
MRCPCHI
Professor
Department of Pediatric Medicine
Medical College Kolkata
Kolkata, West Bengal, India

Jayashree A Mondkar MD DCH
Professor and Head
Department of Neonatology
Lokmanya Tilak Municipal General
Hospital and Lokmanya Tilak
Municipal Medical College
Mumbai, Maharashtra, India

Anil K Monga MS DORL FCPS
Senior Consultant
Department of Otorhinolaryngology
and Head Neck Surgery
Sir Ganga Ram Hospital
New Delhi, India

Uday Monga MS FAGE
Senior Resident
Department of Otorhinolaryngology
and Head Neck Surgery
Uday ENT Hospital
New Delhi, India

Sangeeta S Mudaliar DNB MRCPCH
Consultant
Department of Hemato-Oncology
B J Wadia Children Hospital
Mumbai, Maharashtra, India

Surpreet BS Nagi DCH
Consultant
Department of Pediatrics
Dr Anands Hospital for Children
Mumbai, Maharashtra, India

Premal Naik MS DNB
Hon. Orthopedic Surgeon
NHL Municipal Medical College
Director, Rainbow Superspeciality
Hospital
Ahmedabad, Gujarat, India

Ruchi Nanawati MD
Professor and Head, Department iof
Neonatology, Seth GS Medical College
and KEM Hospital
Mumbai, Maharashtra, India

Narendra R Nanivadekar MD DCH DNB
Consultant, Department of Pediatrics
Aster Aadhar Hospital
Kolhapur, Maharashtra, India

Nikita MD DNB
Senior Resident
Department of Dermatology and STD
Lady Hardinge Medical College and
Associated Hospitals
New Delhi, India

Somashekhar M Nimbalkar MD
Professor
Department of Pediatrics
Pramukhswami Medical College
Karamsad, Gujarat, India

Raghupathy Palany BSc MD DCH FRCP
Professor
Indira Gandhi Institute of Child Health
Bangalore, Karnataka, India

Nitin Pant MS MCh
Assistant Professor
Department of Pediatric Surgery
Kalawati Saran Children's Hospital
Lady Hardinge Medical College
New Delhi, India

Ankit Parakh MD DNB MNAMS
Consultant
Department of Pediatric Pulmonology
Dr BL Kapur Memorial Hospital
New Delhi, India

Ketan P Parikh MS MCh
Consultant Pediatric Surgeon
Department of Pediatric Surgery
Jaslok Hospital
Mumbai, Maharashtra, India

Mandar B Patil DCH DNB
Assistant Professor
Dr DY Patil Medical College
Kolhapur, Maharashtra, India

Sandeep A Patwardhan MS Orth D Orth
Professor
Department of Pediatric Orthopedics
Sancheti Institute
Pune, Maharashtra, India

Sarah Paul DCH MD
Professor
Department of Pediatrics
PSG Institute of Medical Sciences
Coimbatore, Tamil Nadu, India

Ranjan K Pejaver FRCP FRCPCH FIAP FNNF
Professor, Department of Neonatology
Kempegowda Institute of Medical Sciences
Chief Neonatologist, Meenakshi Hospitals
Bangalore, Karnataka, India

Preetham K Poddutoor Dch DNB
Consultant, Department of Intensive Care, Rainbow Children's Hospital
Hyderabad, Telangana, India

Suhas V Prabhu MD DCH MNAMS
Visiting Consultant
Department of Pediatrics
PD Hinduja Hospital and Medical Research Centre
Mumbai, Maharashtra, India

Baldev S Prajapati MD DPed FIAP FICMCH MNAMS
Professor
Department of Pediatrics
GCS Medical College, Hospital and Research Centre
Ahmedabad, Gujarat, India

Rajal B Prajapati MD DPed
Professor
Department of Pediatrics
Sheth V S General Hospital and AMC MET Medical College
Ahmedabad, Gujarat, India

Prema Raghunathan DNB PGDAP
Professor
Department of Pediatrics
Rajarajeswari Medical College
Bangalore, Karnataka, India

Sarbani S Raha MD
Consultant
Child Neurology and Epilepsy Clinic
Vadodara, Gujarat, India

Devinder Rai MS
Vice Chairman
Department of ENT
Sir Ganga Ram Hospital
New Delhi, India

Anand P Rao MD DNB
Consultant
Department of Pediatric Rheumatology
Manipal Hospital
Bengaluru, Karnataka, India

Narendra Rathi MD DNB MNAMS FIAP
Consultant, Department of Pediatrics
Smile Institute of Child Health
Akola, Maharashtra, India

Aarathi R Rau MD
Professor, Department of Pathology
MS Ramaiah Medical College
Bangalore, Karnataka, India

Suyodhan A Reddy MCh DNB
Associate Professor
Department of Pediatric Surgery
BJ Wadia Hospital for Children
Mumbai, Maharashtra, India

Arun G Roy MD DM
Professor
Department of Neurology
Amrita Institute of Medical Sciences
Kochi, Kerala, India

Tapas K Sabui MD
Professor
Department of Pediatric Medicine
RG Kar Medical College
Kolkata, West Bengal, India

Anupam Sachdeva MD DCH
Chariman, Institute of Child Health
Sir Ganga Ram Hospital
New Delhi, India

Abhijeet Saha MD IMS BHU
Associate Professor
Department of Pediatrics
Post Graduate Institute of Medical Education and Research
Dr Ram Manohar Lohia Hospital
New Delhi, India

Bhaskar Saikia MD
Consultant
Max Superspeciality Hospital
New Delhi, India

VK Sairam AB (Ped) AB (Ped. Neph)
Pediatric Nephrologist
Kanchi Kamacoti Childs Trust Hospital
Chennai, Tamil Nadu, India

Dilip Samal
Senior Resident, Department of ENT and Head Neck Surgery Medanta Medicity
Gurgaon, Haryana, India

Jayanth S Sampath MSc FRCSEd
Consultant and Director
Bangalore Institute of Movement Research and Analysis
Bangalore, Karnataka, India

Viraj V Sanghi MD DNB
Consultant, Department of Neurology
Bombay Hospital and Medical Research Centre
Saifee Hospital
Ika Children's Centre
Mumbai, Maharashtra,India

Sarita Sanke MD
Postgraduate
Department of Dermatology and STD
Lady Hardinge Medical College
New Delhi, India

Naveen Sankhyan
Assistant Professor
Department of Pediatric Neurology
Postgraduate Institute of Medical Education and Research
Chandigarh, India

Vijaya Sarathi MD DM
Assistant Professor
Department of Endocrinology
Vydehi Institute of Medical Sciences and Research Center
Bengaluru, Karnataka, India

Moinak S Sarma MD DM
Senior Research Associate
Department of Pediatric Gastroenterology
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Kiran P Sathe DCH DNB
Associate Consultant, Department of Pediatrics and Pediatric Nephrology
Sir HN Reliance Foundation Hospital
Mumbai, Maharashtra, India

Veeraraja B Sathenahalli MD
Assistant Professor
Department of Pediatrics, Jagadguru Jayadeva Murugarajendra Medical College
Davanagere, Karnataka, India

Malathi Sathiyasekaran MD DCH MNAMS DM
Consultant
Department of Gastroenterology
Kanchi Kamakoti CHILDS Trust Hospital and Sundaram Medical Foundation
Chennai, Tamil Nadu, India

Tulika Seth MD ABP
Additional Professor
Department of Hematology
All India Institute of Medical Sciences
New Delhi, India

Ira Shah MD DCH FCPS DNB DPID
Associate Professor
Bai Jerbai Wadia Hospital for Children
Consultant, Department of Pediatric Infectious Diseases and Pediatric Hepatology, Nanavati Hospital
Mumbai, Maharashtra, India

Mehul A Shah MD DCH MD DABPN
Consultant, Department of Pediatric Nephrology, Apollo Health City
Hyderabad, Telangana, India

Raju C Shah MD DPed FIAP
Professor, Department of Pediatrics
Ankur Institute of Child Health
Ahmedabad, Gujarat, India

Jyoti Sharma MD DNB
Consultant
Department of Pediatric Nephrology
King Edward Memorial Hospital
Pune, Maharashtra, India

Pradeep K Sharma MD
Consultant
Sri Balaji Action Medical Institute
New Delhi, India

Sangeetha Shenoy MD
Associate Professor
Department of Pediatrics
MS Ramaiah Medical College
Bangalore, Karnataka, India

Viraj Shingade MS DNB
Director
Children Orthopedic Care Institute
Pravira Hospital
Nagpur, Maharashtra, India

Roli M Srivastava DCH PGDAP
Research Officer
Department of Obstetrics and Gynecology
Ganesh Shankar Vidyarthi Memorial Medical College
Kanpur, Uttar Pradesh, India

Poonam Sidana MD
Senior Consultant
Department of Pediatrics
Max Super Specialty Hospital
New Delhi, India

Sirisharani Siddaiahgari MD DNB MRCPCH
Consultant, Department of Pediatric Hematology Oncology
Rainbow Children's Hospital
Hyderabad, Telangana, India

Aashim Singh MBBS
Junior Resident
Department of Dermatology
Lady Hardinge Medical College and Associated Hospitals
New Delhi, India

Manav D Singh MS
Associate Professor
Department of Ophthalmology
Postgraduate Institute of Medical Education and Research and Dr Ram Manohar Lohia Hospital
New Delhi, India

Preeti Singh MD
Assistant Professor
Department of Pediatrics
Lady Hardinge Medical College and associated Hospitals
New Delhi, India

Noopur Singhal MD
Senior Resident
Department of Pediatrics
Post Graduate Institute of Medical Education and Research
Dr Ram Manohar Lohia Hospital
New Delhi, India

Pratibha D Singhi MD
Professor, Department of Pediatrics
Post Graduate Institute of Medical Education and Research
Chandigarh, India

Anshu Srivastava MD DM
Additional Professor
Department of Pediatric Gastroenterology
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow, Uttar Pradesh, India

Anurag M Srivastava MS
Consultant, Rockland Hospital
New Delhi, India

Nidhi Sugandhi MS MCh
Assistant Professor
Department of Pediatric Surgery
Dr Ram Manohar Lohia Hospital and
Post Graduate Institute of Medical
Education and Research
New Delhi, India

Balasubramanian Sundaram MD DCH
MAMS FIAP FRCPCH
Senior Consultant, Department of
Pediatrics, Kanchi Kamakoti Childs Trust
Hospital and The Child's Trust Medical
Research Foundation
Chennai, Tamil Nadu, India

Deepti Suri MD DNB
Associate Professor
Department of Pediatrics
Postgraduate Institute of Medical
Education and Research
Chandigarh, India

Rhishikesh P Thakre DM MD DNB DCH
FCPS
Professor
Department of Pediatrics
MGM College and Hospital
Director, Neonatology Division
Neo Clinic and Hospital
Aurangabad, Maharashtra, India

S Thangavelu MD DCH DNB MRCP
Senior Consultant and Director
Department of Pediatrics
Mehta Children's Hospitals
Chennai, Tamil Nadu, India

Soumya Tiwari MD
Assistant Professor
Department of Pediatrics
Kalawati Saran Children's hospital
Lady Hardinge Medical College
New Delhi, India

Alpana A Utture Dch MD DM
Associate Professor
Department of Neonatology
Seth Gordhandas Sunderdas Medical
College and King Edward Memorial
Hospital
Mumbai, Maharashtra, India

Jayakumar Vaikundam MD DCH DM
Senior Consultant and Chairman
JK Institute of Neurology
Madurai, Tamil Nadu, India

Kiran SK Vaswani MD DCH PGD-AP Dip
counselling
Consultant
PULSE Child Care Clinic
Mumbai, Maharashtra, India

Anoop K Verma MD FIAP FIAMS
Pediatrician
Swapnil Nursing Home
Raipur, Chhattisgarh, India

Madhava Vijayakumar MD DCH DNB
Additional Professor
Department of Pediatrics
Government Medical College
Kozhikode, Kerala, India

M Vijayakumar MD DCH DM FIAP
Consultant
Department of Pediatric Nephrology
Mehta Children's Hospital
Chennai, Tamil Nadu, India

Vijay Viswanathan DNB DCH
Consultant, Sandhi Children's Clinic
Jupiter Hospital
MGM Hospital
Dr Yewale's Multispecialty Centre
Mumbai, Maharashtra, India

V Viswanathan DCH MRCP PhD
Senior Consultant
Department of Pediatric Neurology
Kanchi Kamakoti Childs Trust Hospital
Apollo Children's Hospital
Chennai, Tamil Nadu, India

Sanjay Wazir DM
Director - NICU, Department of Pediatrics
Cloudnine Hospital
Gurgaon, Haryana, India

Pravesh Yadav MD
Senior Resident
Department of Dermatology and STD
Lady Hardinge Medical College and
Associated Hospitals
New Delhi, India

M Zulfikar Ahamed MD DM
Professor and Head
Department of Pediatric Cardiology
Government Medical College
Thiruvananthapuram, Kerala, India

Foreword

Pramod Jog MD DNB FIAP
Professor of Pediatrics
DY Patil Medical College
President, Indian Academy of Pediatrics (IAP), 2016
Member, Standing Committee, International Pediatric Association (IPA)
Pune, Maharashtra, India

Publication of any book is a process as laborious as the process of delivering a baby. Maturity (contents and the quality), weight gain (number of pages), and intact survival (final copy) all have to be carefully looked after. More so for a book with 156 chapters running in 19 sections with every chapter having at least one algorithm!

Algorithms in Pediatrics have gone through all these laborious processes and have come out as an exclusive book for pediatricians, giving instant guidelines for treatment, bringing uniformity in management, and training minds for protocolized thinking. With each protocol, the book provides concise, precise, and up-to-date information which shall help standardize care in pediatric practice.

When a practitioner is confronted with a clinical problem, he can rarely turn to a textbook for help. What he needs at that time is not a recounting of a long list of differential diagnosis, but practical guidelines as to how to arrive at a particular diagnosis and how to proceed further.

This book on algorithms intends to enable the pediatrician to recognize many disorders in a simplified manner and give practical suggestions in their management, a learning experience in a structured manner.

To put it in the words of Henry David Thoreau, "Our lives are frittered away by detail; simplify, simplify".

Practicing pediatricians are often faced with clinical problems for which they have been rather inadequately trained during their medical curriculum. Textbooks published from the medically advanced countries do not focus enough attention on the prevailing problems and circumstances in the developing countries such as India. The algorithms in this book have been formed keeping in mind the situations prevailing in India, especially the constraints under which the clinicians here have to practice. The main emphasis has been to provide clear-cut guidelines as to how to make a diagnosis on clinical grounds with minimal investigations and to choose the most rational therapy.

Although, prepared specifically to meet the needs of practicing doctors or those who intend to practice in near future, even pediatric residents would find the book extremely useful while preparing for their viva voce at the diploma or MD exams. The book covers most of those aspects which are practically never taught in the curriculum but are nevertheless expected to be known by pediatric postgraduates. It will also assist the students, house officers, and clinicians in the evaluation of common pediatric signs and symptoms in clinical practice.

With the help of history, focused examination, and minimum investigations, pediatricians in office practice can reach a working diagnosis and lay down immediate priorities in management.

There is rarely a single acceptable approach to any given problem, and not all diagnoses can fit neatly into an algorithm. Even though the protocols cannot be considered all-inclusive, the goal is to facilitate a logical and efficient stepwise approach to reasonable differential diagnoses for the common clinical problems. The algorithmic format provides a rapid and concise stepwise approach to a diagnosis. Moreover, it would train the brain to approach a problem.

The explosion of knowledge in pediatrics is phenomenal and fast. If the medical advances and good clinical practice get coupled with effective advocacy, our increasing knowledge will benefit child care in our country.

I am sure that the algorithms will enhance the capabilities of pediatricians, guiding them towards optimal utilization of available investigative and therapeutic resources.

Preface

It gives us immense pleasure to present to you the 1st edition of "Algorithms in Pediatrics". Pediatrics is rapidly advancing with the growth of its subspecialties. At times, it becomes difficult for busy pediatricians, whether in practice, in teaching institutions, or pursuing their postgraduation, to read through lengthy texts of different subspecialties. Keeping this in mind, we thought of bringing forth this concise book on algorithms, which deals with common and practical topics of everyday requirements in different pediatric specialties.

The book has been designed with a practical approach in mind, with an algorithm for each topic, along with a concise text to use the algorithms. The text has been kept simple and easily comprehendible. The book can be consulted rapidly in the emergency room, wards, outpatient departments, or in busy clinics.

The book contains 19 subspecialty sections, with 8–10 chapters in each, a total of 156 chapters. This was an immense work, which could not have been possible without the help and coordination of the section editors. We are very thankful to all the section editors.

A large number of luminaries and experts in the field of pediatrics and its subspecialties have contributed their mind and might in bringing out this book. We are thankful to all these contributors.

We are also thankful to Jaypee Brothers Medical Publishers (P) Ltd. for publishing this book.

We are also grateful to our respective spouses for being tolerant and supportive of us in this endeavor.

Anand S Vasudev
Nitin K Shah

Contents

Section 3: Immunization

Section Editors: Amar J Chitkara, Jaydeep Choudhury

Section 4: Office Emergencies

Section Editors: Anand Shandilya, Rajesh R Chokhani

Section 5: Intensive Care

Section Editors: Praveen Khilnani, Soonu Udani

Section 6: Infectious Diseases

Section Editors: Shyam Kukreja, Tanu Singhal

Section 11: Neurology

Section Editors: Neelu A Desai, Anaita Udwadia Hegde, Vrajesh Udani

Section 12: Nephrology

Section Editors: Anand S Vasudev, Pankaj V Deshpande

Section 13: Endocrinology

Section Editors: Vaman V Khadilkar, Anju Virmani

Section 14: Rheumatology

Section Editor: Priyankar Pal

Section 15: Pediatric Surgery

Section Editors: Anurag Krishna, Rasik S Shah

Section 16: Dermatology

Section Editor: Vibhu Mendiratta

Section 17: Ophthalmology

Section Editor: Shashi Vashisht

Section 18: Ear, Nose, and Throat

Section Editor: Girish Raheja

Section 19: Orthopedics

Section Editors: Taral V Nagda, Rujuta Mehta

SECTION 1: NEONATOLOGY

CHAPTER 1

Neonatal Resuscitation

Rhishikesh P Thakre

INTRODUCTION

Birth of newborn is a potential medical emergency. Up to half of newborns who require resuscitation have no identifiable risk factors before birth. Preparation and anticipation is the key. All babies need assessment for resuscitation at birth. Up to 10% of babies need some resuscitation and less than 1% need major resuscitation.

STANDARD PRECAUTIONS

All resuscitation should be conducted under strict asepsis. All resuscitation apparatus should be clean and sterile, and where indicated, disposable. Suction catheters, mucus extractor, umbilical catheters, syringes, needles, endotracheal (ET) tubes, feeding tubes should be single use, sterile, and disposable.

PREPARATION PRIOR TO BIRTH

Equipment Check

- All equipment should be available in various sizes for different gestation
- A checklist should be used to ensure that the equipment is functional
- Following equipment are "desirable" for resuscitation: compressed air, blender, continuous positive airway pressure (CPAP), pulse oximeter + probe and plastic wrap.

Personnel

- At every delivery, there should be at least one person whose primary responsibility is the baby and who is capable of initiating resuscitation positive pressure ventilation (PPV) and chest compression (CC). Skilled personnel for complete resuscitation be readily available, if needed
- Two persons or more are required in "high risk" delivery.

Identifying High Risk Delivery

Focused questions (help prepare and anticipate problems during resuscitation) include: (1) What is the gestational age? (2) Is the amniotic fluid clear? (3) How many babies are expected? (4) Are there any additional risk factors?

ASSESSMENT AT BIRTH

Need for resuscitation can generally be identified by a rapid assessment by asking "Is the infant breathing or crying?" If the baby is breathing or crying, the newborn does not require any further resuscitation. Early skin-to-skin contact with mother be practiced and newborn assessed for breathing, color, and activity.

If the baby is not breathing or crying, a series of steps may be needed to establish breathing sequentially performing initial steps, PPV, CC, intubation, and/or administration of drugs.

Assessing the breathing is by observing the baby's chest movements. Breathing is adequate if a baby is vigorously crying or has good regular chest movements with no pauses or indrawing with associated good tone. Gasping or labored breathing should not be mistaken for normal breathing.

CORD CLAMPING

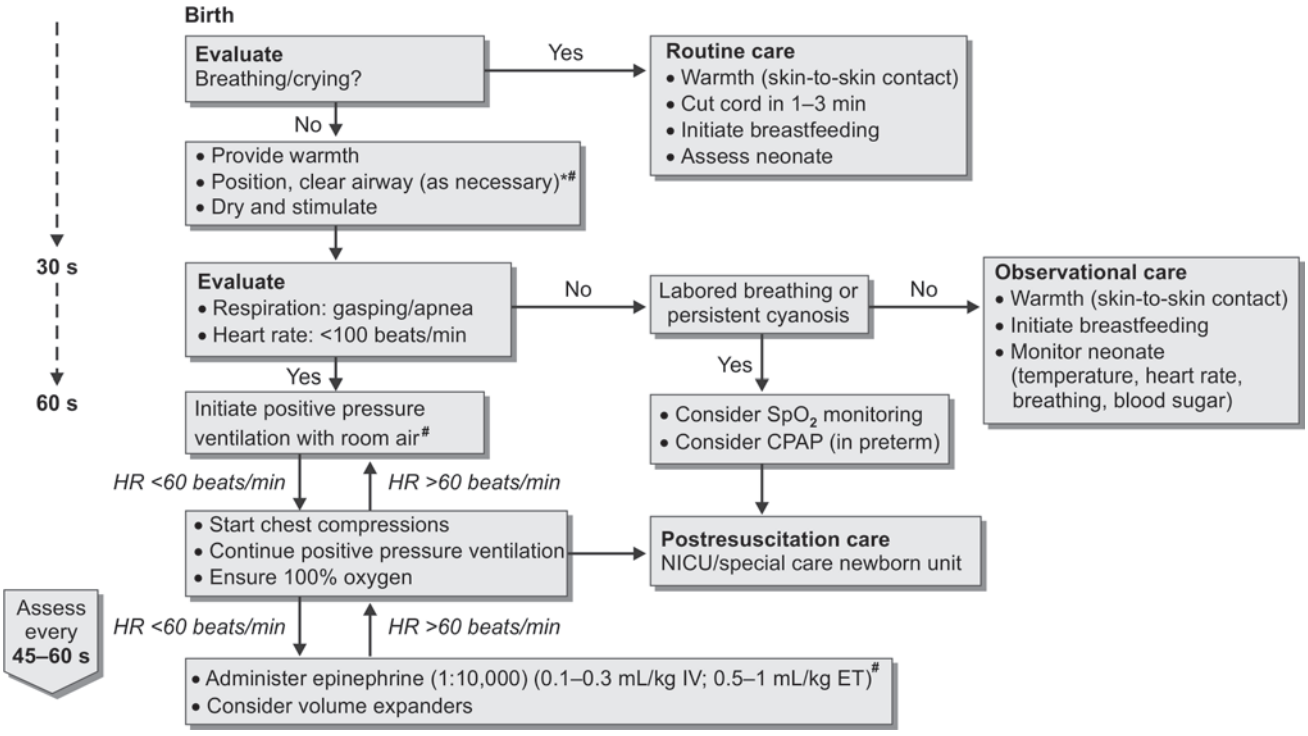
All babies who establish spontaneous respiration at birth should have cord clamping delayed for more than 1 minute. It is a safe procedure in term, preterm, and low birth weight (LBW) babies with improved iron status, higher blood pressures during stabilization, and a lower incidence of intraventricular hemorrhage (IVH) and fewer blood transfusions in preterms.

STEPS IN NEONATAL RESUSCITATION

A baby who is not breathing or crying at birth should undergo following steps of resuscitation with ongoing assessment and reassessment at every step (Algorithm 1).

ALGORITHM 1

Indian Academy of Pediatrics Neonatal Resuscitation Program First Golden Minute algorithm for neonatal resuscitation



*In meconium stained depressed neonates after oral suction, endotracheal suction may be considered.
#Endotracheal intubation may be considered at several steps.
CPAP, continuous positive airway pressure, HR, heart rate; ET, endotracheal; IV, intravenous; NICU, neonatal intensive care unit.

Initial Steps

A baby who is not breathing or crying should be received in dry, prewarmed cloth with immediate cord clamping and placed under a heat source. The head, trunk, and the limbs should be dried firmly and quickly. Suction of mouth followed by nose may be done if there is obvious obstruction to airway. Stimulation is done by rubbing the back or flicking the soles. The newborn is repositioned and simultaneous assessment of respiration and heart rate (HR) is done.

Response to resuscitation is best judged by increasing HR and later by establishment of spontaneous breathing. The HR is easiest and quickest assessed by palpating at the base of umbilical cord, but auscultation of precordium is most reliable.

Positive Pressure Ventilation

Positive pressure ventilation is indicated if the newborn has apnea or gasping respiration, HR less than 100 beats per minute or SpO_2 below target values despite supplemental oxygen being increased to 100%. A flow-inflating bag, a self-inflating bag, or a pressure-limited T-piece resuscitator can be used for PPV. Call for help and ask assistant to apply pulse oximeter, if available, to right hand/wrist of the newborn. In all newborns (term or preterm), PPV should be started with room air. Provide breaths at a rate of 40–60 per minute using "breathe–two-three" and assess for efficacy after 5–10 breaths. Check for rise in HR and oximetry. If there is no HR rise, check for air entry and chest movement. If not, take corrective measures for ventilation—mask reposition, reposition airway, suction, open mouth and ventilate, pressure increase, and consider alternate airway measures (MRSOPA). Heart rate is assessed every 30 seconds. Consider inserting orogastric tube if ventilation is prolonged.

Positive pressure ventilation is discontinued if there is rise in HR greater than 100 beats per minute and onset of spontaneous respiration. If despite adequate PPV, there is no desired response, one may consider intubation or initiate CC if HR is less than 60 beats per minute.

Intubation

Intubation is considered if ventilation is ineffective, newborn is nonvigorous with meconium stained liquor, need for CC, administration of drugs, or suspected congenital diaphragmatic hernia. Intubation is performed in time limit of 30 seconds. There is no role of cuffed ET tubes. Two common and serious errors of ET intubation are malplacement of the ET tube and the use of the wrong sized tubes.

Chest Compression

Heart rate less than 60 beats per minute despite adequate ventilation is indication to start CC. One should ensure that assisted ventilation is being delivered optimally before starting CCs. Consider intubation if CC is to begin. The

2 thumb encircling hands technique may generate higher peak systolic and coronary perfusion pressure than the 2 finger technique, hence the 2 thumb encircling hands technique is recommended for performing CCs in newly born infants. The 2 finger method should be reserved only for brief applications while an emergent umbilical venous catheter is established and then should be converted back to the 2 thumb method. A ratio of three CC to one ventilation is delivered in 2 seconds for uninterrupted 45–60 seconds compressing the 1/3 anteroposterior diameter of the chest and HR is checked every 45–60 seconds.

If the HR less than 60 beats per minute, CC with intubation is continued with administration of adrenaline; if the HR is 60–100 beats per minute, CC is stopped and ventilation continued and if the HR is greater than 100 beats per minute with spontaneous breathing, PPV is discontinued.

Medications

Bradycardia in the newborn infant is usually the result of inadequate lung inflation or profound hypoxemia, and establishing adequate ventilation is the most important step to correct it. Medications are indicated if the HR is less than 60 beats per minute despite 45–60 seconds of adequate CC and ventilation. The preferred mode of drug delivery is umbilical venous route. Epinephrine is administered in 1:10,000 concentration at dose of 0.1–0.3 mL/kg, IV (ET: 0.5–1 mL/kg) as fast as possible. Heart rate is assessed after 1 minute of adrenaline administration.

Volume expanders, normal saline or ringer lactate, 10 mL/kg over 5–10 minutes may be administered if there is no response to resuscitation and signs of poor peripheral perfusion or history suggestive of blood loss. There is no role of naloxone in delivery room. Endotracheal drug administration does not give reliable effects.

PRETERM RESUSCITATION

Additional personnel and equipment are required. Preterm/LBW babies not requiring resuscitation at birth can be kept on mother's chest in skin-to-skin contact for thermoregulation. Ensure the area is preheated using a warmer or portable pad. Food grade, clean, plastic wrapping may be done before drying in less than 32 weeks' gestation as soon as the baby is born to ensure thermal care. If preterm is breathing spontaneously with labored respiration or is cyanotic or low SpO_2, consider initiating CPAP. Gentle handling, avoiding head-down position, avoiding excess pressures of PPV or CPAP, administering surfactant after stabilization, using pulse oximeter as a guide to oxygenation and avoiding rapid infusions are good resuscitation practices.

SPECIAL CIRCUMSTANCES

Meconium Stained Liquor

The resuscitation is based on whether the newborn is vigorous or not. A vigorous infant is defined as one who has strong respiratory efforts, good muscle tone, and a HR greater than 100 beats per minute, and needs no intervention.

A nonvigorous infant needs immediate intubation, under vision tracheal suction skipping the initial steps of resuscitation. If tracheal intubation is unsuccessful or there is severe bradycardia, then proceed to PPV.

Role of Oxygen

Need for oxygen is based on oximetry. Pulse oximeter working on a "signal extraction technique" that is designed to reduce movement artifact with a neonatal probe is ideal. Administration of supplementary oxygen should be regulated by blending oxygen and air, and the concentration delivered is guided by oximetry. Healthy infants born at term may take more than 10 minutes to achieve a preductal oxygen saturation greater than 95% and nearly 1 hour to achieve postductal saturation greater than 95%. If the saturation is less than desired, start supplemental oxygen. Use 100% oxygen if the newborn needs CC. Minute specific oxygen saturation targets for newborns are provided in table 1.

Pneumothorax

Transillumination using a cold light source may be used for diagnosing pneumothorax bedside, if facility exists. In absence of cold light source, use a butterfly with a three way and syringe to tap in the second intercostal space on the suspected side.

Therapeutic Hypothermia

Currently, therapeutic hypothermia is not defined as standard of care in India. However, if facility exists, such therapy may be used but only after taking informed consent from parents.

Resuscitation of Babies Outside Hospital/Home Delivery

Special attention should be paid to maintaining normal temperature of the baby by closing the windows to prevent draughts, use dry warm cloth, baby cap, and skin-to-skin contact. Resuscitation can also be performed keeping baby on mother's abdomen. Baby should be transferred to facility in skin-to-skin contact with mother.

To Resuscitate or Not

The decision of when not to resuscitate or how much to resuscitate is complex. Such decisions are best made with

TABLE 1: Target oxygen saturation

Time (min)	Preductal SpO_2 after birth
1	60–65%
2	65–70%
3	70–75%
4	75–80%
5	80–85%
10	85–95%

an understanding of the relevant neonatal data and ethical issues, including the rights of the newborn and the parents. The ideal situation is one where the healthcare team and family come together and make the best possible decision for all involved.

POSTRESUSCITATION CARE

The postresuscitation care has been described in table 2.

HARMFUL PRACTICES IN NEWBORN RESUSCITATION

- Routine suction of mouth and nose
- Routine stomach-wash of the baby
- Prolonged flicking the soles or rubbing or slapping the back when baby is depressed
- Putting the baby upside down for postural drainage.

TABLE 2: Postresuscitation care

	Routine care	Observational care	Postresuscitation care
When?	For all spontaneous breathing newborns not requiring resuscitation	Post initial steps or brief positive pressure ventilation (<1 min)	Post positive pressure ventilation (>1 min), need for chest compressions, intubation or drugs
Where?	Mother	Supervised in nursery	Neonatal intensive care unit
Care?	Assess for color, activity, and breathing	Observe for temperature, respiration, heart rate, blood sugar	Sick newborn care and monitoring

Clinical Pearls

- Failing to prepare is preparing to fail. Personnel and equipment preparation is essential
- Discontinuation of resuscitative efforts may be appropriate if resuscitation of an infant with cardiac arrest does not result in spontaneous circulation within 10 minutes
- Use of pulse oximetry is desirable in following conditions: anticipated need for resuscitation, positive pressure ventilation, supplemental oxygen, continuous positive airway pressure, evaluation of cyanosis
- Free-flow oxygen can be delivered by holding tube near the nostrils, using face mask and flow-inflating bag. It cannot be delivered by self-inflating bag.

KEY POINTS

- ☞ Rapid assessment for need for resuscitation and initial steps should be performed within 30 seconds and positive pressure ventilation initiated not later than 60 seconds of life constitutes the "golden minute"
- ☞ The most sensitive measure of response to resuscitation is prompt improvement in heart rate
- ☞ The most important and effective step in resuscitation is ventilation
- ☞ Initiate resuscitation with room air for all newborns
- ☞ Cord clamping should be delayed for atleast 1 minute in babies not requiring resuscitation.

SUGGESTED READINGS

1. NRP Addendum. Consensus document by IAP NNF NRP India Task Force (2012).
2. Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, et al. Part 11: neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010;122 (Suppl 2):S516-38.

CHAPTER 2

Apnea

Naveen Jain

INTRODUCTION

Apnea is a common problem in clinical practice of pediatricians managing preterm babies. It is a symptom of serious concern as timely intervention may be necessary to prevent death/serious hypoxia and associated morbidities. Many apnea events or a single serious apnea event may lead the clinician to investigate extensively and initiate empirical therapies ranging from antibiotics to treatment for reflux. A clinical approach guideline may optimize interventions.

Cessation of breathing lasting long enough (defined as >20 seconds, but time never measured in clinical practice!) to cause hypoxia (saturation <80%), bradycardia [heart rate (HR) <100 beats per minute] or poor perfusion or poor tone.

CLINICAL EVALUATION

Apnea is always a life-threatening emergency and treatment (resuscitation) precedes evaluation. In practice, good observation is possible only after resuscitation. Classical description of apnea has been central/obstructive and mixed based on whether baby is breathing or not at the time of apnea.

However, it is more useful to classify babies as:

- Well preterm baby with apnea: possibly apnea of prematurity (AOP)
- Sick baby with apnea: one who has low saturations and needs oxygen to saturate even after effective breathing is established and has either poor sensorium or tone, poor perfusion, abnormalities of glucose, temperature instability, or feed intolerance. Apnea in this circumstance is usually secondary to a cause, i.e., symptomatic apnea and needs specific investigation and treatment.

Apnea of prematurity needs only stimulation of respiratory center with xanthines. Symptomatic apnea may also benefit with the xanthines/continuous positive airway pressure (CPAP)/nasal intermittent mandatory ventilation (NIMV), but treatment of primary cause is more important. Recurrent and severe apnea may require intubation and ventilation in both situations.

Clinical Pearls

- Is the baby completely well after the apnea (apnea of prematurity likely)
- Or does the baby still need oxygen to saturate, has poor sensorium or activity, hypo-/hyperthermia, poor perfusion, abnormal sugars—look for a cause and treat.

COMMON CAUSES OF APNEA

- Pneumonia, sepsis, necrotizing enterocolitis
- Central causes: perinatal asphyxia, seizures, birth trauma, meningitis, intracranial hemorrhage [intraventricular hemorrhage (IVH), subdural hemorrhage], periventricular leukomalacia (PVL), and hydrocephalus
- Hypoglycemia
- Dyselectrolytemia: hyponatremia, hypocalcemia, hypokalemia
- Anemia
- Hypo- and hyperthermia
- Airway obstruction
- Drug toxicity, e.g., phenobarbitone
- Cardiac causes: patent ductus arteriosus (PDA).

DIFFERENTIAL DIAGNOSIS

- Periodic breathing (cessation of breathing with no cyanosis or bradycardia)
- Subtle seizures
- Gastroesophageal reflux disease (GERD)

INVESTIGATIONS

Based on the expected cause, investigations should be planned:

- Blood sugar, serum electrolytes, and serum calcium
- Sepsis screen including blood culture
- Hemoglobin for anemia

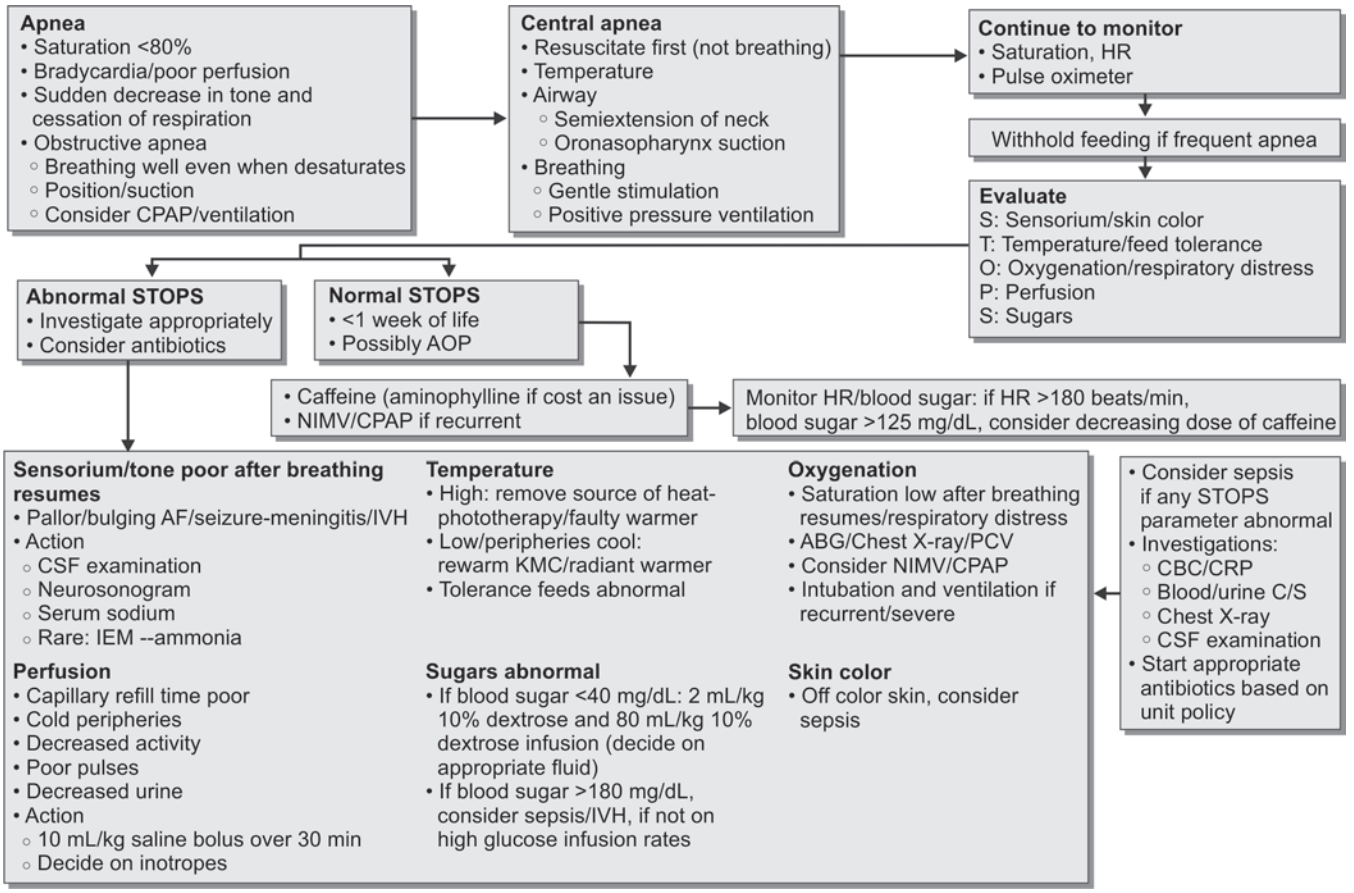
- Ultrasonography head to rule out IVH, PVL, and hydrocephalus
- Echocardiography to rule out PDA
- Chest X-ray for pneumonia
- Serum phenobarbitone level
- Arterial blood gas.

MANAGEMENT (ALGORITHM 1)

- Emergency:
  - Warmth, airway, position to semiextension of neck, and suction of oronasopharynx
  - Gentle stimulation of sole or rubbing back followed by positive pressure ventilation (PPV) if no respiration after simulation (as in Neonatal Resuscitation Program)
- Oxygen, if baby is hypoxic, to maintain SpO_2 in the range of 90–95%
- Temporarily withhold feeds
- Right lateral position with head elevated in suspected GERD
- Methylxanthines (caffeine and aminophylline): these are adenosine receptor antagonists and are primarily used in AOP
  - Caffeine (Standard dose regime) 10 mg/kg of caffeine base as loading dose over 30 minutes followed by 5 mg/kg/day of caffeine base in once a day dose regimen reduces apnea. To be continued till baby is apnea free for 7 days or more than 34 weeks postconceptional age. Caffeine may also be used in periextubation period to reduce the need for reintubation in very low birth weight babies. High dose up to 20 mg/kg/day has not been reported to have any adverse effects on neurodevelopment
  - Aminophylline (Loading dose) 8 mg/kg intravenous infusion over 30 minutes followed by 1.5–3 mg/kg per dose every 8–12 hourly. Caffeine is the preferred drug because of higher therapeutic safety, more reliable enteral absorption, less fluctuation of plasma levels owing to its long half-life, ease of administration (once daily), and few peripheral side effects like

ALGORITHM 1

Management of newborn with apnea



CPAP, continuous positive airway pressure; HR, heart rate; AOP, apnea of prematurity; NIMV, nasal intermittent mandatory ventilation; AF, anterior fontanelle; IVH, intraventricular hemorrhage; IEM, inborn error of metabolism; CBC, complete blood count; CRP, C-reactive protein; KMC, kangaroo mother care; ABG, arterial blood gas; PCV, packed cell volume.

tachycardia and feed intolerance as compared to aminophylline
  - Use of caffeine in babies less than 1,250 g or less than 28 weeks of gestation has been shown to decrease bronchopulmonary dysplasia and survival with better neurodevelopmental outcome at 18 months of corrected age. There is no role of prophylactic use of either aminophylline or caffeine in the prevention of AOP. Caffeine may have action for days after stopping, and babies must be monitored in hospital for recurrence of apnea for 5–7 days after stopping caffeine

Clinical Pearls

- Caffeine/aminophylline may decrease incidence and severity of apnea episodes; this must not delay investigating for a cause or planning for continuous positive airway pressure/ventilation
- Aminophylline is similar in effectiveness; close monitoring for tachycardia and feed intolerance may be required (most centers are not monitoring drug levels in India) if cost limits use of caffeine.

- Continuous positive airway pressure: continuous positive airway pressure should be used in apnea if xanthines fail. Continuous positive airway pressure is the preferred mode of treatment if baby has retractions or need for oxygen in addition to apnea. Postextubation CPAP reduces chances of extubation failure due to apnea
- High flow nasal cannula: flow of gases greater than 2 L/min produces CPAP like benefit. The mixture of air and oxygen should be warmed and humidified
- Noninvasive ventilation with nasal prongs in the form of NIMV and synchronized NIMV
- Intubation and ventilation: if the baby has frequent apnea on CPAP and NIMV, intubation and mechanical ventilation should be considered
- Supportive care:
  - Transfusion of packed red blood cells: if packed cell volume less than 30% and no other evident cause of apnea
  - Antibiotics should be initiated in all sick babies with apnea, and pending reports of blood culture.

AREAS OF UNCERTAINTY IN CLINICAL PRACTICE

- The duration and frequency of apneas that can be safely tolerated
- Effect of treated and untreated apneas on neurodevelopment.

KEY POINTS

- ☞ It is important to differentiate if the baby looks well or not
- ☞ A well baby is likely to have apnea of prematurity
- ☞ Investigations are required in a sick baby to find other causes of apnea.

SUGGESTED READINGS

1. Butcher-Puech MC, Henderson-Smart DJ, Holley D, Lacey JL, Edwards DA. Relation between apnoea duration and type and neurological status of preterm infants. Arch Dis Child. 1985;60(10):953-8.
2. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Cochrane Database Syst Rev. 2010;(12):CD000140.
3. Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. Cochrane Database Syst Rev. 2010;(12):CD000432.
4. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev. 2010;20(1):CD000273.

CHAPTER 3

Respiratory Distress in Newborn

Reeta Bora

INTRODUCTION

Respiratory distress is a common problem in newborn and is encountered in almost 6–7% of neonates. The clinical presentation of respiratory distress in the newborn includes tachypnea (respiratory rate of >60 breaths per min), retraction of chest (intercostals, subcostal, or supraclavicular), grunting, cyanosis, inspiratory stridor, and nasal flaring. However, conventionally, presence of any two out of retraction, grunt, and tachypnea is defined as respiratory distress. There are many conditions in newborn which can lead to respiratory distress and many of them are preventable. Some of them last for few hours only while some may be persistent and if not managed urgently, may lead to death. Early recognition and management is necessary to prevent mortality and to decrease morbidity.

COMMON CAUSES OF RESPIRATORY DISTRESS IN NEWBORN

Preterm Baby

- Pulmonary:
  - Respiratory distress syndrome (RDS) (hyaline membrane disease)
  - Congenital pneumonia
  - Aspiration pneumonia
  - Transient tachypnea of newborn (TTNB)
- Cardiac:
  - Congenital heart disease
  - Myocardial dysfunction
- Central nervous system:
  - Asphyxia
  - Intraventricular hemorrhage
- Metabolic:
  - Hypoglycemia
  - Acidosis
  - Hypothermia
- Surgical causes: pneumothorax, congenital malformation like tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, Pierre-Robin syndrome.

Term Baby

- Pulmonary:
  - Transient tachypnea of newborn
  - Meconium aspiration syndrome (MAS)
  - Congenital and acquired pneumonia
- Cardiac, central nervous system, metabolic, and surgical causes are similar to those of preterm babies.

APPROACH TO A NEONATE WITH RESPIRATORY DISTRESS

History

A detailed good history is very important to come to a diagnosis. It is important to know if the baby is a term (>37 completed weeks of gestational age) or a preterm baby (<37 weeks of gestation). If preterm, the exact gestational age helps us to assess the risk of RDS or hyaline membrane disease. It is important to know in case of preterm baby whether antenatal steroid has been received or not. If there is history of prolonged rupture of membrane, congenital pneumonia should be suspected. History of diabetes mellitus in mother in a preterm, late preterm, or term baby may be indicator of hyaline membrane disease; similarly, history of meconium stained liquor with poor Apgar score and distress soon after birth would indicate MAS. The importance of determining the time of onset of distress needs to be emphasized, as this may vary depending upon the etiology. Respiratory distress syndrome, TTNB, and MAS are some conditions which would present in a neonate soon after birth. If feeding problems are present, such as choking or aspiration during a feed, and distress occurred after some duration after birth, aspiration pneumonia may be thought of as a cause. Congenital heart disease usually

manifests with symptoms like respiratory distress after some duration after birth; acquired pneumonias will also manifest later than 48 hours after birth.

Clinical Examination

The neonate should then be assessed for severity of respiratory distress, any associated neurological signs like level of alertness, bulged fontanelle, tone anomaly, etc. One should also look for any signs suggestive of cardiac problem like prolonged capillary refill time, poor pulse volume, a hepatomegaly, presence of any murmur, and any abnormality in blood pressure. Any signs indicating presence of sepsis should be looked for. If malformations are present in any part of body, it may indicate a surgical cause or a cardiac cause as the possibility for respiratory distress. Excessive frothing with inability to pass a feeding tube may indicate presence of tracheoesophageal fistula while deterioration of a baby on bag and mask ventilation and associated scaphoid shape of abdomen would indicate presence of diaphragmatic hernia. In a dehydrated baby, metabolic acidosis may be the cause. History of meconium stained liquor, and on clinical examination, meconium staining of nails, skin, umbilicus, etc. with a hyperinflated chest would indicate MAS.

Clinical Pearl

- A detailed history and clinical examination is very important to find the cause of respiratory distress in a newborn.

The Downes' score is commonly used for assessing severity of respiratory distress objectively in a newborn as well as to assess whether baby is improving or deteriorating later on (Table 1).

A score of 6 or more indicates severe respiratory distress and impending failure with need for respiratory support. A score of less than 6 indicates respiratory distress and may indicate oxygen supplementation with a hood and a score of 4–6 indicates moderate respiratory distress with need for support with continuous positive airway pressure (CPAP).

Investigations

Based on probable diagnosis reached after thorough history and clinical examination, investigations need to be planned to confirm diagnosis. If history of prolonged rupture of membrane is present in a neonate with respiratory distress, sepsis screen which includes estimation of total leukocyte count, absolute neutrophil count, estimation of C-reactive protein level, band cell count and micro-erythrocyte sedimentation rate, and blood culture needs to be done. Shake test should be done if RDS is suspected. Shake test is a simple bedside test and should be done in preterm babies with respiratory distress, especially if there is no history of administration of antenatal steroid. The gastric aspirate (0.5 mL) is mixed with 0.5 mL of absolute alcohol in test tube. This is shaken for 15 seconds and allowed to stand for 15 minutes. A negative shake test, i.e., no bubbles or bubbles covering less than one-third of the rim indicates a high risk of developing RDS and the presence of bubbles at more than two-third of the rim indicates lung maturity and decreased risk of developing RDS. A chest X-ray helps to differentiate different conditions like RDS, TTNB, MAS, pneumonia, and different surgical conditions like tracheoesophageal fistula and diaphragmatic hernia (Figs 1 to 5). Cardiomegaly in chest X-ray may indicate cardiac abnormality as a cause of respiratory distress. An arterial blood gas (ABG) helps further in establishing diagnosis.

TABLE 1: Score for respiratory distress (Downes' score)

Score	0	1	2
Respiratory rate	<60	60–80	>80
Central cyanosis	None	None with 40% FiO_2	Need >40% FiO_2
Retractions	None	Mild	Severe
Grunting	None	Minimal	Obvious
Air entry	Good	Decreased	Very poor

MANAGEMENT (ALGORITHM 1)

General Management

Irrespective of cause, the principles of supportive therapy for respiratory distress in newborn is same and crucial in all. All babies with respiratory distress would need constant monitoring. The parameters to be monitored to find whether baby is improving or deteriorating with any indication for respiratory support are the respiratory rate, presence of grunting, chest indrawing, or any episode of apnea. Babies should be assessed for Downes' score at intervals to access improvement or deterioration. Monitoring should be

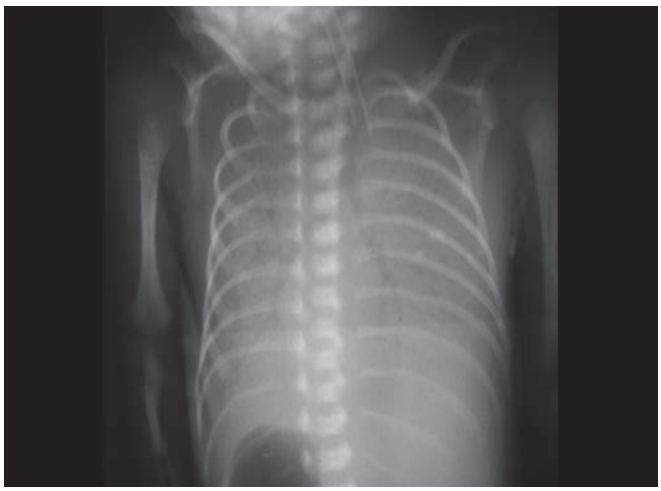


Fig. 1: Chest X-ray anteroposterior view of a premature baby showing respiratory distress syndrome, with bilateral lung fields showing ground glass appearance (RDS) with air bronchogram. If a preterm baby has respiratory distress within the first 6 hours of birth and is cyanosed or needs oxygen to maintain oxygen saturation, the diagnosis is RDS unless proved otherwise. X-ray findings would be a reticulogranular pattern in mild disease and a "white out" picture in severe disease.

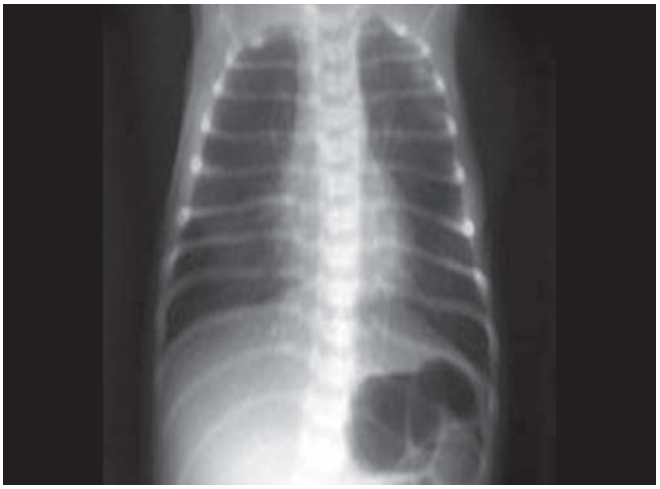


Fig. 2: Chest X-ray showing hyperinflation of lung fields, bilateral streaky opacities radiating from hilum and fluid in the horizontal fissure of right lung suggestive of transient tachypnea of newborn. Transient tachypnea of the newborn is a benign condition usually seen in term babies born by cesarean section. These babies are well and have only tachypnea with rates as high as 80–100breaths per minute. The breathing is shallow and rapid without any significant chest retractions. It occurs because of delayed clearance of lung fluid. Management is supportive and prognosis is excellent.

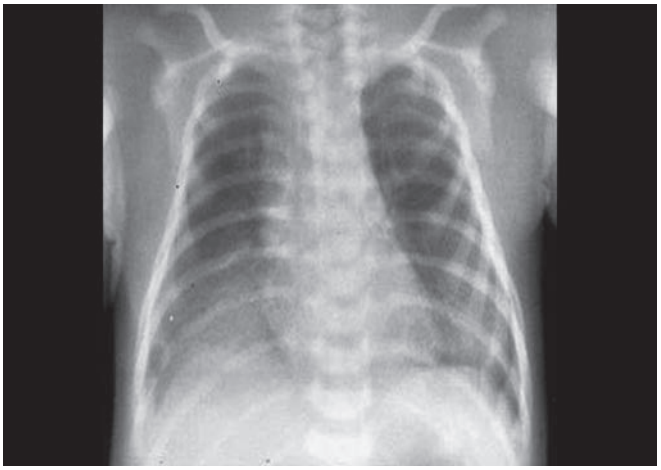


Fig. 3: Chest X-ray showing infiltrates in right lower lung which is asymmetrical bilaterally with history of prolonged rupture of membrane, suggesting congenital pneumonia. In developing countries, pneumonias account for more than 50% cases of respiratory distress in newborn. In congenital pneumonia, respiratory distress is noticed soon after birth or during first 24 hours. Auscultatory signs may be nonspecific. The newborn may die from pneumonia without manifesting distress. Neonates may develop pneumonia postnatally as a consequence of septicemia, aspiration of feeds, and ventilation for respiratory failure.

continued till baby no longer requires oxygen for at least a minimum period of 24 hours.

Based on severity of respiratory distress, baby would require oxygen (Downes' score 1–3), continuous positive pressure ventilation (Downes' 4–6), or mechanical ventilation (Downes' score >6). Oxygen can be provided with oxygen hood

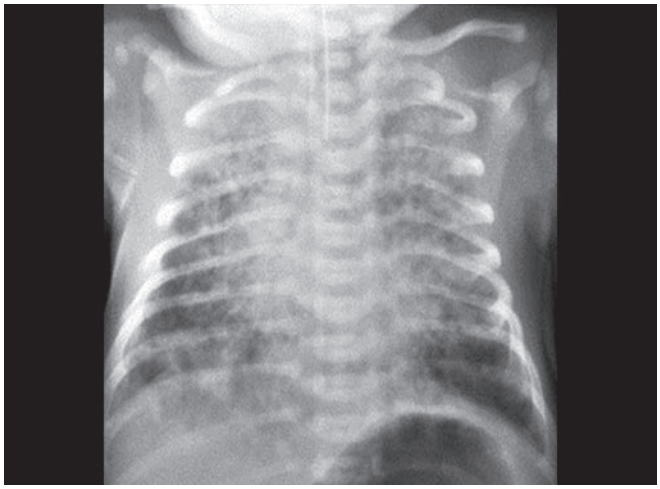


Fig. 4: Patchy opacities with intermittent hyperlucent areas suggestive of air entrapment are seen in MAS. Babies born through meconium stained liquor could have meconium aspiration syndrome (MAS) and aspiration may occur *in utero*, during delivery or immediately after birth. Thick meconium could block air passages and cause atelectasis and air leak syndromes.

or nasal cannula for achieving appropriate oxygen saturation (88–92% in preterm and 90–93% in term). Oxygen when given therapeutically should always be warmed and humidified. When oxygen hood is used for administering oxygen, oxygen flow rate should be 5–6 L/min. Flow rate less than 3 L/min is not appropriate as may lead to carbon dioxide rebreathing. If an oxygen hood is used with all side ports closed and flow rate of 5 L/min, the baby would receive around 80% oxygen, if one side port is kept open with same flow rate, baby would receive 60% oxygen while baby would receive 40% oxygen if both side ports are kept open. The percentage of oxygen needed by baby can be determined by oxygen saturation reading shown in pulse oximeter. The aim should be to maintain oxygen saturation in the range of 90–94%. Another useful method of providing oxygen is nasal prongs. Appropriate sized prongs which fit into neonate's nostrils should be used. If baby's oxygen saturation is acceptable, we can slowly wean off oxygen.

Clinical Pearl

- During oxygen therapy, percentage of oxygen needed should be determined in a neonate by oxygen saturation reading in a pulse oximeter. Oxygen is a drug and overdose should be avoided. Target SpO_2 should be 90–94% in neonates.

The body temperature of the neonate should be maintained in normal range (36.5–37.5°C). Fluid and electrolyte balance should be maintained. If baby is having moderate-to-severe respiratory distress, baby can be maintained on intravenous fluid. If mild respiratory distress is there, as assessed by Downes' score, baby can be fed expressed breast milk by tube feeding. Blood sugar should be monitored and kept in normal range (40–125 mg/dL). If baby has apnea, baby should be stimulated

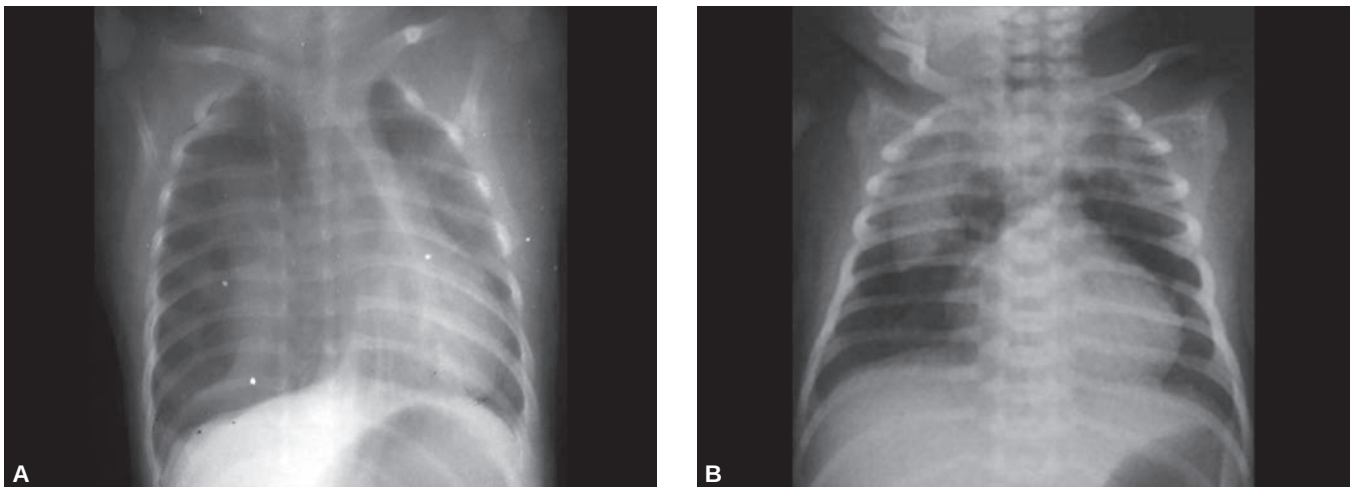
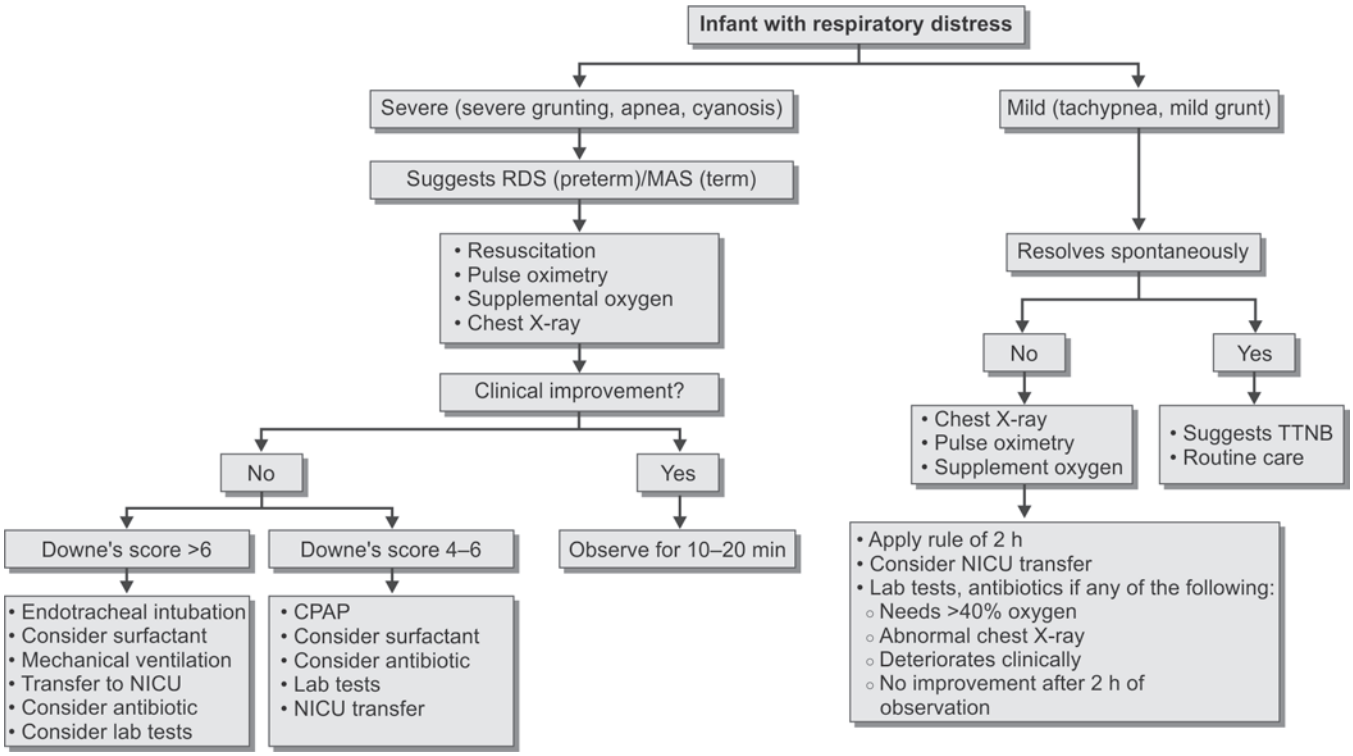


Fig. 5: Showing presence of pneumothorax on chest X-ray **A,** Right sided pneumothorax and **B,** bilateral pneumothorax. Pneumothorax in neonates could be spontaneous but is more often due to meconium aspiration syndrome or staphylococcal pneumonia. It is important to recognize pneumothorax because quick recognition and prompt treatment could be life-saving. The distress is usually sudden in onset and heart sounds become less distinct. Immediate management in hemodynamically unstable neonate is by a needle aspiration and later chest tube drainage.

ALGORITHM 1

Management of neonatal respiratory distress



MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome; TTNB, transient tachypnea of newborn; CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit.

by providing tactile stimulation or positive pressure ventilation by bag and mask. Repeated episodes might indicate need for CPAP or mechanical ventilation, if severe. Such babies would need transfer to centers with facility for CPAP or mechanical ventilation if these are not available locally.

All babies with respiratory distress do not need antibiotics. Babies with TTNB do not need antibiotics. However, if respiratory distress is persistent or risk factors for sepsis are present, antibiotics should be started after taking cultures. If cultures come negative and clinically baby does not seem to have infection, antibiotics can be stopped.

Continuous positive airway pressure is indicated for neonates with respiratory distress if Downes' score is 4–6. Experience is required for the successful application of CPAP,

especially with short binasal prongs. Single prong method may be beneficial for nurseries who have less experience with short binasal prongs or when application of short binasal prongs is problematic. While commencing CPAP, it can be given at a pressure of 6–8 cm of water with sufficient oxygen to maintain target saturation. An orogastric tube needs to be passed to decompress the stomach. While baby is on CPAP, continuous monitoring of saturation, heart rate, respiratory rate is indicated. Blood gases are indicated when pressures or oxygen percentage are changed or patient's condition shows some change. The circuit integrity should be checked periodically.

Clinical Pearl

- Downes' score of 4–6 is an indication for continuous positive airway pressure. A score of greater than 6 is an indication for mechanical ventilation.

Baby's improvement would be indicated by reduction in respiratory rate, stabilization or reduction of oxygen requirement to maintain saturation of 92–95%, reduction in sternal and intercostal retraction, reduction in grunt, and improved ABG reports. The need for CPAP for acute lung conditions usually lasts for 1–3 days.

Weaning is commenced when saturation is more than 96%, retraction, grunt disappears, and respiratory rate stabilizes with normal blood gas reports. While weaning, initially FiO_2 is brought down and then pressure is reduced by 1–2 cm/h until a pressure of 5 cm is reached. When neonate is stabilized in 21% oxygen and 5 cm H_2O, ceasing CPAP is considered. However, recommencing CPAP may be needed at times if work of breathing is increased or oxygen requirement increases. Complications of CPAP, like pneumothorax, must be excluded in such babies.

Continuous positive airway pressure is said to be failed if there is rapid rise for oxygen requirement, respiratory acidosis or partial pressure of carbon dioxide greater than 60 mmHg, recurrent apnea and increased work of breathing indicated by excessive retraction grunt and retraction, or if agitation is not relieved.

There can be at times complications of CPAP like pneumothorax, nasal trauma or CPAP belly, i.e., distension of abdomen.

If CPAP fails or Downes' score is more than 6, there is need for mechanical ventilation.

Specific Management

In case of pneumonia, antibiotic is indicated. Antibiotic of choice should be based on local antibiotic sensitivity pattern. In case of hyaline membrane disease, surfactant replacement therapy is indicated. If pneumothorax occurs, needle decompression or chest tube drainage may be required. Small pneumothoraces can be treated in term infants without invasive management through nitrogen washout. Administration of 100% oxygen can accelerate the resolution of the pneumothorax as readily absorbed oxygen replaces nitrogen in the extrapulmonary space. Neonates with respiratory distress due to surgical conditions, like tracheoesophageal fistula, diaphragmatic hernia, etc., would need surgical intervention. Respiratory distress due to cardiac failure would need management of cardiac failure.

KEY POINTS

- ☞ Respiratory distress occurs in 6–7% of all neonates
- ☞ Early identification and appropriate and timely management is the key to success in management
- ☞ Oxygen saturation in pulse oximeter should be maintained at 90–94%
- ☞ Oxygen should be used judiciously and overdose should be avoided
- ☞ Antibiotic use is not indicated in all patients with respiratory distress.

SUGGESTED READINGS

1. Facility based care of sick neonate at referral health facility. Participant's manual. National Neonatology Forum and UNICEF, 2008.
2. Frey B, Shan F. Oxygen administration in infants. Arch Dis Child Fetal Neonatal Ed. 2003;88:F84-8.
3. Hein HH, Ely JW, Lofgren MA. Neonatal respiratory distress in the community hospital: when to transport, when to keep. J Fam Pract. 1998;46:284-9.
4. Hermansen CL, Lorah KM. Respiratory distress in newborn. Am Fam Physician. 2007;76:987-94.

CHAPTER 4

Respiratory Support in Newborns

Jayashree A Mondkar, Alpana A Utture

INTRODUCTION

Respiratory disorders are one of the commonest reasons for admission to the neonatal unit. Innovations in neonatal respiratory care over the past few decades resulting in the availability of a number of noninvasive and invasive modalities of therapy have revolutionized the management of babies with respiratory disorders, especially the very low birth weight (VLBW) group.

The aims of respiratory support are to maintain adequate oxygenation and ventilation, to reduce respiratory work and to prevent lung injury.

The modalities of respiratory support commonly available in our neonatal intensive care units (NICUs) include:

Oxygen Therapy

- As a standalone therapy or
- As part of all respiratory support modalities mentioned below.

Noninvasive Modes of Respiratory Support

- Continuous positive airway pressure (CPAP)
- Heated, humidified high flow nasal cannula
- Nasal intermittent positive pressure ventilation (NIPPV).

Invasive Ventilation

- Conventional ventilation using a variety of modes
- High frequency ventilation.

Respiratory Adjuncts

- Surfactant therapy
- Adjuncts for persistent pulmonary hypertension of the newborn (PPHN): nitric oxide, sildenafil.

COMMON CLINICAL INDICATIONS FOR RESPIRATORY SUPPORT IN NEONATAL INTENSIVE CARE UNIT

Pulmonary Disorders

- Respiratory distress syndrome (RDS)
- Meconium aspiration syndrome (MAS)
- Congenital pneumonia
- Community acquired pneumonia
- Persistent pulmonary hypertension of the newborn
- Air leak syndromes
- Chronic lung disease
- Pleural effusion
- Pulmonary hypoplasia
- Upper airway disorders.

Surgical Respiratory Disorders

- Esophageal atresia with tracheoesophageal fistula
- Congenital diaphragmatic hernia (CDH)
- Congenital cystic adenomatoid malformation of the lung
- Congenital lung cysts, bronchogenic cysts.

Cardiopulmonary Disorders

- Neonatal septic shock
- Cardiogenic shock associated with structural cardiac defects.

Central Nervous System Disorders

- Perinatal asphyxia and hypoxic ischemic encephalopathy
- Apnea of prematurity
- Neonatal encephalopathy
- Neuromuscular disorders.

OXYGEN THERAPY

Indications

Oxygen therapy is indicated for hypoxemia resulting from reduced alveolar oxygen content, low ventilation-perfusion ratio, reduced diffusion capacity, or extrapulmonary right-to-left shunts. The aim of therapy is to achieve adequate tissue oxygenation without creating oxygen toxicity and oxidative stress. Strategies to "normalize" oxygenation with use of high FiO_2 result in high rates of retinopathy of prematurity, chronic lung disease, brain, and other organ injury, especially in the premature infant.

Clinical Pearl

- Oxygen therapy should be used judiciously and blended air-oxygen mixture using a blender preferably with an oxygen analyzer should be used at all times to target oxygen saturation between 90 and 95%.

Oxygen is usually administered:

- By means of a head box, mask, nasal cannula. Here, an external air-oxygen blender should be used to titrate the fraction of oxygen delivered. It is used for mild-to-moderately severe respiratory disorders in term babies without evidence of respiratory failure
  It is important to note that in preterm with RDS, there is little role for standalone oxygen therapy as the priority is to recruit adequate lung volume by early use of continuous distending airway pressure
- As part of assisted therapy: CPAP or mechanical ventilation wherein supplemental oxygen is administered by the mixture of air and oxygen in the ventilator or CPAP device.

Clinical Pearl

- Gas warming and humidification is essential to avoid drying of the airways and secretions as well as to avoid convective heat losses when using head box, nasal cannulas, or assisted ventilation.

NONINVASIVE RESPIRATORY SUPPORT

Noninvasive respiratory support has become the mainstay of respiratory therapy in the NICU so as to reduce complications of invasive mechanical ventilation like ventilator associated pneumonias and chronic lung disease.

Continuous Positive Airway Pressure

Continuous positive airway pressure is the application of continuous distending pressure to the airways of spontaneously breathing baby. Current evidence strongly supports the role of early use of CPAP to reduce the need for intubation, invasive ventilation, and surfactant therapy for extremely low birth weight (ELBW) babies by 50%.

Mechanism of Action

- Alveolar stabilization and maintenance of functional residual capacity (FRC)
- Facilitates gas exchange by preventing collapse of the alveoli at end expiration
- Decreases the work of breathing as the pressure required to overcome the collapsing forces generated by surface tension is reduced when the alveolus is partially inflated.
- Conserves surfactant
- Decreased ventilation-perfusion mismatch
- Helps maintain upper airway stability by stenting the airway and decreasing obstruction
- Lowers airway resistance to gas flow in patients with obstructive lung disease and apnea
- Augments stretch receptors and decreases diaphragmatic fatigue
- Reduces intracardiac left-to-right shunt.

Indications

- Any respiratory distress with or without low FRC and not because of listed contraindication
- Postextubation
- Meconium aspiration syndrome
- Tracheomalacia, bronchomalacia with terminal airway collapse
- Some congenital heart defect with increased pulmonary blood flow
- Partial paralysis of diaphragm.

Contraindications

- Pneumothorax
- Choanal atresia
- Cleft lip or palate
- Congenital diaphragmatic hernia
- Tracheoesophageal fistula
- Cardiac failure or hemodynamic instability.

Types of Continuous Positive Airway Pressure Delivery Systems

- Continuous flow CPAP system: continuous flow CPAP consists of gas flow generated at a source and directed against the resistance of the expiratory limb of the circuit. Ventilator derived CPAP and bubble or underwater CPAP are examples of continuous flow devices
- Ventilator based CPAP: ease of use, pressure stability, and an effective alarm system. Ventilator CPAP is typically used for infant extubated from mechanical ventilator
- Bubble CPAP: In this system of delivery, short binasal prongs are attached to a circuit with a gas source providing blended, warm, humidified gas at flow rate of 5–8 L/min; the expiratory limb is partly submerged under water. The height of the submerged water column in centimeters represents CPAP pressure in centimeters. The benefits of bubble CPAP are ease of setup and low cost. However, as there is no audible pressure disconnect alarm, no warning occurs even when there are leaks in the system. Visual alarm of "no bubbling" and clinical observations of the patient are essential to maintaining patient safety

- Variable flow CPAP: variable flow CPAP represents a sophisticated technology of CPAP delivery with visual and audible alarms. The major benefit is a decrease in the work of breathing due to the variable flow. However, it requires specific equipment such as flow drivers, generators, and circuits that are expensive. Although data suggests that some of these systems are superior to others, in clinical practice, the stability of the nasal interface is probably the most important factor determining the success or failure of this form of respiratory support.

Clinical Pearl

- Endotracheal continuous positive airway pressure should never be used as it significantly increases the work of breathing. It is like breathing through a straw.

Interface Used for Delivery of Continuous Positive Airway Pressure

Short binasal prongs are most effective due to reduced airway resistance. Nasal masks are also finding favor as a CPAP interface.

Initiating Continuous Positive Airway Pressure

- Continuous positive airway pressure should be initiated soon after birth in infants who have sufficient respiratory drive and evidence of respiratory distress, especially in ELBW babies. More than 50% of ELBW infants who are not depressed at birth can be managed successfully with nasal continuous positive airway pressure (NCPAP), avoiding the use of invasive ventilation. For any preterm with RDS, CPAP should be promptly instituted if the Silverman Anderson score is greater than or equal to 3 or the FiO_2 requirement is greater than or equal to 30%
- Place the baby supine with a slight head extension
- Choose the appropriate sized short binasal prongs size 0 or 1. Avoid pressure of the prongs against the nasal septum
- Start with a CPAP of 5–6 cm H_2O, flow of 5–7 L/min of blended, warm, humidified gas
- Use appropriate FiO_2 to maintain SaO_2 between 90 and 95%
- Titrate CPAP pressure till the grunting and retractions are relieved or till a maximum of 8 cm H_2O
- If FiO_2 requirement is greater than or equal to 0.4, administer surfactant as early rescue therapy by intubation-surfactant-extubation (INSURE) technique.

Clinical Pearls

- Any kind of noninvasive support demands same vigilance as invasive support
- Adequacy of flow is decided by bubbling at expiratory limb; adequacy of oxygenation is decided by SpO_2 on pulse oximeter; and adequacy of pressure is decided by chest retractions.

Continuous Positive Airway Pressure Failure

- Oxygen requirement greater than 60% to maintain saturation 91–95% and CPAP greater than 8 cm H_2O
- A respiratory acidosis, pH less than 7.20 with partial pressure of carbon dioxide greater than 60 mmHg
- Recurrent apneic episodes
- Increased work of breathing (sternal and intercostal recession/grunt/tachypnea).

Clinical Pearl

- Before using alternative mode of ventilation for continuous positive airway pressure failure, quickly go through check list to ensure adequate flow delivery, adequate pressure, and position of interface.

Complications

Pneumothorax: incidence varies between 0.5 and 2% though the Continuous Positive Airway Pressure or Intubation at Birth (COIN) study showed a higher incidence of 9%. In this trial, CPAP pressure of 8 cm H_2O was used compared to conventional 5–6 cm of NCPAP.

Continuous Positive Airway Pressure belly: benign gaseous abdominal distention that can be minimized by evacuating the gas in the stomach routinely every 3 hours and by maintaining an open-to-air orogastric tube while on CPAP

Nasal septum damage: this occurs due to care-related problems and is preventable with proper prong size and position, minimizing tubing torque, gentle intermittent cleansing, and proper heating and humidification.

Clinical Pearl

- Advantage of noninvasive respiratory support outweighs complications related to it.

Heated Humidified High Flow Nasal Cannula

The heated and humidified high flow nasal cannula (HH-HFNC) is a simple, noninvasive method of oxygen delivery that can produce positive pressure in the airways. The system consists of delivery of heated and humidified, blended air-oxygen gas delivered to the baby by nasal cannula with short binasal prongs. Blended gas administered at flow rates of more than 1 L/min produces distending airway pressure. The distending pressure generated depends on the size of the nasal cannula, and the flow rate. Generally, flow rates of 3–6 L/min are used. Care should be taken to ensure that the nasal prongs do not fit the nares tightly as very high distending pressure can be generated.

The benefits of HH-HFNC are the simplicity of use, less risk of damage to the nares and nasal septum, and comfort for more mature babies with RDS. The risk of using HH-HFNC lies in the inability to effectively measure distending pressure.

Noninvasive Positive Pressure Ventilation

This is a method of assisted ventilation without an endotracheal (ET) tube in the trachea, and using either nasal prongs or nasal mask as the interface. The ventilator delivers peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP) at the set inspiratory time, rate, and FiO_2.

The common methods of delivery used are:

- Nasal intermittent positive pressure ventilation
- Synchronized nasal intermittent positive pressure ventilation (SNIPPV).

Mechanism of Action

Like CPAP, nasal intermittent positive pressure ventilation expands the lung, increases FRC, prevents alveolar collapse, and improves ventilation-perfusion mismatch.

Synchronized NIPPV results in a higher tidal volume compared to NCPAP breaths and nonsynchronized NIPPV. Whether synchronized or not, NIPPV improves thoracoabdominal asynchrony and chest wall stabilization, resulting in a decreased work of breathing.

Indications for Use

- Postextubation support: several randomized controlled trials have demonstrated a reduction in extubation failure using synchronized nasal ventilation compared to CPAP but not when nonsynchronized NIPPV was used
- Apnea of prematurity: NIPPV has been found to be more effective than NCPAP
- Respiratory distress syndrome as primary support: few small studies have reported improved carbon dioxide removal, reduced apnea, and shorter duration of ventilation in the NIPPV group. A significant reduction in bronchopulmonary dysplasia (BPD) has been reported when NIPPV is used as respiratory support after extubation or as a primary mode for RDS. It appears that nonsynchronized early NIPPV seems to be beneficial for slightly mature and heavier infants when compared with NCPAP. However, SNIPPV presents potential advantages over NCPAP and NIPPV, but more studies are needed for generalization

  Potential drawbacks include the likelihood of gastrointestinal complications due to the additional pressure, risk for air leaks, and nasal damage as seen for CPAP therapy.

Clinical Pearl

- So far, evidences that favor noninvasive ventilation are mainly related to its use in postextubation neonates.

MECHANICAL VENTILATION

Conventional Ventilation

Indications

- Apnea
- Respiratory failure characterized by:
  - PaO_2 less than 50 mmHg on FiO_2 of 100%
  - $PaCO_2$ greater than 55–60 mmHg with pH less than 7.25
- Continuous positive airway pressure failure
- Shock.

Clinical Pearl

- Decision to provide ventilatory support should not be exclusively based on blood gas.

Modes of Ventilation

Conventional ventilation is time-cycled pressure-limited. Currently, patient triggered modes of ventilation like synchronized intermittent mandatory ventilation (SIMV) and assist control are preferred. Pressure support ventilation (PSV) is a mode of ventilation in which patient's spontaneous breaths are augmented by supplemental inspiratory pressure. This may be used along with SIMV or CPAP. It is particularly useful in weaning off ventilation.

Flow cycling is increasingly being used wherein the breath is terminated not at a set inspiratory time but when inspiratory flow is reduced to 30% of the peak flow.

Flow cycling gives inspiratory as well as expiratory synchrony.

Controls in Ventilation

Although pressure controlled ventilation has been used traditionally, volume targeting to reduce volutrauma, the major factor implicated in BPD is increasingly being preferred. This can be delivered by using volume controlled ventilation or in the pressure limited mode with volume guarantee, volume limit, or hybrid modes like pressure regulated volume control. The tidal volume is set, and once reached, the breath is terminated. Set tidal volume 4–6 mL/kg for preterm and 6–8 mL/kg for term infants.

Ventilation Strategies

Ventilator-associated lung injury has been traditionally thought to result from high pressures and barotruma. However, studies have shown that it is the high volumes and volutrauma responsible for major lung damage. Lung injury is also caused by repeated collapse and reopening of the alveoli which occurs with very low end-expiratory pressures.

Respiratory distress syndrome

- Provide adequate PEEP to avoid atelectasis 5–6 cm
- Provide PIP enough to achieve adequate oxygenation and ventilation.

Meconium aspiration syndrome

Due to the risk of hyperinflation, low PEEP 4–5 cm, moderate pressure, and rapid rates are often needed. Analgesia and sedation may also be required.

Bronchopulmonary dysplasia

Moderate pressure required, may require longer inspiratory time of 0.4–0.5 seconds.

Management after Initiating Ventilation

- Check adequacy of mechanical breaths: good air entry heard over both sides of the chest, chest rise, and synchronization. Chest wall expansion must be just adequate and not excessive
- Maintain saturation between 91 and 95%; reduce FiO_2 clinically on the pulse oximeter
- If retractions persist after breaths are synchronized: PEEP/PIP need to be adjusted
- Monitor pulses, noninvasive blood pressure, capillary refill time
- After stabilizing the baby, check an arterial blood gas (ABG)
- Do a chest X-ray: look for position of the ET tube.

Ventilator Adjustments

- To improve oxygenation: increase FiO_2, mean airway pressure (MAP), inspiratory time, respiratory rate
- To improve ventilation and decrease $PaCO_2$: increase MAP or respiratory rate.

Sudden Deterioration

- Look for inadvertent extubation, malposition of ET tube (right mainstem) or ET tube occlusion
- Suction the ET to remove secretions
- Auscultate for air entry. Remove from ventilator and stabilize by bag and tube ventilation
- Rule out ventilator malfunction
- Do an ABG and chest X-ray. Emergency reintubation may be needed

TABLE 1: Suggested initial settings on ventilator

Settings	Normal lung	RDS	MAS
PIP (cm H_2O)	12–14	16–18	16–18
PEEP (cm H_2O)	3–4	5–7	4–5
FiO_2	10% higher than head box or CPAP FiO_2		
Rates (per min)	25–30	40–60	40–60
Flow (L/min)	8–10	8–10	8–10
Inspiratory time (s)	0.36–0.40	0.36–0.40	0.36–0.38

RDS, respiratory distress syndrome; MAS, meconium aspiration syndrome; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

TABLE 2: Target blood gases

	Preterm	Term
pH	7.25–7.35	7.35–7.45
PaO_2	50–70	60–80
$PaCO_2$	45–55	35–45

PaO_2, partial pressure of arterial oxygen, $PaCO_2$, partial pressure of arterial carbon dioxide

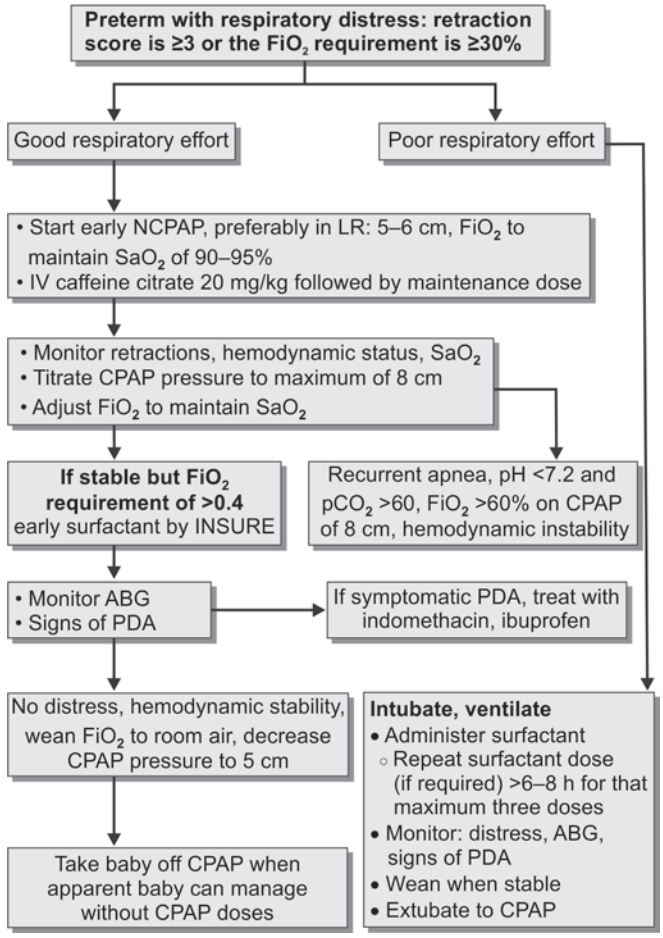
- Pneumothorax may be diagnosed by auscultation, transillumination, or chest X-ray. An emergency thoracentesis may be required
- Reset ventilator by settings used during hand ventilation.

Weaning

- Once the patient is clinically stable, blood gases have normalized, and X-ray shows improvement, the ventilator settings are gradually decreased keeping in mind the progress of disease process
- Improvement of lung compliance on the pressure volume loops and tidal volume scalers is a good indicator for considering weaning
- Diuresis in preterm is also a good indicator of improving lung function. Decrease the most damaging parameters, i.e., FiO_2 and PIP first
- Changes are accomplished in small decrements (PIP 2 cm H_2O, FiO_2 5%, rate 5 beats per min).

ALGORITHM 1

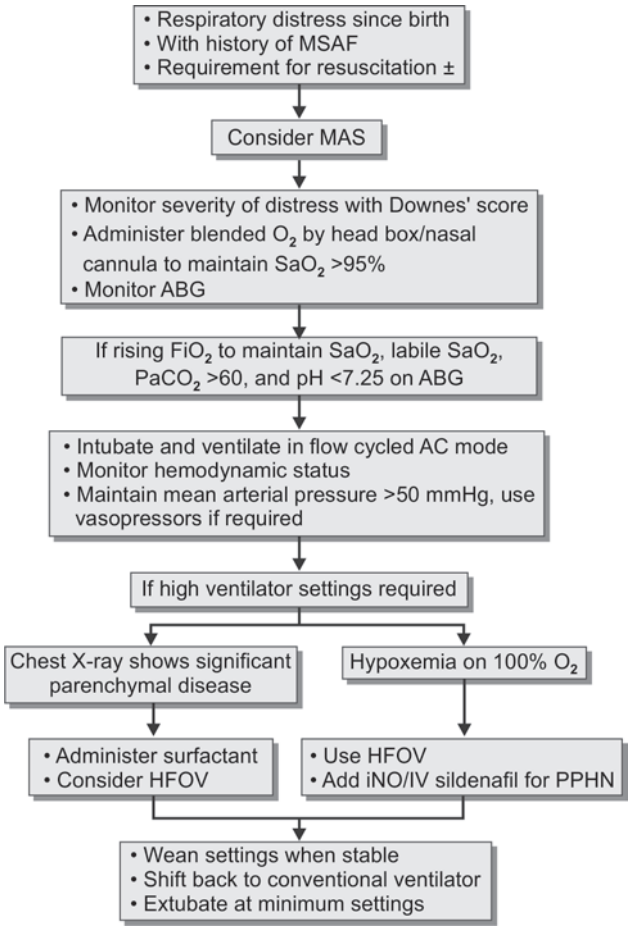
Algorithm for management of respiratory distress syndrome



NCPAP, nasal continuous positive airway pressure; RDS, respiratory distress syndrome; ABG, arterial blood gas; PDA, patent ductus arteriosus; FiO_2, fraction of inspired oxygen; SaO_2, arterial oxygen saturation; $PaCO_2$, partial pressure of arterial carbon dioxide; INSURE, intubatio-surfactant-extubation; LR, labor room.

ALGORITHM 2

Management of meconium aspiration syndrome



MSAF, meconium stained amniotic fluid; MAS, meconium aspiration syndrome; ABG, arterial blood gas; HFOV, high frequency oscillatory ventilation; iNO, inhaled nitric oxide; PPHN, persistent pulmonary hypertension of the newborn.

Extubation Criteria

- 12–14 cm H_2O (larger babies may be extubated with PIP 14)
- Respiratory rate of 20–25 beats per minute
- FiO_2 requirement less than 40%
- Extubation to nasal CPAP/NIPPV is especially useful in VLBW babies
- Postextubation, periodic suctioning as needed, gentle chest physiotherapy, and nebulization with ipratropium help stabilization.

High Frequency Oscillatory Ventilation

High frequency oscillatory ventilation (HFOV) is a type of mechanical ventilation that uses a constant distending pressure (MAP) with pressure variations (δP) oscillating around the MAP at very high rates (up to 900 cycles per min). This creates small tidal volume, often less than the dead space.

Indications

At present, HFOV is generally used as a rescue therapy.

- Failure of conventional ventilation in the term infant: persistent pulmonary hypertension of the newborn, MAS
- Air leak syndromes [pneumothorax, pulmonary interstitial emphysema (PIE)]
- Congenital diaphragmatic hernia: certain centers use HFOV as a primary modality of respiratory therapy for CDH
- Failure of conventional ventilation in the preterm infant (severe RDS, PIE, pulmonary hypoplasia) or to reduce barotrauma when conventional ventilator settings are high.

Initial Settings on High Frequency Oscillatory Ventilation

On an HFOV ventilator, the oxygenation is controlled by changing the MAP also called Paw or by the FiO_2.

Ventilation is controlled by the amplitude (δP) and the frequency.

In contrast to conventional ventilation, decreasing the frequency increases the tidal volume delivered, thereby increasing the carbon dioxide washout.

Initial settings: aim is to maximize recruitment of alveoli:

- Set MAP 2–3 cm H_2O above the MAP on conventional ventilation
- Set frequency to 8–10 Hz for term babies and 10–12 Hz for preterms
- Generally, the frequency is set at 10 Hz, inspiratory time at 33%, and rarely require change throughout the course of ventilation
- Set amplitude to get good vibrations (wobble) of chest, abdomen, and upper thighs.

Ventilator Setting Adjustments on High Frequency Oscillatory Ventilation

Table 3 describes ventilator adjustments on high frequency oscillatory ventilation.

Chest X-ray

Follow-up chest radiograph in 4–6 hours is recommended to assess the expansion.

Thereafter, repeat chest radiography with acute changes in patient condition.

TABLE 3: Ventilator adjustments on high frequency oscillatory ventilation

Poor oxygenation	Over-oxygenation	Under-ventilation	Over-ventilation
Increase FiO_2	Decrease FiO_2	Increase amplitude	Decrease amplitude
Increase MAP (Paw)* (1–2 cm H_2O)	Decrease MAP (1–2 cm H_2O)	Decrease frequency by 1–2 Hz	Increase frequency by 1–2 Hz

*Pressure airway.

MAP, mean airway pressure.

Suctioning

- Suction is indicated for diminished chest wall movement (chest wobble), elevated carbon dioxide, and/or worsening oxygenation suggesting airway or ET tube obstruction, or if there are visible/audible secretions in the airway
- Avoid in the first 24 hours of HFOV unless clinically indicated
- Press the "stop" button briefly while quickly inserting and withdrawing suction catheter (PEEP is maintained).

Weaning

- Reduce FiO_2 to less than 40% gradually
- Reduce MAP when chest radiograph shows evidence of overinflation (>9 ribs) or hyperoxemia on ABG
- Reduce MAP by 1–2 cm H_2O to 8–10 cm H_2O
- In air leak syndromes, reducing MAP takes priority over weaning the FiO_2
- Wean the amplitude in 2–4 cm H_2O decrements based on $PaCO_2$
- Discontinue HFOV when MAP 8–10 cm H_2O and amplitude 20–25
- If infant is stable, oxygenating well and blood gases are satisfactory, then infant could be extubated to CPAP or switched to conventional ventilation.

KEY POINTS

- ☞ Decision to provide respiratory support to neonate is never solely based on blood gas
- ☞ Noninvasive support is a preferable modality to avoid lung injury
- ☞ So far, no continuous positive airway pressure machine has shown superiority over other as far as outcome is concerned
- ☞ Irrespective of the mode being used, always adjust ventilator settings, keeping in mind pathophysiology of the disease state
- ☞ High frequency ventilator has proven role as a rescue ventilator. It is not a panacea of all respiratory problems of neonate.

SUGGESTED READINGS

1. Boost II collaborative groups. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368:2094-104.
2. Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC (Eds). Fanaroff and Martin's Neonatal-perinatal Medicine: Diseases of the Fetus and Infant, 9th edition. Philadelphia: Mosby/Elsevier; 2011.
3. Goldsmith J, Karotkin E. Assisted Ventilation of the Neonate, 5th edition. Saunders publication; 2010.
4. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358(7):700-8.

CHAPTER 5

Persistent Pulmonary Hypertension of the Newborn

Ram G Holla, Ira J Holla

INTRODUCTION

The fetal circulation is characterized by two parallel circulations, with a high pulmonary vascular resistance (PVR) and right-to-left shunting at the levels of the ductus arteriosus and foramen ovale. At birth, there is a fall in the PVR due to lung expansion and a simultaneous rise in systemic vascular resistance (SVR). Humoral mediators released in response to elevated arterial oxygen content and pH further constrict the ductus. This transforms the fetal circulation, characterized by pulmonary and systemic circuits in series to the adult circulation, in which the two circuits function in parallel.

Failure to achieve or sustain the normal decrease in PVR at birth, results in persistent pulmonary hypertension of the newborn (PPHN).

Persistent pulmonary hypertension of the newborn is a clinical syndrome characterized by sustained elevation in PVR at birth, with resulting shunting from right to left through persistent fetal channels.

MECHANISMS LEADING TO PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (TABLE 1)

Normal pulmonary vascular development in infancy requires maintenance of low PVR after birth and is necessary for normal lung function and growth. The developing lung is subject to multiple genetic, pathological, and/or environmental influences that can adversely affect lung adaptation, development, and growth, leading to pulmonary hypertension.

Clinical Pearl

- Persistent pulmonary hypertension of the newborn is caused by failure of pulmonary pressures to fall after birth leading to right-to-left shunting, hypoxemia, acidosis, and shock.

CLINICAL MANIFESTATIONS OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Profound Hypoxemia and Labile Oxygenation

- Hypoxemia out of proportion to the degree of parenchymal lung disease. The outstanding feature of PPHN is central cyanosis that responds poorly to near 100% oxygen given by hood, but may respond to oxygen by ventilation
- Symptoms generally begin at birth, but definitely before 12 hours
- Differential saturation: preductal oxygen saturation may be 10% higher (or more) than postductal saturation. Arterial

TABLE 1: Mechanisms leading to pulmonary hypertension in the newborn

Abnormally constricted blood vessels	Structurally abnormal pulmonary vasculature	Hypoplastic pulmonary vasculature	Functional obstruction to pulmonary flow
• Acute perinatal hypoxia • Meconium aspiraton • Sepsis or pneumonia • Respiratory distress syndrome • Hypoventilation • Central nervous system depression • Hypothermia • Hypoglycemia	• Placental insufficiency • Prolonged gestation • *In utero* closure of ductus arteriosus: aspirin, nonsteroidal anti-inflammatory drugs • Idiopathic	• Diaphragmatic hernia • Lung dysgenesis • Pleural effusion • Congential lung hypoplasia • Potter syndrome • Thoracic dystrophies	• Polycythemia • Hyperfibrinogenemia

blood gas may show similar findings (PaO_2 >20 mm, higher in the preductal sample). A subset of infants may have right-to-left shunting only at the level of the foramen ovale and not at the ductus, and may fail to show differential cyanosis.

Respiratory symptoms are related to the underlying disease, distress being the most severe in meconium aspiration syndrome, diaphragmatic hernia, respiratory distress syndrome, pneumonia, etc.

DIFFERENTIAL DIAGNOSIS

Primary pulmonary disease without elevated PVR and structural heart disease associated with right-to-left shunting should be excluded before a diagnosis of PPHN can be made.

Clinical Pearl

- Differential oxygenation: SpO_2 10% higher, PaO_2 20 mmHg higher in preductal than postductal samples.

Clinical Signs Favoring Cyanotic Congenital Cardiac Disease over Persistent Pulmonary Hypertension of the Newborn

- Cardiomegaly
- Weak pulses
- Active precordium
- Pulse differential between upper and lower extremities
- Pulmonary edema
- Grade 3+ murmur
- Persistent pre- and postductal arterial oxygen tension (PaO_2) at or less than 40 mmHg.

INVESTIGATIONS AND DIAGNOSIS

- Chest X-ray usually shows the underlying pulmonary disease or may be normal. The cardiac silhouette is usually normal. Pulmonary blood flow may be diminished
- The electrocardiogram is usually normal for age
- An echocardiography must be performed in every baby with PPHN for diagnosis and exclusion of cardiac disease. The size, direction, and location of shunt should be assessed. In all cases, response to treatment, particularly changes in cardiac output and direction of ductal shunting, should be assessed by repeated echocardiographic assessments
- Hyperoxia test: hyperoxia with or without hyperventilation can help to predict the presence and reversibility of pulmonary hypertension. Details are given in algorithm 1.

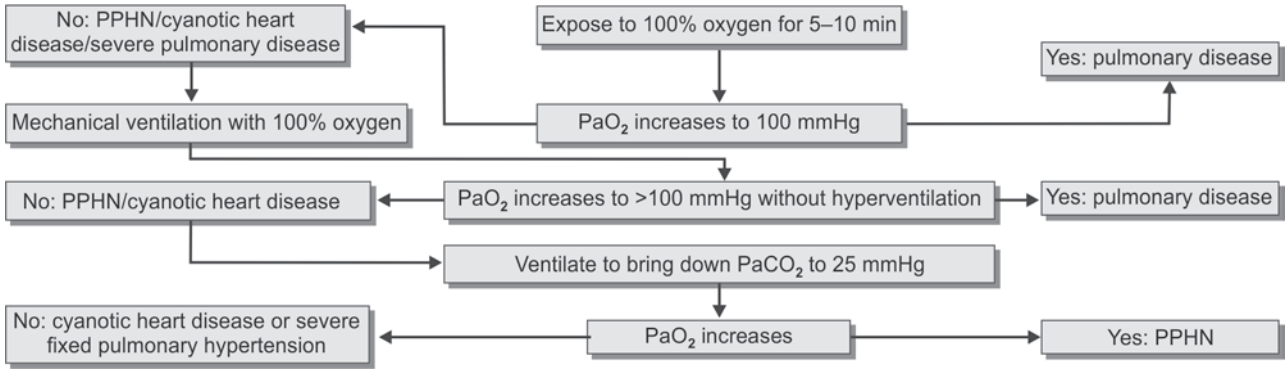
MANAGEMENT

Management of a neonate with PPHN (Algorithm 2) constitutes a medical emergency in which correction of hypoxia is important for reversal of pulmonary hypertension, limitation of shunting, establishment of systemic perfusion, and prevention of end-organ damage.

- *General measures:*
  - Correct underlying metabolic/hematological derangements:
    - Correct acidosis, hypoglycemia, hypocalcemia, polycythemia, hypothermia
    - Treatment directed at the specific disorder causing PPHN, e.g., congenital diaphragmatic hernia
  - *Monitoring:*
    - Blood pressure—preferably intra-arterial
    - Pulse oximetry (both pre- and postductal)
    - Transcutaneous oxygen/carbon dioxide
    - End-tidal CO_2
    - Frequent postductal blood gas assessments
    - Monitoring of blood gas should be accompanied by charting of trends in PaO_2, $PaCO_2$, alveolar-arterial oxygen gradient ($AaDO_2$), and oxygenation index (see appendix 'A')
  - Sedation/paralysis: the hyper-reactive pulmonary circulation is highly sensitive to catecholamines leading to increased PVR. Stress should be blocked by silence, avoidance of disturbance, gentle handling, and sedation
    - Fentanyl (2–5 μg/kg/h)
    - Morphine (5–10 μg/kg/h) infused continuously
    - Very agitated or unstable neonates, particularly if breathing out of phase, may be paralyzed with pancuronium (0.1 mg/kg/dose; every 1–4 h PRN) or vecuronium
  - Maintain hematocrit above 45%

ALGORITHM 1

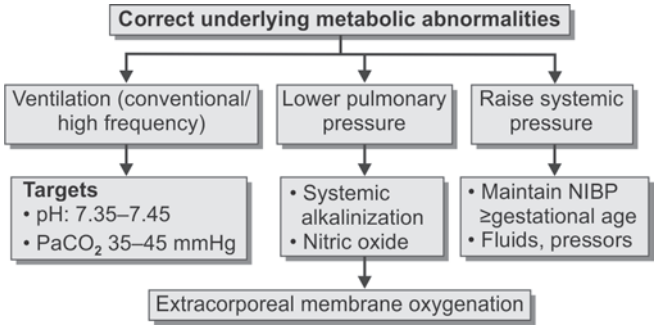
Hyperoxia/hyperventilation test



PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PPHN, persistent pulmonary hypertension of the newborn.

ALGORITHM 2

Outline of management of persistent pulmonary hypertension of the newborn



NIBP, noninvasive blood pressure; $PaCO_2$, partial pressure of arterial carbon dioxide.

- Ventilation: optimize lung recruitment and reduce ventilation-perfusion mismatch: specific approaches to respiratory support and mechanical ventilation vary. A gentle approach that maintains adequate oxygenation and mild hyperventilation ($PaCO_2$ 35–45 mmHg, and pH at 7.35–7.45), generally lowers the PVR to the extent of abolishing right-to-left shunting. The state of the underlying lung should dictate the specific respiratory management strategy, keeping always in mind that high intrathoracic pressure may worsen the situation by impeding cardiac output and elevating PVR. High frequency oscillatory ventilation (HFOV) is often useful in treating infants whose PPHN is associated with severe pulmonary parenchymal disease. Neonates with PPHN are unstable in their cardiopulmonary status and weaning from ventilation should be done very gradually to prevent reversal. Surfactant therapy should be used where applicable
- Optimize cardiac output and left ventricular function, maintenance of systemic blood pressure: the aim of cardiovascular management is to optimize systemic blood pressure to levels above the pulmonary pressure in order to minimize or eliminate right-to-left shunt. Target mean blood pressure levels would be 45–55 mmHg. Low blood pressure may be normalized by the use of:
  - Volume expansion: especially in hypovolemic conditions (e.g., hemorrhage, hydrops, capillary leak) or decreased SVR (e.g., septic shock) or systemic hypotension
  - Vasopressors: dopamine, dobutamine, and/or adrenaline often are necessary to achieve adequate cardiac output. Dopamine in doses more than 10 μg/kg/min and adrenaline increase SVR through stimulation of α- and β-receptors. High doses of both may stimulate pulmonary α-receptors, leading to increased PVR. When cardiac function is poor, cardiotonic medications, such as milrinone that both enhance cardiac output and lower PVR, might be useful
- Decrease PVR:
  - Alkalinization: alkalosis reduces PVR. Alkalosis can be achieved by gentle hyperventilation and/or conservative use of metabolic therapy with sodium bicarbonate, aiming for a pH of 7.35–7.45
  - Nitric oxide: nitric oxide relaxes the vascular smooth muscle and causes pulmonary vasodilation. Inhaled nitric oxide (iNO) is administered by conventional or high frequency ventilation in doses of 5–20 ppm, diffuses into ventilated alveoli, causes localized vasodilatation and improves oxygenation, in addition to decreasing PVR
- Extracorporeal membrane oxygenation (ECMO): ECMO often is lifesaving therapy for infants with PPHN who fail conventional management and/or iNO treatment.

Ligation or pharmacological closure of the duct is not useful and may be detrimental. There is insufficient data to justify the use of other proposed medical therapies including sildenafil, magnesium sulfate, calcium channel blockers, adenosine, inhaled prostacyclin, ethyl nitrite, bosentan (endothelin receptor antagonist), and inhaled or intravenous tolazoline.

Appendix

1. $$PaO_2 = \frac{[(\text{Barometric pressure} - \text{Partial pressure of water vapor}) \times FiO_2] - PaCO_2}{RQ}$$

$$= \frac{[(760 - 47) \times 0.21] - 40}{0.8}$$

$$= 150 - 50 = 100 \text{ (approximately)}$$

Alveolar to arterial oxygen gradient = $PaO_2 - PAO_2$

Where RQ indicates respiratory quotient; PaO_2, alveolar oxygen gradient; PAO_2, arterial oxygen gradient; and $PaCO_2$, partial pressure of CO_2.

2. Oxygenation index: $$\frac{(MAP \times FiO_2 \times 100)}{PaO_2}$$

KEY POINTS

- ☞ Persistent pulmonary hypertension of the newborn (PPHN) is more common in term and post-term newborns
- ☞ Assessment of pre- and postductal saturations helps in early diagnosis
- ☞ Congenital heart disease should always be ruled out in a patient having clinical features of PPHN
- ☞ High frequency oscillatory ventilation and inhaled nitric oxide have revolutionized the treatment of PPHN.

SUGGESTED READINGS

1. Baquero H, Sloiz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. Pediatrics. 2006;117(4):1071-83.
2. Konduri GG, Solimano A, Sokol GM, Singer J, Ehrenkranz RA, Singhal N, et al. A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. Pediatrics. 2004;113:559-64.
3. Steinhorn RH, Farrow KN. Pulmonary hypertension in the neonate. Neo Reviews. 2007;8:e14-21.
4. Wood BR. Physiological principles. In: Goldsmth JP, Karotkin EH (Eds). Assisted ventilation of the neonate, 4th ed. Philadelphia: WB Saunders; 2003. pp. 19-46.

CHAPTER 6

Bronchopulmonary Dysplasia

Naveen Bajaj, Ruchi Nanawati

INTRODUCTION

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) is a clinical syndrome following very preterm delivery that results in decreased oxygenation, an increased work of breathing, and lung abnormalities that persist into childhood. In very low birth weight (VLBW) babies, overall incidence is 22% and is inversely related to gestational age and birth weight. Although it can occur in full term infants, it is uncommon in infants born after 32 weeks.

Clinical Pearl

- Bronchopulmonary dysplasia mainly occurs in very low birth weight babies.

DEFINITION

Bronchopulmonary dysplasia has been defined by different authors as the need of supplemental oxygen either at 28 days of life or at 36 weeks of postconceptional age. The most recent National Institute of Health (NIH) consensus definition is described in table 1.

The more specific old term BPD instead of more recent term CLD is preferred, because this disease is clearly distinct from the multiple CLDs of later life.

Old and New Bronchopulmonary Dysplasia

In recent years, with improved survival of extreme premature infants, the clinical and X-ray findings that define BPD has changed and a milder clinical disease called "new BPD" has emerged (Table 2).

Clinical Pearl

- New bronchopulmonary dysplasia (BPD), a milder form of disease is more common than old BPD nowadays.

TABLE 1: National Institute of Health definition: bronchopulmonary dysplasia diagnostic criteria

Gestational age	<32 weeks	>32 weeks
Time point of assessment	36 weeks PMA or discharge to home whichever comes first	>28 days but <56 days postnatal age or discharge to home whichever comes first
Treatment with oxygen >21% for at least 28 days PLUS		
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air at 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 weeks PMA or discharge, whichever comes first	Need for <30% oxygen at 56 days postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV/NCPAP) at 36 weeks PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (PPV/NCPAP) at 56 days postnatal age or discharge, whichever comes first

BPD, bronchopulmonary dysplasia; PMA, postmenstrual age; NCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation.

PATHOGENESIS

Bronchopulmonary dysplasia is caused by multiple adverse events during pre- and postnatal period (Algorithm 1).

Predisposing Factors

- High intermittent positive pressure ventilation/oxygen requirement
- Barovolutrauma
- High initial fluid intake

TABLE 2: Old versus new bronchopulmonary dysplasia

	Old BPD (Classic BPD)	New BPD (Atypical BPD)
Infants at risk	Larger, more mature	Very low birth weight
Airway injury	Severe	Mild-to-none
Fibrosis	Severe	Minimal
Alveoli	Develop in regions without fibrosis	Uniform arrested development
Causes	Oxygen, ventilation	Interference with development
X-ray	Overinflation and cystic emphysema	Diffuse haziness or fine, lacy pattern

BPD, bronchopulmonary dysplasia.

- Respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), pulmonary interstitial emphysema
- Chorioamnionitis: fetal inflammatory response syndrome
- Nosocomial infections
- Colonization with *Ureaplasma urealyticum*
- Genetic predisposition.

Clinical Pearl

- Prematurity, respiratory distress syndrome, ventilation, and infections are common predisposing factors.

CLINICAL FEATURES

Bronchopulmonary dysplasia usually develops in premature neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly due to RDS. It is often anticipated when mechanical ventilation or oxygen dependence extend beyond 10–14 days. Common clinical pointers are:

- Preterm on ventilator, failure to wean, extubation failures
- Persistent or increased oxygen requirement
- Signs of respiratory distress
- Barrel shaped chest
- Severe bronchospasm
- Cardiomegaly, hypertension, and cor pulmonale
- Copious secretions, tracheo- and bronchomalacia
- Feed intolerance, failure to thrive.

Clinical Pearl

- Ventilatory or oxygen dependency beyond 2 weeks of life is an early suspicious sign of bronchopulmonary dysplasia.

Chest X-ray

Northway originally described the four stages of radiographic appearances in BPD (Table 3). The new BPD on X-ray only shows diffuse haziness, occasionally, infiltrates or segmental atelectasis.

ALGORITHM 1

Bronchopulmonary dysplasia pathogenesis

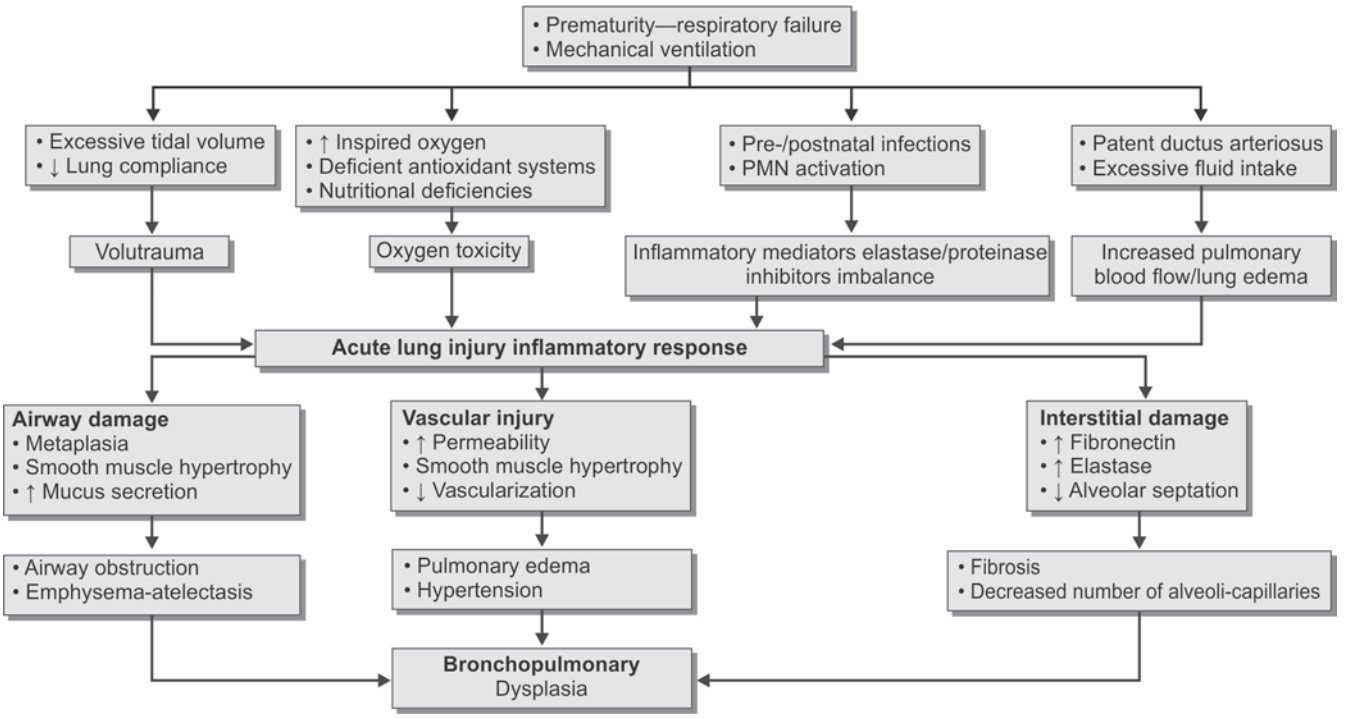


TABLE 3: X-ray staging and appearance of bronchopulmonary dysplasia

Stage	Day	X-ray appearance
Stage I (mild)	2–3 days	Identical to respiratory distress syndrome
Stage II (moderate)	4–10 days	Pulmonary parenchymal opacities
Stage III (severe)	10–20 days	Radiolucent cysts giving bubbly lung appearance
Stage IV (advanced)	30 days	Marked hyperinflation, emphysematous lung, fibrous streaks, and cardiomegaly

Pulmonary Functions

- Increased airway hyper-reactivity, high airway resistance, and decreased compliance results in markedly increase work of breathing, hypoventilation, and hypercapnia
- Airway resistance increases markedly during active expiratory efforts such as in physical agitation
- Flow volume loops: ski slope sign in severe cases
- Functional residual capacity is initially normal or low but increases in advanced stages.

Echocardiography

Pulmonary hypertension may be seen in established BPD and reflects the severity of disease.

DIFFERENTIAL DIAGNOSIS

- Bacterial or viral pneumonia
- Pulmonary lymphangiectasia
- Recurrent aspirations
- Total anomalous pulmonary venous connections.

TREATMENT STRATEGIES FOR SUSPECTED BRONCHOPULMONARY DYSPLASIA

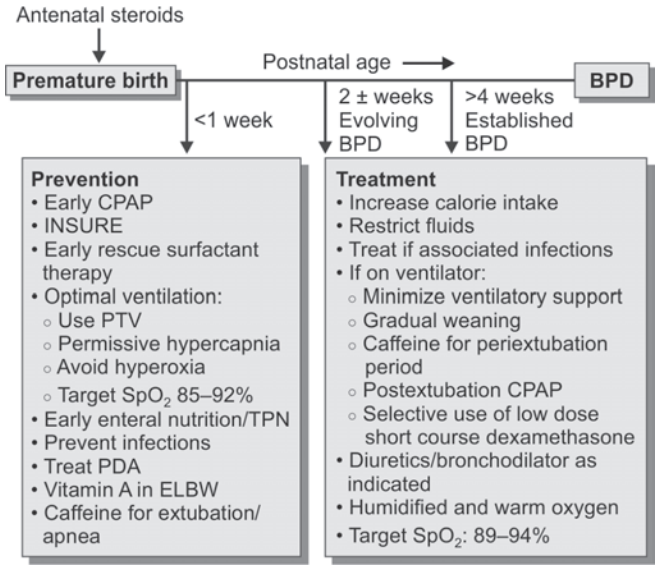
Though there is no single magical therapy for BPD, but multiple "best practices" result in better outcome of these infants. These include multidisciplinary preventive and treatment strategies. Algorithm 2 depicts the timeline and management strategies of BPD.

Respiratory support: gentle ventilation to maintain adequate gas exchange while minimizing ventilator induced lung injury. The aim is to ventilate for the shortest possible time, wean gradually, use methylxanthines (caffeine preferred than aminophylline) for apneas and in periextubation period, and extubate to nasal continuous positive airway pressure (CPAP) as early as possible. The ventilator strategy and the targets used in these cases are summarized in table 4.

Postextubation physiotherapy is helpful in managing segmental collapse and increased airway secretions.

ALGORITHM 2

Management strategies for bronchopulmonary dysplasia



BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; PTV, patient triggered ventilation; TPN, total parenteral nutrition; PDA, patent ductus arteriosus; ELBW, extremely low birth weight; SpO_2, blood oxygen saturation level.

TABLE 4: Ventilatory strategy and arterial blood gas targets in bronchopulmonary dysplasia

Ventilatory strategy	Target arterial blood gas values
Slow rates: 20–40/min	pH: 7.25–7.3
Lowest possible PIP: 15–20 cm H_2O	PaO_2: 60–80 mmHg
Moderate PEEP: 5–6 cm H_2O	$PaCO_2$: 55–60 mmHg
Inspiratory time: 0.3–0.5 s	SpO_2: 89–94%
Tidal volume: 5–8 mL/kg	$PaCO_2$ levels can be ignored if pH >7.25

PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; Ti, inspiratory time, SpO_2, blood oxygen saturation level; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide.

Clinical Pearl

- Gentle ventilation, early extubation, and use of noninvasive ventilation are the goals.

Delivery of oxygen: warm humidified oxygen by nasal cannula or hood to maintain SpO_2 between 89 and 94%. Infants with no other medical problem can be given home oxygen therapy by nasal cannula from a portable oxygen cylinder/oxygen concentrator. Monitor oxygen requirement and weight gain.

Desaturation during and after feeding: managed by increasing the inspired oxygen concentration.

Bronchopulmonary dysplasia spells: BPD spells which are sudden episodes of cyanosis and desaturation due to expiratory flow limitation may require sedation and paralysis.

Fluid and nutrition: even though these neonates have an augmented metabolic demand requiring higher intake of calories (120–160 kcal/kg/day) to sustain growth, they cannot tolerate increased fluid volumes. Hence, fluids are restricted to 120–150 mL/kg/day. Neonates who cannot be fed should be given parenteral nutrition. Those on oral feeds may be fed calorie-dense feeds (24–30 kcal/oz) by fortification of expressed breast milk with human milk fortifier or by using high calorie formula. Supplementation with medium chain triglyceride oil is another option. Adequate intake of calcium, phosphorus, vitamins, and iron should be ensured.

Treatment of infections: bacterial or fungal infections are frequent in BPD infants and worsen the lung damage and should be investigated and treated.

Drug treatment (Table 5): before a drug is initiated in a case of BPD, one should always revisit the decision and seriously consider if that drug is required.

Follow these principles of a drug therapy:
- All drugs have adverse effects
- Anticipate that a drug may have no therapeutic effect
- If you start a drug, be willing to stop it.

Clinical Pearl

- Avoid using drug, especially steroids. Use steroids only in ventilator dependent babies who are more than 1 week of life, in smallest possible dose and for shortest duration.

Preventive Strategies

Avoidance of factors that predispose to lung injury is cornerstone of management of BPD. Some of the proven strategies in the management of BPD are as follows:
- Antenatal steroids
- Early surfactant therapy
- Ventilation strategies: aim is to minimize lungs injury by optimizing the ventilator strategies which includes:
  - Early institution of CPAP
  - Use of intubation-surfactant-extubation (INSURE) technique followed by CPAP
  - Use of patient triggered ventilation: more physiological
  - Permissive hypercapnia: accepting PCO_2 levels as high as 55 mmHg with pH greater than or equal to 7.25
  - Avoidance of hyperoxia: target SpO_2: 85–92% in acute phase of ventilation
  - High frequency oscillation: less injurious to lungs, but no evidence for its benefits in routine use.
- Early use of caffeine therapy: within first 72 hours, preferably as early as feasible
- Low fluid intake
- Aggressive nutrition strategies
- Prevention of nosocomial infections
- Aggressive treatment of PDA
- Vitamin A: essential for lung development and differentiation. Its use in extremely low birth weight (ELBW) babies as 5,000 IU IM three times/week for 4 weeks reduces risk of BPD
- Inhaled nitric oxide: proven role yet to be established
- Corticosteroids: not recommended.

TABLE 5: Drug dosage

Drug	Dosage	Side effects
Caffeine	• Loading: 20–25 mg/kg IV over 30 min or PO (equivalent to 10–12.5 mg/kg caffeine base). • Maintenance: 5–10 mg/kg of caffeine citrate IV or PO once daily	• Restlessness, vomiting, and tachycardia
Diuretics		
Furosemide	• IV: 1–2 mg/kg/dose q 12–24 hourly	• Hypercalciuria
	• Oral: 2–6 mg/kg q 6–8 hourly	• Nephrocalcinosis
Chlorthiazides	• 10–20 mg/kg q 12 hourly	• Ototoxicity
Spironolactone	• 0.5–1.5 mg/kg q 12 hourly	• Hypokalemia, alkalosis
Bronchodilators	Inhalation	
Salbutamol	• 0.1–0.5 mg/kg q 2–6 hourly	• Tachycardia, tremors
Ipratropium	• 0.025 mg/kg q 8 hourly	
Dexamethasone		
Use minimal possible dose and for minimum duration of 3–7 days and only in infants who are >7 days old and cannot be weaned off from mechanical ventilation	• 0.15 mg/kg/day x 3 days • 0.1 mg/kg/day x 2 days • 0.05 mg/kg/day x 2 days in two divided doses	• Hyperglycemia, hypertension, gastrointestinal hemorrhage, and perforation • Poor neurodevelopment outcome

IV, intravenous; PO, per os.

Clinical Pearl

- Respiratory strategies aim to minimize lung injury and early use of caffeine reduces the chances of developing bronchopulmonary dysplasia..

INFANT STIMULATION AND PARENTAL SUPPORT

Infants with severe BPD may be ventilator dependent for many weeks or months and thus, deprived of normal parental stimulation. A well-organized stimulation program and parental participation helps in reducing infant's neurodevelopmental delays and allaying parental anxiety.

DISCHARGE PLANNING

Usually, oxygen can be discontinued in before discharge. However, home oxygen therapy is a safe alternative to long-term hospitalization in selected cases:

- Stable babies with no other medical illness
- Stable oxygen requirement
- Parents prepared and trained
- Follow-up is ensured.

OUTCOME

The outcome has improved because of better management and milder form of the disease.

Mortality is low; however, when it occurs is usually because of respiratory failure, infections, pulmonary hypertension, and cor pulmonale. Infants with severe BPD are at higher risk of:

- Growth failure
- Feeding problems and gastroesophageal reflux
- Recurrent chest infections
- Hyper-reactive airway disease
- Long-term neurodevelopmental sequelae
- Recurrent hospitalization.

KEY POINTS

- ☞ Bronchopulmonary dysplasia (BPD) is mainly a disease of extreme preterm and very low birth weight babies, contributing to morbidities like neurodevelopment impairment, recurrent respiratory illnesses, and growth failure
- ☞ Prematurity, severity of respiratory disease, and ventilation are the main risk factors
- ☞ Preventive strategies like antenatal steroids, early use of surfactants, gentle ventilation, early and aggressive use of continuous positive airway pressure, and early caffeine therapy reduce the incidence of BPD
- ☞ Early extubation should be the goal for all preterm babies requiring mechanical ventilation
- ☞ Systemic steroids should be used only in selective cases
- ☞ Nutrition, early stimulation, and parental anxiety should be addressed timely
- ☞ Use of anti-inflammatory agents like inhaled nitric oxide, late use of surfactant and antioxidants may be promising therapies in the future.

SUGGESTED READINGS

1. Bancalari EH, Walsh MC. Bronchopulmonary dysplasia. In: Martin RJ, Fanaroff AA, Walsh MC (Eds). Fanaroff and Martin's Neonatal-Perinatal Medicine Disease of the Fetus and Infant, 9th ed. Elsevier; 2011. pp. 1179-91.
2. Davis JM, Rosenfield WN. Bronchopulmonary dysplasia. In: MacDonald MG, Seshia MMK, Mullett MD (Eds). Avery's Neonatology Pathophysiology and Management of the Newborn, 6th ed. Lippincott Williams and Wilkins; 2005. pp. 568-99.
3. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723-9.
4. Korones Sheldon B. Complications. In: Goldsmith JP, Karotkin EH (Eds). Assisted Ventilation of the Neonate, 5th ed. Saunders; 2011. pp. 389-425.
5. Patel RM, Leong T, Carlton DP, Vyas-Read S. Early caffeine therapy and clinical outcomes in extremely preterm infants. J Perinatol. 2013;33(2):134-40.

CHAPTER 7

Patent Ductus Arteriosus

Kiran P Sathe, Anjali Kulkarni

INTRODUCTION

It is the abnormal persistence of the normal fetal vessel joining the pulmonary trunk to the descending aorta. It is one of the commonest congenital cardiac anomaly in neonatal period especially in the preterm neonates. It may result in altered hemodynamics and can complicate the clinical course in the inital days of life in sick neonates.

INCIDENCE

Vermont Oxford Network (2006) of nearly 40,000 preterm infants with a birthweight 501–1,500 g showed the overall incidence of patent ductus arteriosus (PDA) to be 37.2%. The incidence of PDA in infants with gestational ages of 24, 25, and 26 weeks was 76.9, 69.5, and 61.5%, respectively. Although spontaneous permanent ductus arteriosus closure occurs in nearly 34% of extremely low birth weight neonates 2–6 days postnatally and in the majority of very low birth weight neonates within the first year of life, 60–70% of preterm infants of less than 28 weeks' gestation receive medical or surgical therapy for a PDA.

PATHOPHYSIOLOGY

During fetal life, ductus arteriosus helps to shunt blood away from the high resistance pulmonary circulation (Fig. 1). Postdelivery, the pulmonary vascular resistance falls with increase in the oxygen tension. This coupled with increase in systemic vascular resistance following clamping of the cord, results in reversal of the ductal shunt, eventually resulting in closure of the ductus. While functional closure occurs within first 4 days of life, anatomical closure occurs by second week of life. Failure of the ductal closure results in PDA.

Predisposing Factors

- Prematurity less than 34 weeks
- Respiratory distress syndrome and surfactant administration

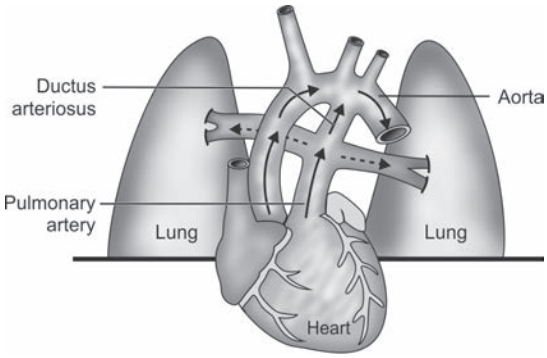


Fig. 1: Normal flow of blood through the ductus during the fetal life (marked by solid arrows) compared to the flow during the extrauterine life (marked by dotted arrows)

- Intravenous fluid overload
- Perinatal asphyxia
- Congenital syndromes
- High altitude.

Clinical Pearl

- Patency or closure of ductus depends on the balance between vasodilator and vasoconstrictive factors. Oxygen therapy in preterm neonates has a vasoconstricting effect while prostaglandins (PGE2) have vasodilator effect.

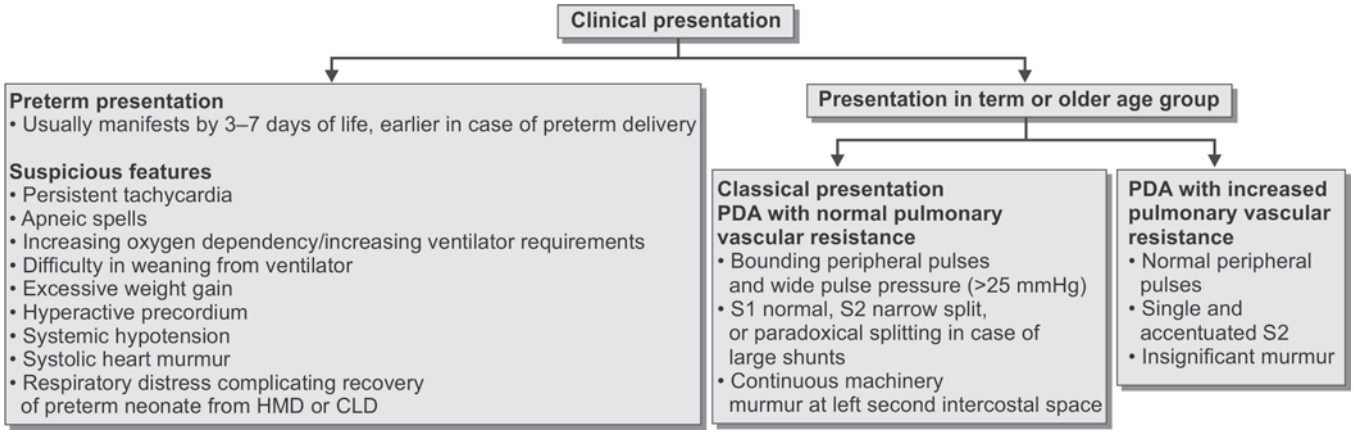
CLINICAL PRESENTATION

Clinical presentation of PDA has been discussed in detail in algorithm 1.

In one study, pulse quality (43%) and murmur (42%) had the highest mean sensitivities. Corresponding specificities were 74% for pulse volume and 87% for murmur. The combination of a cardiac murmur with an abnormal pulse volume had the highest positive predictive value (77%). The radiological examination did not improve the observers' ability to distinguish between patients with and without PDA.

ALGORITHM 1

Clinical presentation of patent ductus arteriosus



PDA, patent ductus arteriosus; HMD, hyaline membrane disease; CLD, chronic lung disease.

Clinical Pearls

- Increase in the pulmonary fluid in an infant with previously improving or stable respiratory status should raise a suspicion of underlying patent ductus arteriosus (PDA)
- Similar findings can occur with other cardiac lesions, such as aortic-pulmonary window or an arteriovenous fistula
- Clinical signs are very unreliable for diagnosis of PDA in preterm infants. Echocardiography should always be used for diagnosis.

INVESTIGATIONS

Two-dimensional echocardiography with Doppler ultrasound: identifies of PDA, associated cardiac defects and direction of flow with cardiac contractility. Signs of hemodynamically significant duct on echocardiography are:

- Left atrium-to-aortic root diameter ratio of greater than or equal to 1.4 in the parasternal long axis view
- Ductus arteriosus diameter of greater than or equal to 1.4 mm/kg body weight
- Holodiastolic flow reversal in the descending aorta
- Pulse wave Doppler main pulmonary artery demonstrates turbulent systolic and diastolic flow and abnormally high antegrade diastolic flow (≥0.5 m/s).

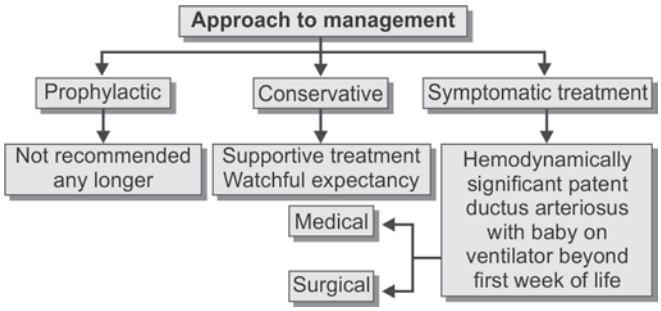
Clinical Pearls

- Always rule out a duct dependent lesion on echocardiogram in case the facility is available before starting pharmacotherapy
- Duct dependent pulmonary or systemic blood flow should be identified on echocardiography, as patent ductus arteriosus closure is contraindicated in such patients.

MANAGEMENT (ALGORITHM 2)

ALGORITHM 2

Management of patent ductus arteriosus



Prophylactic Treatment

- Treatment either medical or surgical closure of PDA before the symptoms began
- Was practiced earlier but no longer recommended as associated with side effects like increased bronchopulmonary dysplasia (BPD) in those who never developed PDA and the fact that most PDAs don't require treatment.

Conservative Treatment

Managing PDAs with supportive therapies as discussed in the chapter and waiting for a spontaneous closure as can happen in approximately 30% cases in first week and many can close spontaneously in the first year.

Symptomatic Treatment

- Treatment only when the PDA is causing significant morbidity and not responding to treatment
- Indications:
  - Hemodynamically significant PDA on ventilator beyond first week of life and not improving despite supportive treatment
  - Hemodynamically significant PDA with necrotizing enterocolitis (NEC) or renal failure (in such cases ibuprofen or surgery is preferred over indomethacin
- Second course may be used in case the baby remains on ventilator despite the use of one course of pharmacotherapy. The reported closure rate with the second dose is 40%.

Clinical Pearl

- Not all patent ductus arteriosus require closure. The optimal current management approach is not known as there is paucity of large randomized controlled trials comparing the three approaches in the current era of neonatal practice.

Supportive Treatment

- Thermoneutral environment
- Maintenance of hematocrit >35% to increase the pulmonary vascular resistance
- High positive end-expiratory pressure and lower inspiratory time
- No loop diuretics: results in increased ductal patency because of vasodilatory prostaglandin E2 release and increased incidence of side effects. If required, use thiazide diuretics
- Moderate fluid restriction: 110–130 mL/kg/day
- Monitoring of weight at least twice daily
- Serum electrolytes and renal functions are to be monitored twice daily
- Daily ultrasonography (USG) head.

Clinical Pearl

- Feeding during treatment with pharmacotherapy can continue with enteral trophic feeds preferably human milk.

Agents Used for Pharmacotherapy

Indomethacin

- Dose: 0.2 mg/kg/dose every 12 hours for three doses
- Targeted treatment: discontinuing treatment when the sequential echoes show closure even before the full course. Similar closure rates comparable to full course are there but a nonstatistical trend toward higher intraventricular hemorrhage (IVH) in the targeted group does not warrant using this approach till further trials
- Long course: 0.1–0.2 mg/kg/dose once a day for 5 days is not recommended now as although the closure rates were similar, the incidence of NEC was increased
- Side effects: decreased blood flows to different organs resulting in cerebral ischemia, renal failure, and NEC. There is also increased risk of intestinal perforation in those with concomitant use of hydrocortisone
- Contraindications:
  - Blood urea greater than 60 mg/dL
  - Serum creatinine greater than 0.8 mg/dL
  - Urine output less than 1 mL/kg/h
  - Platelet count less than 50,000/mm^3
  - Necrotizing enterocolitis
  - Active bleeding
  - Intraventricular hemorrhage grade III/IV or if progression of IVH is demonstrated in earlier cranial USG.

Ibuprofen

- Similar efficacy as compared to indomethacin with lesser NEC and renal dysfunction. There is, however, few case reports of persistent pulmonary hypertension of the newborn with ibuprofen use and nonstatistical increase in the incidence of chronic lung disease with its use
- Dose: 10 mg/kg first dose followed by 5 mg/kg for two more doses 24 hours apart
- Intravenous formulations mostly tried but since this one is not available in India at present, one should use the oral form despite the paucity of literature on the same.

Paracetamol

- Mainly observational data, no randomized controlled trial available at present
- Dose 60 mg/kg/day in four divided doses for 2–5 days
- Indications: failure to respond to or contraindication to use of cyclooxygenase (COX) inhibitors
- Safety not established at present
- Not currently recommended.

Surgical Ligation

- Indications: failure of two courses or contraindication for use of COX inhibitors who have a large PDA and on high ventilator settings
- Increased adverse effects with ligation, hence not preferred
- Postoperative: risk of significant brain injury due to intraoperative compromise or postoperative hemodynamic instability. Use of functional echocardiography after surgery should be considered to manage shock.
- Coil or device closure for symptomatic PDA with normal pulmonary artery pressure in children with more than 3 kg.

KEY POINTS

- ☞ Patent ductus arteriosus (PDA) is the persistence of normal fetal vessel and usually complicates preterm deliveries
- ☞ Nonspecific clinical presentation mandates echocardiographic evaluation to conclusively diagnose PDA and assess for any associated cardiac comorbidities
- ☞ Nonjudicious use of oxygen therapy in preterm babies can be harmful and can inadvertently lead to ductus closure in cases with duct dependent lesions
- ☞ Therapeutic closure of ductus is not warranted except in symptomatic cases
- ☞ Medical closure is easier, effective, safer, and preferred over surgical closure.

SUGGESTED READINGS

1. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. J Perinatol. 2006;26:S14-8.
2. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal. 2007;92(6):F424-7.
3. Niu MC, Mallory GB, Justino H, Ruiz FE, Petit CJ. Treatment of severe pulmonary hypertension in the setting of the large patent ductus arteriosus. Pediatrics. 2013;131(5):e1643-9.
4. Sasi A, Deorari A. Patent ductus arteriosus in preterm infants. Indian Pediatr. 2011;48:301-8.
5. Sekar KC, Corff KE. Treatment of patent ductus arteriosus: indomethacin or ibuprofen? J Perinatol. 2008; 28(1):S60-2.

CHAPTER 8

Neonatal Shock

Ranjan K Pejaver, Manisha Halkar

INTRODUCTION

The term "shock" denotes a complex clinical syndrome characterized by acute failure of the circulatory system to maintain adequate tissue and organ perfusion which leads to inadequate oxygen and nutrient substrate delivery to body tissues and compromised metabolic waste product removal.

INCIDENCE

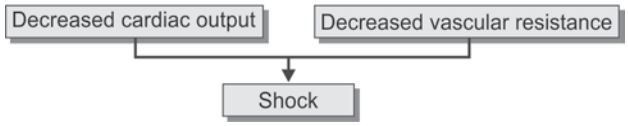
Shock is a common morbidity which presents as a neonatal emergency. As it is a multi factorial disorder the true incidence is difficult to estimate.

PATHOPHYSIOLOGY OF SHOCK

The pathophysiology of shock has been outlined in algorithm 1.

ALGORITHM 1

Pathophysiology of shock



ETIOLOGY OF SHOCK

Box 1 describes etiology of different types of shock.

Box 1: Etiology of shock

Hypovolemic shock

- Acute and/or chronic blood loss
  - Placental abruption or placenta previa
  - Uterine/umbilical cord rupture
  - Difficult delivery leading to trauma and/or hypoxia
  - Maternal-fetal transfusion
  - Twin-to-twin transfusion

Continued

Continued

  - Sequestered blood
  - Accidental or incorrect removal of arterial lines
  - Iatrogenic causes such as iatrogenic laboratory blood outs
- Plasma or fluid losses
  - Effusions (erythroblastosis fetalis, nonimmune hydrops)
  - Break in skin integrity
  - Myelomeningocele, gastroschisis
- Dehydration
  - Emesis or diarrhea, insensible water loss or repeated discarding of the gastrointestinal residuals

Cardiogenic shock

- Left ventricular outflow tract obstruction
  - Hypoplastic left heart syndrome, critical aortic stenosis or coarctation of aorta
- Large left-to-right shunts
  - Ventricular septal defect
  - Atrial septal defect
  - Patent ductus arteriosus
- Infective myocarditis
  - Enterovirus
  - Herpes simplex virus-2
- Cardiomyopathy
  - Dilated cardiomyopathy
  - Hypertrophic cardiomyopathy (infant of diabetic mother)
- Dysrhythmia
  - Prolonged, unrecognized supraventricular tachycardia
  - Bradyarrhythmias
  - Complete heart block (systemic lupus erythematosus in mother)
  - Intrapartum or postpartum asphyxia
  - Metabolic acidosis
  - Severe hypoglycemia, hypocalcemia
  - Inborn error of metabolism (glycogen storage disease, muco-polysaccharidoses, disorders of fatty acid metabolism)
- Distributive shock
  - Sepsis
- Obstructive shock
  - Tension pneumothorax
  - Congenital diaphragmatic hernia

Clues on History Suggesting Etiology

- Significant blood loss from placental anomalies; hypovolemic shock
- Maternal chorioamnionitis; septic shock
- Hydrops fetalis; distributive shock
- Maternal history of systemic lupus erythematosus or Sjögren's syndrome; cardiogenic shock
- Prior maternal history of stillbirth
- Foul smelling or meconium stained amniotic fluid; septic shock
- Antenatal asphyxia with abnormal heart rate pattern; cardiogenic shock
- Congenital heart disease detected by prenatal ultrasound; cardiogenic shock

DIAGNOSIS

- Neonates with shock present with diverse signs and symptoms
- In clinical practice, the reference range blood pressure limits are defined as the gestational and postnatal age dependent blood pressure values between the 5th (or 10th) and 95th (or 90th) percentiles
- However, by the third day of life, most preterm infants, even with 24–26 weeks' gestation, have a mean blood pressure of 30 mmHg or greater (Table 1)
- As a rough rule of thumb, the lower limit of normal mean blood pressure in mmHg on the day of birth is approximately equal to the gestational age in weeks (Table 2)
- Measurement of neonatal blood pressure can be completed directly through invasive techniques, i.e., direct manometry using an arterial catheter or use of an in-line pressure transducer or indirectly through noninvasive techniques which include manual oscillometric techniques and automated Doppler techniques.

TABLE 1: Blood pressure range in preterm infants by age

Day	Systolic range (mmHg)	Diastolic range (mmHg)
1	48–63	25–35
2	54–63	30–39
3	53–67	31–43
4	57–71	32–45
5	56–72	33–47
6	57–71	32–47
7	61–74	34–46

TABLE 2: Blood pressure ranges in term infants

Age	Systolic (mmHg)	Diastolic (mmHg)	Mean (mmHg)
1 h	70	44	53
12 h	66	41	50
Day 1	71 ± 9	43 ± 10	55 ± 9
Day 3	77 ± 12	49 ± 10	63 ± 13
Day 6	76 ± 10	49 ± 11	62 ± 12
Week 2	78 ± 10	50 ± 9	–
Week 4	85 ± 10	46 ± 9	–

Clinical Pearl

- Noninvasive methods may overestimate the blood pressure in hypotensive infants.

INVESTIGATIONS IN NEONATAL SHOCK

Investigations to be done in neonatal shock have been enlisted in table 3.

TABLE 3: Investigations in neonatal shock

For determining the cause of shock	For management of shock
Sepsis screen and blood culture: rule out sepsis	Blood gas to alter ventilation and look for acidosis
Echocardiography if cardiogenic shock is suspected	Serum lactate: serial monitoring to gauge the progress
Chest X-ray to rule out pneumothorax or other respiratory pathologies and cardiac disease	Functional echo: to study the superior vena cava flow and study the right ventricular and left ventricular output
Kleihauer-Betke test to rule out fetomaternal hemorrhage	Ionized calcium: correcting hypocalcemia may improve cardiac contractibility
Ultrasonography head to rule out intraventricular hemorrhage	Serum cortisol to correct relative adrenal insensitivity
Serum biochemistry	

Clinical Pearl

- Use of functional echocardiography aids assessment of cardiac output and may help choice of inotropes.

MANAGEMENT OF NEONATAL SHOCK

Management of neonatal shock has been outlined in algorithm 2.

Clinical Pearls

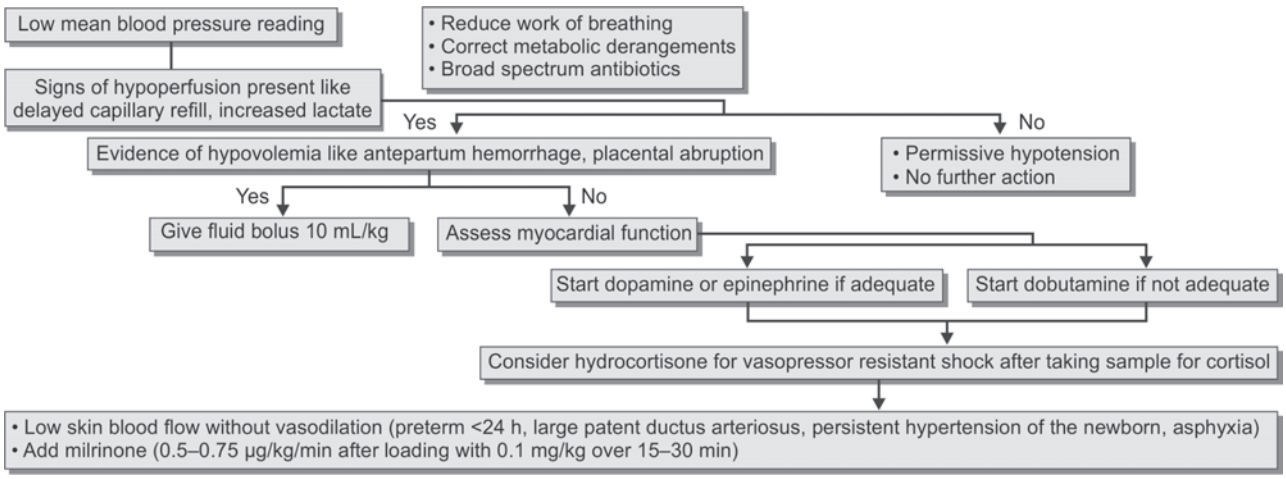
- Low blood pressure in a preterm baby may not need to be treated unless associated with signs of poor perfusion
- Since dopamine and dobutamine have a half-life of 2 minutes, any change in their concentration would result in steady state in 10 minutes, and hence, changes in their dosage should be made every 15 minutes till the blood pressure stabilizes.

Vasoactive Agents Used in Neonatal Shock

Vasoactive agents used in neonatal shock have been discussed in table 4.

ALGORITHM 2

Management of neonatal shock



SBF, skin blood flow; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn.

TABLE 4: Vasoactive agents used in neonatal shock

Agent type	Agent	Dosage	Comments
Volume expanders	Isotonic sodium chloride solution	10–20 mol/kg IV	Hypovolemic shock, readily available
	Plasma	10–20 mL/kg IV	Disseminated intravascular coagulation, expensive
	Whole blood products	10–20 mL/kg IV	Hypovolemic due to blood loss
	Reconstituted blood products	10–20 mL/kg IV	Use O negative
Vasoactive drugs	Dopamine	5–20 µg/kg/min IV	Inotropic sympathomimetic amine acting on α and β dopaminergic receptors. Lower doses myocardial contractility and higher doses peripheral vasoconstriction
	Dobutamine	5–20 µg/kg/min IV	Inotropic sympathomimetic amine acting on α and β receptors. Increases myocardial contractility and peripheral vaso-dilatation suitable for hypotension associated with myocardial dysfunction and low cardiac output
	Epinephrine	0.05–1 µg/kg/min IV	Stimulates α1, α2, β1, β2; vasodilatation at low doses, inotropic action, significant vasoconstriction at higher doses. Treatment of refractory hypotension
	Norepinephrine	0.05–1 µg/kg/min IV	Used in refractory hypotension. Stimulates β1- and α-adrenergic receptors, increasing cardiac muscle contractility and heart rate, as well as vasoconstriction
	Milrinone	75 µg/kg over 60 min; Maintenance infusion 0.5–0.75 µg/kg/min	Selective phosphodiesterase inhibitor, inotrope, and vasodilator

KEY POINTS

- ☞ Neonatal shock can present with varied signs and symptoms
- ☞ It is important to differentiate cardiac causes of shock to enable prompt treatment of the cause
- ☞ Repeated volume replacements are not indicated in newborns as it may lead to fluid overload and associated complications. One should have a low threshold for starting vasopressor drugs
- ☞ Shock must be corrected before it becomes irreversible causing multiorgan failure.

SUGGESTED READINGS

1. Al-Aweel I, Pursley DM, et al. Variations in prevalence of hypotension, hypertension, and vasopressor use in NICUs. J Perinatol. 2001;21(5):272-8.
2. Haque KN. Understanding and optimizing outcome in neonates with sepsis and septic shock. In: Yearbook of intensive care and emergency medicine. London: Springer; 2007. pp. 55-68.
3. Kourembanas S. Shock. In: Cloherty JP, Eichenwald EC, Stark AR (Eds). Manual of Neonatal Care, 6th ed. Philadelphia: Lippincott; 2008. p. 176.
4. Lee J, Rajadurai VS, Tan KW. Blood pressure standards for very low birthweight infants during the first day of life. Arch Dis Child Fetal Neonatal Ed. 1999;81: F168-70.
5. Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. Clin Perinatol. 1999;26:981-96.
6. Seri I, Evans J. Controversies in the diagnosis and management of hypotension in the newborn infant. Curr Opin Pediatr. 2001;13(2):116-23.
7. Wynn JL, Wong HR. Pathophysiology and treatment of septic shock in neonates. Clin Perinatol. 2010;37(2):439-79.
8. Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. J Perinatol. 1995;15(6): 470-9.

CHAPTER 9

Anemia in Neonate

Nandkishor S Kabra

INTRODUCTION

Anemia is one of the common hematological abnormalities in newborn. Normal erythropoiesis in newborn is influenced by several factors, especially erythropoietin. Erythropoietin stimulates maturation of red blood cell (RBC) precursors.

It is defined as hemoglobin or hematocrit value that is more than 2 standard deviations below the mean for age (Table 1 and 2).

ETIOLOGY

Three general causes include blood loss, increased RBC destruction, and decreased RBC production.

1. Blood loss, the commonest cause of neonatal anemia, includes:
   - Obstetrical causes: placental abruption, placenta previa, trauma to placenta or umbilical cord during delivery, and rupture of anomalous placental vessels
   - Fetomaternal transfusion: 8% of normal pregnancies have some admixture
   - Fetoplacental transfusion due to positioning of infant above level of placenta after delivery, partial cord occlusion (e.g., with nuchal or prolapsed cord).
   - Twin-twin transfusion: occurs only with monochorionic (i.e., monozygotic) twins and when there are placental vessels which allow shunting of blood from one twin to the other. Donor will have anemia of variable severity and recipient will have polycythemia of variable severity
   - Internal hemorrhage such as intracranial hemorrhage (ICH), intraventricular periventricular hemorrhage, subgaleal hemorrhage, cephalohematoma, adrenal hemorrhage, subcapsular hematoma of liver, or ruptured viscus (e.g., spleen)
   - Iatrogenic blood loss secondary to sampling of blood for laboratory tests. This is the commonest cause of anemia (and transfusion) in small premature infants.

TABLE 1: Normal hematological values in full term infants

Age (days)	Hb (g/dL)	PCV (%)	Reticulocyte count (%)
1	19.0 ± 2.2	61 ± 7	3.2 ± 1.4
2	19.0 ± 1.9	60 ± 6	3.2 ± 1.3
3	18.7 ± 3.4	62 ± 9	2.8 ± 1.7
4	18.6 ± 2.1	57 ± 8	1.8 ± 1.1
5	17.6 ± 1.1	57 ± 7	1.2 ± 0.2
6	17.4 ± 2.2	54 ± 7	0.6 ± 0.2
7	17.9 ± 2.5	56 ± 9	0.5 ± 0.4
Age (weeks)			
1–2	17.3 ± 2.3	54 ± 8	0.5 ± 0.3
2–3	15.6 ± 2.6	46 ± 7	0.8 ± 0.6
3–4	14.2 ± 2.1	43 ± 6	0.6 ± 0.3
4–5	12.7 ± 1.6	36 ± 5	0.9 ± 0.8
5–6	11.9 ± 1.5	36 ± 6	1.0 ± 0.7

PCV, packed cell volume; Hb, hemoglobin.

TABLE 2: Normal hemoglobin levels (g/dL) in preterms

Birth-weight (g)	Postnatal age (weeks)				
	2	4	6	8	10
800–1,000	16.0 (14.8–17.2)	10.0 (16.8–13.2)	8.7 (7.0–10.2)	8.0 (7.1–9.8)	8.0 (6.9–10.2)
1,001–1,200	16.4 (14.1–18.7)	12.8 (7.8–15.3)	10.5 (7.2–12.3)	9.1 (7.8–10.4)	8.5 (7.0–10.0)
1,201–1,400	16.2 (13.6–18.8)	13.4 (8.8–16.2)	10.9 (8.5–13.3)	9.9 (8.0–11.8)	9.8 (8.4–11.3)
1,401–1,500	15.6 (13.4–17.8)	11.7 (9.7–13.7)	10.5 (9.1–11.9)	9.8 (8.4–12.0)	9.9 (8.4–11.4)
1,501–2,000	15.6 (13.5–17.7)	11.0 (9.6–14.0)	9.6 (8.8–11.5)	9.8 (8.4–12.0)	10.1 (8.6–11.8)

2. Increased RBC destruction:
   - Intrinsic causes: hereditary RBC disorders (rare), including RBC enzyme defects (e.g., glucose-6-phosphate dehydrogenase (G6PD) deficiency, hexokinase deficiency, pyruvate kinase deficiency), RBC membrane defects (e.g., hereditary spherocytosis, elliptocytosis, stomatocytosis), hemoglobinopathies (e.g., α-thalassemia)
   - Extrinsic causes: immune hemolysis (Rh incompatibility, ABO incompatibility, minor blood group incompatibility, e.g., Kell, Duffy).
   - Acquired hemolysis: infection, disseminated intravascular coagulation, drugs
3. Decreased RBC production:
   - Anemia of prematurity due to transient deficiency of erythropoietin
   - Aplastic or hypoplastic anemia (e.g., Diamond-Blackfan)
   - Bone marrow suppression (e.g., with rubella or parvovirus B19 infection)
   - Nutritional anemia (e.g., iron deficiency), usually after neonatal period.

Clinical Pearl

- Anemia in neonates is the commonest hematologic abnormality.

CLINICAL FINDINGS

This will vary with the severity of anemia and other associated conditions. The major physiologic impact of anemia is decreased oxygen delivery to tissues, resulting in compensatory responses and acute/chronic consequences. There may be no signs with mild anemia. With more severe anemia, examination findings include: pallor, tachycardia, tachypnea, apnea, increase in oxygen requirements, lethargy, poor feeding, hepatosplenomegaly (hemolytic disease), jaundice, wide pulse pressure, hypotension, metabolic acidosis.

CLINICAL APPROACH

History

- Family history: anemia, jaundice, gallstones, splenectomy, ethnicity
- Maternal history: anemia, blood group and Rh type, transfusions, viral exanthematous illness during pregnancy, per vaginal bleeding, multiple gestation: twin-to-twin transfusion, type of delivery (instrumental), complications of labor and delivery
- Neonatal history: age at onset, physical findings, to know the cause of anemia (Table 3).

Physical Examination

- Look for cephalohematoma, subgaleal bleed, petechiae, and overt bleeding from gastrointestinal tract and umbilical cord
- Pallor with prolong capillary refill time: tachycardia and hypotension: acute blood loss
- Pallor without signs of decompensation: chronic blood loss
- Pallor, jaundice, hepatosplenomegaly: chronic hemolysis
- Failure to thrive may be a manifestation of chronic anemia
- Examination of placenta: for evidence of hematoma, retroplacental clots, infection, and arteriovenous anastomosis in monochorionic placenta.

Clinical Pearl

- A systemic approach is required to identify exact cause of anemia and a protocol base management is must to correct it.

TABLE 3: Classification of anemia in the newborn

Reticulocytes	Bilirubin	Coombs test	RBC morphology	Diagnostic possibilities
Normal or ↓	Normal	Negative	• Normal	• Physiologic anemia of infancy or prematurity; congenital hypoplastic anemia; other causes of decreased production
Normal or ↑	Normal	Negative	• Normal	• Acute hemorrhage (fetomaternal, placental, umbilical cord, or internal hemorrhage)
↑	↑	Positive	• Hypochromic microcytes • Spherocytes	• Chronic fetomaternal hemorrhage • Immune hemolysis (blood group incompatibility or maternal autoantibody)
Normal or ↑	↑	Negative	• Spherocytes • Elliptocytes • Hypochromic microcytes • Spiculated RBCs • Schistocytes and RBC fragments • Bite cells (Heinz bodies with supravital stain) • Normal	• Hereditary spherocytosis • Hereditary elliptocytosis • α- or γ-thalassemia syndrome • Pyruvate kinase deficiency • Disseminated intravascular coagulation; other microangiopathic processes • Glucose-6-phosphate dehydrogenase deficiency • Infections; enclosed hemorrhage (cephalohematoma)

RBC, red blood cell.

Source: Christou HA. Anemia. In: Cloherty JP, Eichenwald EC, Hanson AR, Stark AR, editors. Manual of Neonatal Care. 7th ed (South Asian Edition). Philadelphia: Wolters Kluwer, LWW; 2012. p. 563-71.

INVESTIGATIONS (ALGORITHM 1)

- Complete hemogram with peripheral smear and reticulocyte count and RBC indices
- Blood group and direct Coombs test
- Serum bilirubin: increased levels of indirect bilirubin suggestive of chronic hemolysis
- Kleihauer-Betke test of mother's blood: estimation of fetal blood lost into maternal circulation can be made by using the formula 2400 × fetal/maternal cells = mL of fetal blood, e.g., 1/600 red cells in mother's circulation is fetal, then 2,400 × 1/600 = 4 mL of fetal blood in maternal circulation
- Thick and thin peripheral smear for malarial parasites
- Urine for hematuria
- Stool for occult blood
- TORCH screen (toxoplasma, rubella, cytomegalovirus, herpes, parvovirus B19, coxsackie): baby and mother
- Ultrasound skull for evidence of ICH/intraventricular hemorrhage
- Test for G6PD deficiency
- Bone marrow examination, if indicated.

MANAGEMENT

- Fluid resuscitation: normal saline push followed by packed cell transfusion: acute blood loss
- Treat the underlying cause, e.g., treatment of sepsis and toxoplasmosis
- Iron therapy: 6 mg/kg/day for 3 months: chronic blood loss.

Clinical Pearl

- In preterm and term infants, packed red blood cells transfusion should be considered if an immediate need for increased oxygen delivery to tissues is clinically desired.

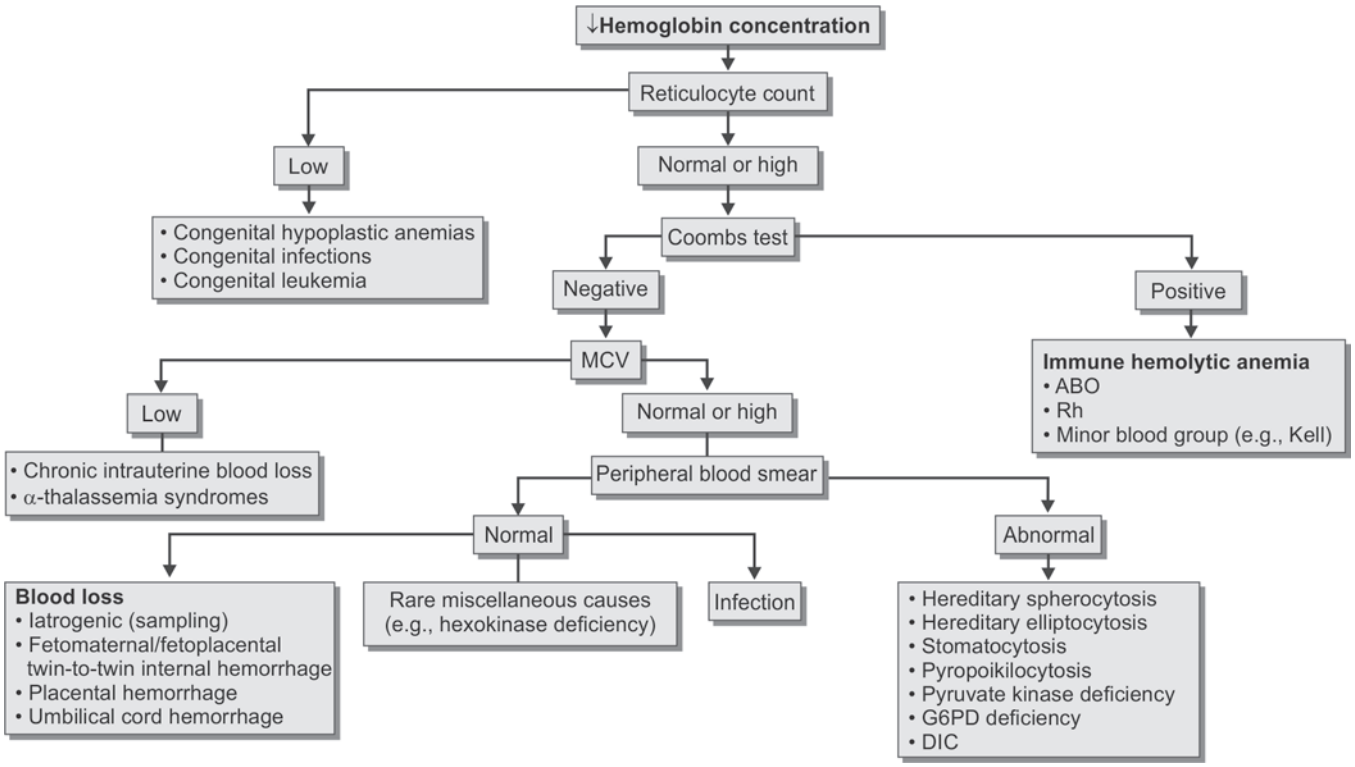
Red Blood Cell Transfusion Guidelines for Premature Infants

Consider RBC transfusions in the following conditions:

- For infants requiring significant mechanical ventilation, defined as FiO_2 greater than 40% and/or pressor support if the central hematocrit is less than 40% (hemoglobin <11 g/dL)
- For infants requiring minimal mechanical ventilation, with FiO_2 less than 35%, if the central hematocrit is less than 35% (hemoglobin <10 g/dL)
- For infants on supplemental oxygen who are not requiring minimal mechanical ventilation, with FiO_2 less than 25%, if the central hematocrit is less than 25% (hemoglobin <8 g/dL), one or more of the following is present:
  - More than 24 hours of tachycardia (heart rate >180/min) or tachypnea (respiratory rate >80 breaths per min)
  - An increased oxygen requirement from the previous 48 hours, define as greater than fourfold increase in nasal cannula flow (i.e., 0.25–1 L/min) or an increase in nasal continuous positive airway pressure (CPAP) more than 20% from the previous 48 hours (i.e., 5–6 cm H_2O)

ALGORITHM 1

Approach to anemia in newborn



DIC, disseminated intravascular coagulation; MCV, mean corpuscular volume; G6PD, glucose-6-phosphate dehydrogenase.

- Weight gain less than 10 g/kg/day over the previous 4 days while receiving more than 100 kcal/kg/day
- An increase in the number or severity of apnea and bradycardia (in general >10 spells or >3 spells requiring bag and mask ventilation; however, absolute number is up to individual interpretation)
- Infant undergoing surgery

- For infants without any symptoms, if the central hematocrit is less than 20% hemoglobin (<7 g/dL) and the absolute reticulocyte count is less than 3%
- For infants with a cumulative blood loss of 10% or more of blood volume in 72-hour period when infant has significant cardiorespiratory illness, if further blood sampling is anticipated. Stable infants are not transfused only to replace blood lost through phlebotomy. If an erythrocyte transfusion is not given, "blood out" may be replaced mL for mL with 0.9% saline when 10–15 mL of blood per kg body weight is reached, in order to avoid hypovolemia. In addition to the saline used for the above indication, clinicians may administer additional albumin, fresh frozen plasma, platelet transfusions as they deem clinically indicated. Whenever possible, RBC transfusion should be given as 10–20 mL/kg, intravenously, infused slowly over 3–4 hours under cardiorespiratory monitoring. Packed RBCs volume may be restricted to 10 mL/kg in infants perceived to be at risk of necrotizing enterocolitis (NEC). Few studies have demonstrated that preterm very low birth weight (VLBW) infant if kept nil by mouth during the period of transfusion reduce the risk of transfusion related NEC. Small packs (triple and penta packs) of blood should be made available through blood bank for blood transfusion.

Complications Associated with Blood Transfusions

- Immunologic reactions:
  - Acute hemolytic reactions
  - Delayed hemolytic reactions
  - Transfusion associated acute lung injury
  - Allergic reaction
  - Graft versus host disease
- Infections: human immunodeficiency virus, hepatitis B and C, cytomegalovirus, malaria, syphilis
- Volume overload
- Transfusion related acute gut injury in premature infants
- Hypocalcemia
- Transfusion with adult packed RBCs may theoretically increase the release of oxygen and may cause hyperoxemia and toxicity
- Hypothermia, if large quantity of cold blood is used.

Prevention of Anemia of Prematurity

- Maintain record of phlebotomy losses: transfuse the babies to replace phlebotomy losses, if exceeding 10% of blood volume in 72 hours (only in babies with significant cardiorespiratory illness)
- Prophylactic iron therapy:
  - Babies less than 1500 g = 3–4 mg/kg/day starting at 2 weeks of life
  - Babies more than 1500 g = 2–3 mg/kg/day starting at 2 weeks of life.

Clinical Pearl

- Delay the cord clamping at birth in preterm infants to improve hemoglobin levels and reduce future transfusion needs.

- Use of recombinant human erythropoietin (rhEPO)
  - Indication: prevention of anemia of prematurity in VLBW
  - Dose: 100–300 IU/kg/dose subcutaneously on alternate day for 6 weeks (start at 2 weeks of age)
  - Supplement with iron (6 mg/kg/day)
  - In exclusively breastfed preterm infants, vitamin E supplementation is not indicated.

AREAS OF UNCERTAINTY

- When infants are transfused at lower hemoglobin values for the gestational age, postnatal age, and the need for assisted respiratory support (oxygen, CPAP, mechanical ventilation), it is considered as restricted transfusion approach. The use of restrictive as compared to liberal hemoglobin thresholds in infants of VLBW results in modest reductions in exposure to transfusion and in hemoglobin levels. Restrictive practice does not appear to have a significant impact on death or major morbidities at first hospital discharge or at follow-up. However, given the uncertainties of these conclusions, it would be prudent to avoid hemoglobin levels below the lower limits tested in clinical studies
- Early administration of rhEPO (started before 8 days of age) reduces the use one or more red blood cell transfusions, the volume of RBC transfused, and the number of donors and transfusions the infant is exposed to following study entry. The small reductions are of limited clinical importance.

KEY POINTS

- ☞ Anemia in neonates is the commonest hematologic abnormality
- ☞ Causes of anemia include blood loss, increased red blood cell (RBC) destruction and decreased RBC production
- ☞ While investigating a newborn with anemia, a systematic approach as depicted in algorithm 1 is desirable
- ☞ Delay the cord clamping at birth in preterm infants to improve hemoglobin levels and reduce future transfusion needs
- ☞ Use laboratory tests judiciously
- ☞ Monitor phlebotomy losses
- ☞ Start oral iron therapy in preterm infants by 2 weeks of age as infant is established on full enteral feeds
- ☞ Consider for erythropoietin therapy from first week of life in extremely low birth weight infants
- ☞ In preterm and term infants, packed RBCs transfusion should be considered if an immediate need for increased oxygen delivery to tissues is clinically desired.

SUGGESTED READINGS

1. Aher S, Ohlsson A. Early versus late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2012 Oct 17; 10:CD004865.
2. Aher S, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev. Cochrane Database Syst Rev. 2012 Sep 12;9:CD004868.
3. Blanchette V, Dror Y, Chan A. Hematology. In: McDonald MG, Mullet MD, Seshia MMK, (Editors). Avery's Neonatology, Pathophysiology and Management of the Newborn, 6th ed. (Indian edition). Philadelphia: Lippincott Williams and Wilkins; 2005. pp. 1169-234.
4. Christou HA. Anemia. In: Cloherty JP, Eichenwald EC, Hanson AR, Stark AR , (Editors). Manual of Neonatal Care, 7th ed. (South Asian Edition)., Philadelphia: Wolters Kluwer, LWW;, 2012. pp. 563-71.
5. Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr. 2006; 149:301-07.
6. Mentzer WC, Glader BE. Erythrocyte disorders in infancy. In: Taeusch HW, Ballard RA, Gleason CA, (Editors). Avery's Diseases of the Newborn, 8th ed. Philadelphia: Saunders; 2004. pp. 1180-214.
7. Ohlsson A,. Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2012 Sep 12; 9:CD004863.
8. Paul DA, Leef KH, Locke RG, Stefano JL. Transfusion volume in infants with very low birth weight: a randomized trial of 10 versus 20 ml/kg. J Pediatr Hematol Oncol. 2002; 24:43-6.
9. Roberts IAG, Murray NA., Hematology. In: Rennie JM, (Editors). Robertson's Textbook of Neonatology, 4th ed. Philadelphia: Elsevier Churchill Livingstone; 2011. pp. 739-72.
10. Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. Cochrane Database Syst Rev. 2011 Nov 9; 11:CD000512.

CHAPTER 10

Bleeding Neonate

Deepak Chawla

INTRODUCTION

Bleeding is an alarming symptom at any age, more so in a young infant. Loss of blood from intravascular space may manifest as overt bleeding like upper or lower gastrointestinal bleeding or pulmonary hemorrhage or as covert bleeding like intracranial hemorrhage. In addition, a neonate may manifest bleeding tendency by development of facial purpura after birth, prolonged bleeding from venipuncture sites and oozing from umbilical cord. Objective of this chapter is to delineate an approach to diagnose underlying cause and plan treatment of a bleeding neonate.

HEMOSTASIS IN NEONATE

Knowledge of components of hemostatic system and their physiological variation in term and preterm neonates is essential to develop understanding of causes of bleeding and to correctly interpret results of laboratory investigations. Components of hemostatic system include procoagulant factors, inhibitors of coagulation, fibrinolytic system, platelets, and endothelium (Algorithm 1). In neonates, there is decreased activity of procoagulant system which is balanced by decreased activity of coagulation inhibitors and fibrinolytic system so that a healthy term neonate does not develop bleeding or thrombosis despite passing through birth canal and undergoing postnatal extracellular fluid constriction (Table 1).

Clinical Pearl

- Laboratory values of coagulant factors in neonates should be based on gestation- and postnatal-age-based reference values.

CAUSES OF BLEEDING IN NEONATES

Bleeding in neonates may result from decreased number or function of platelets and specific deficiencies of coagulation factors (Table 2). Some systemic disorders can cause more widespread disturbance in hemostatic mechanism.

ALGORITHM 1

Coagulation factors (solid boxes) and their inhibitors (dashed boxes)

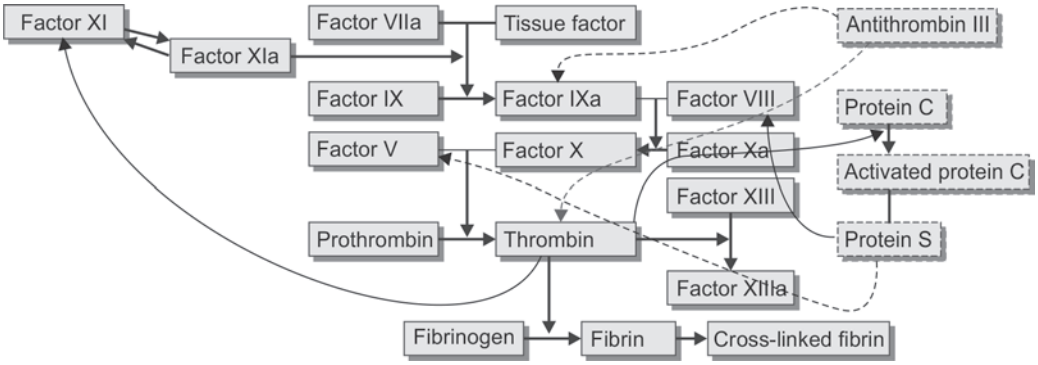


TABLE 1: Hemostatic system in a neonate in comparison to adults

Component of hemostatic system	Alteration
Platelets	• Platelet count comparable to adults • Smaller and more immature megakaryocytes • Lower thrombopoietin levels in thrombocytopenic neonates
Fibrinogen, factor V and factor VIII	• Comparable to adults
von Willebrand factor	• Increased
Other coagulation factors	• Decreased (by 50% as compared to adults)
Antithrombin III, protein C and protein S	• Decreased
Plasminogen	• Decreased

TABLE 2: Common causes of bleeding in neonates

Platelets	Coagulation factors
Early onset (within 72 h of birth) • Pregnancy complications (gestational hypertension, intrauterine growth restriction) • Early-onset sepsis • Neonatal alloimmune thrombocytopenia • Neonatal autoimmune thrombocytopenia • TORCH infections Late onset (after 72 h of birth) • Late-onset sepsis • Necrotizing enterocolitis • TORCH infections	• Vitamin K deficiency ○ Early (within 24 h) ○ Classical (24 h to 7 days) ○ Late (2–12 weeks) • Hemophilia A (classical hemophilia due to factor VIII deficiency) • Hemophilia B (factor IX deficiency) • Disseminated intravascular coagulation • Liver disease

TORCH, toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes infections.

Clinical Pearl

- Pregnancy complications are the most common underlying cause of early-onset thrombocytopenia. Systemic infections are most common underlying cause of late-onset thrombocytopenia.

APPROACH TO A BLEEDING NEONATE

History and Physical Examination

Detailed maternal history should be taken to rule out thrombocytopenia due to immune causes. Neonatal alloimmune thrombocytopenia (NAIT) is frequently suspected if there is history of bleeding or thrombocytopenia in previous siblings. Thrombocytopenia can also develop due to transplacental passage of antibodies from a mother affected by autoimmune thrombocytopenia or systemic lupus erythematosus. Thrombocytopenia is common but rarely severe to cause bleeding in neonates born to pregnancies complicated by gestational hypertension; intrauterine growth restriction, or hemolysis, elevated liver enzyme levels, and a low platelet count syndrome. History must be sought for systemic disorders which can cause disseminated intravascular coagulation like birth asphyxia and neonatal sepsis. Inherited deficiencies of coagulation factors can be suspected if parents have a consanguineous marriage or previous siblings are affected. Hemophilia A and B are X-linked recessive disorders while von Willebrand factor deficiency can be autosomal dominant or recessive. Presence of skeletal abnormalities like absent thumb or absent radius bone indicates Fanconi anemia or thrombocytopenia-absent radius syndrome. Chromosomal disorders like trisomy 13, 18, or 21 can be associated with thrombocytopenia.

Clinical Pearl

- Detailed family history should be taken to rule out inherited or maternal causes of bleeding in a neonate.

Gestation at birth, age at onset of bleeding, and site of bleeding can indicate underlying cause. Bleeding in an otherwise healthy term or late preterm neonate indicates either coagulation factor deficiency or NAIT. Early-onset thrombocytopenia (within 72 h of birth) in a preterm neonate is most commonly due to maternal illness while late-onset thrombocytopenia (after 72 h of birth) is most commonly due to sepsis or necrotizing enterocolitis. Intracranial bleed without significant birth trauma indicates presence of underlying bleeding disorder. Subdural hemorrhage is more common with hemophilia while intraparenchymal bleed is more common with thrombocytopenia (e.g., NAIT). Other common sites of bleeding in coagulation factor deficiency include oozing from umbilical stump, prolonged bleeding from venipuncture or heel stick sites, large caput succedaneum, or large cephalhematoma without birth trauma. Mucosal bleeds, e.g., from oral mucosa or gastrointestinal bleeds, are more commonly observed in thrombocytopenia.

Clinical Pearl

- Intracranial bleed in a term neonate should raise suspicion of coagulation dysfunction. Mucosal bleed is most commonly due to platelet disorders.

History should be sought about maternal intake of medications and administration of vitamin K at birth. Maternal intake of antitubercular or antiepileptic drugs may be associated with development of early onset vitamin K deficiency bleeding (VKDB) which presents within first 24 hours of birth. Neonates not receiving the recommended dose of vitamin K at birth may develop classical (24 h to 7 days after birth) or late onset (2–12 weeks) VKDB.

Laboratory Investigations

Essential laboratory investigations which should be done in neonates with bleeding include platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen levels (Algorithm 2). Prothrombin time is prolonged in deficiency of vitamin K dependent coagulation factors (II, VII, IX, and X). Activated partial thromboplastin time is prolonged in deficiency of vitamin K dependent coagulation factors and deficiency of contact factors (XI, XII, prekallikrein, and high molecular weight kininogen). If PT, APTT, and platelets counts are normal, bleeding may occur because of decreased factor XIII, α2-antiplasmin activity or abnormal platelet functions. In a sick neonate, more widespread derangement of the laboratory markers indicates decreased synthesis due to liver disorder or consumption coagulopathy.

Clinical Pearl

- Initial workup in a bleeding neonate should include platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen levels.

Specific factor assay can be done on clinical suspicion. However, results need to be interpreted carefully in view of altered levels in neonates. Levels of factor VIII are comparable to adults. Therefore, classical hemophilia can be diagnosed in neonates. On the other hand, levels of factor IX are about 15% of adult level and, therefore, hemophilia B can be diagnosed only by 6–12 months of age, when levels reach the adult range. Prothrombin time and APTT are influenced by ratio of blood and citrate in the sample; therefore, care must be taken while withdrawing the sample.

Additional laboratory investigations may be warranted as per clinical suspicion. For example, severe early-onset thrombocytopenia (platelet count <50,000/μL) in a preterm neonate may be because of congenital infections for which appropriate diagnostic test should be done. Conversely, mild early-onset transient thrombocytopenia in a small-for-gestation neonate may be because of gestational hypertension in mother and no further investigations are needed.

MANAGEMENT

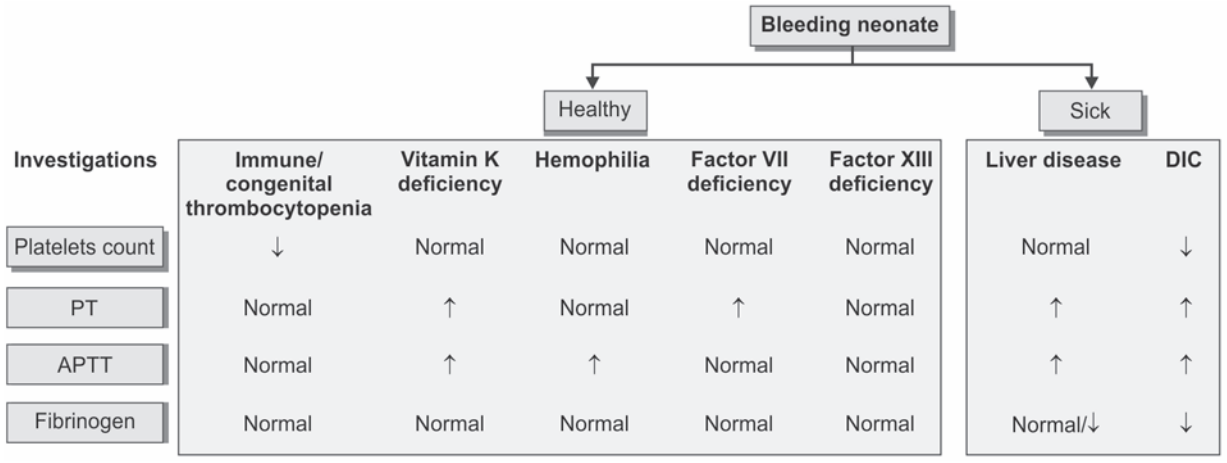
Thrombocytopenia

Management of thrombocytopenia consists of treating underlying cause and if needed giving platelet transfusion. In case of NAIT, platelet transfusion is indicated if platelet counts are below 30,000/μL. In case of active bleeding, platelet transfusion can be given if platelet count is below 50,000/μL. If available, single donor platelets which are human platelet antigen compatible with the neonate are preferred. If these are not available without delay, random donor platelets can be transfused. Administration of intravenous immunoglobulin (1 g/kg for 2 days or 0.4 g/kg/day for 5 days) may increase platelet count in immune thrombocytopenia. Platelet counts need to be monitored for first 10–14 days after birth.

Due to lack of demonstrable efficacy in preventing serious hemorrhages, threshold platelet count below which platelet transfusion is given has become more stringent with time. Most of neonates with platelet count above 20,000/μL will not develop a serious bleed. Therefore, this cutoff may be used in otherwise healthy neonates with thrombocytopenia. Higher cutoff of 30,000/μL may be used in neonates at higher risk of bleeding which include extremely low birthweight neonates in their first week after birth, unstable blood pressure records, previously existing grade 3 or 4 intraventricular hemorrhage, current minor bleeds, coexisting coagulopathy or before exchange transfusion or surgery. In case of active major bleeding, platelet count may be maintained above 50,000/μL. Platelets can be obtained by pooling from multiple donors (platelet concentrate) or by apheresis from a single donor

ALGORITHM 2

Laboratory investigations in a bleeding neonate



PT, prothrombin time; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation.

(apheresis unit). It is stored at room temperature and has a shelf-life of 5 days. A dose of 10 mL/kg is usually sufficient to increase the platelet count above therapeutic threshold.

Clinical Pearl

- Platelet count should be maintained above 50,000/μL in a neonate with active bleeding and above 30,000/μL in a neonate without active bleeding.

Coagulopathy

Vitamin K deficiency can be treated by administration of vitamin K by subcutaneous or intravenous route. Effect of parenteral vitamin K starts within 4 hours. In case of active bleeding, fresh frozen plasma (FFP) can be administered.

In case of classical hemophilia, treatment of choice is administration of factor VIII concentrate. If not available, cryoprecipitate or FFP can be given. Dose of cryoprecipitate is 2 mL/kg or I unit/7 kg. Fresh frozen plasma can be administered in a dose of 10-20 mL/kg. Specific deficiencies of other coagulation factors are rare and can be managed by administration of cryoprecipitate or FFP.

Supportive and specific care for underlying systemic causes of bleeding like sepsis and NEC should be given.

KEY POINTS

- ☞ In neonates, coagulation cascade remains same as pediatric patients, while causes for bleeding differ. It involves factors related to maternal causes and intrapartum insults
- ☞ Laboratory values of coagulation factors are different than adults
- ☞ Platelet and component therapy should be used very judiciously. Clinical status need be considered while planning for the transfusions.

SUGGESTED READINGS

1. Bussel JB, Sola-Visner M. Current approaches to the evaluation and management of the fetus and neonate with immune thrombocytopenia. Semin Perinatol. 2009;33:35-42.
2. Moskowitz NP, Karpatkin M. Coagulation problems in the newborn. Curr Paediatr. 2005;15:50-6.
3. Poterjoy BS, Josephson CD. Platelets, frozen plasma, and cryoprecipitate: what is the clinical evidence for their use in the neonatal intensive care unit? Semin Perinatol. 2009;33:66-74.
4. Sola-Visner M. Platelets in the neonatal period: developmental differences in platelet production, function, and hemostasis and the potential impact of therapies. Hematology Am Soc Hematol Educ Program. 2012;2012:506-11.
5. te Pas AB, Lopriore E, van den Akker ES, Oepkes D, Kanhai HH, Brand A, et al. Postnatal management of fetal and neonatal alloimmune thrombocytopenia: the role of matched platelet transfusion and IVIG. Eur J Pediatr. 2007;166:1057-63.

CHAPTER 11

Neonatal Hyperbilirubinemia (Unconjugated)

Poonam Sidana, Gaurav Mandhan

INTRODUCTION

Unconjugated neonatal hyperbilirubinemia (NNH) is one of the commonest problems faced by pediatricians attending to neonates. Incidence is reported as 60% in term and around 80% in preterm neonates. Incidence and severity are inversely related to gestational age at birth. It is a benign condition which resolves by itself in most of the cases. However, neurotoxic potential of the unconjugated bilirubin which can result in permanent neurodevelopmental sequelae in some neonates is well known. Hence, it is necessary that all those neonates who are at high risk are identified and managed appropriately.

Clinical Pearl

- There is no single level of serum bilirubin which applies to all the babies. Instead, various nomograms are available to evaluate risk and decide intervention for a particular neonate.

Unconjugated hyperbilirubinemia may be categorized as physiological/pathological or exaggerated physiological. For a clinician, it is important to know how to differentiate between these categories. Also it is extremely important to decide which babies are at risk of developing NNH level that may need investigations and/or intervention. Table 1 lists some important differentiating points for various categories.

TABLE 1: Differentiating points for various categories of unconjugated hyperbilirubinemia

Physiological jaundice	Pathological jaundice
• Appears at >24 h and <72 h • Peak level of 12–15 mg/dL is seen at 3–5 day of life in term and 5–7 day in preterm • Usually, needs no intervention • Disappears without intervention by 7th and 14th day in term and preterm neonates respectively	• Appears within 24 h of life • Increases >5 mg/dL/24 h OR >0.5 mg/dL/h • Peak level crosses 95th centile for age in hours/in intervention zone • Persists >14 days in term • Conjugated serum bilirubin >2 mg/dL • Process may be delayed/ prolonged in preterm neonate; peak levels may be higher • Needs intervention

EXAGGERATED PHYSIOLOGICAL JAUNDICE

Time of appearance and rate of rise does not match that of pathological jaundice. However, absolute total serum bilirubin value tends to be higher than that expected for physiological jaundice. Investigations do not reveal any specific cause.

Following groups of neonates are more prone to develop significant NNH.

Risk Factors For Pathological Neonatal Hyperbilirubinemia

- Jaundice noted before 24 hours/after 72 hours
- Gestational age less than 38 weeks
- ABO/Rh incompatibility setting
- Predischarge serum bilirubin in intermediate/high risk zone
- Previous sibling with jaundice
- Extraneous blood source: cephalohematoma, bruising
- Infant of diabetic mother, exclusive but inadequate breastfeeding/poor feeder, race glucose-6-phosphate dehydrogenase.

Risk Factors for Neurotoxicity

- Isoimmune hemolytic disease
- Glucose-6-phosphate dehydrogenase deficiency
- Perinatal asphyxia
- Sepsis
- Acidosis
- Serum albumin <3.0 mg/dL.

In order to plan appropriate investigations, one needs to know the causes of NNH presenting at various neonatal ages. Common causes of pathological NNH are given in table 2.

TABLE 2: Common causes of pathological neonatal hyperbilirubinemia

<24 hours	24–72 hours	>72 hours
Hemolytic disease of newborn: ABO/Rh incompatibility	Physiological	Sepsis
G6PD/pyruvate kinase deficiency, membrane defects	Sepsis	Extraneous blood like cephalohematoma or IVH or bruising
Infections	• Polycythemia • Extraneous blood like cephalohematoma or IVH or bruising • Poor feeding	• Neonatal hepatitis/extrahepatic biliary atresia • Breastfeeding/milk jaundice • Metabolic causes

G6PD, glucose-6-phosphate dehydrogenase; IVH, intraventricular hemorrhage.

Clinical Pearl

- All infants discharged at less than 72 hours should be seen within 2 days of discharge to ensure diagnosis of pathological jaundice.

INVESTIGATIONS

The following investigations may be done, in the order of priority, depending on clinical evaluation:

- Serum bilirubin, total and conjugated, can use transcutaneous bilirubin if baby >35 weeks/>24 h/not under phototherapy
- Blood group of the baby and the mother
- Direct Coombs test in Rh isoimmunized/ABO incompatibility
- Hemogram, reticulocyte count, peripheral smear for hemolysis/red blood cell morphology
- Glucose-6-phosphate dehydrogenase level in a male neonate in high prevalence areas
- Sepsis workup in sick neonate
- Thyroid profile
- Investigations for rare causes as applicable.

MANAGEMENT PLAN FOR A JAUNDICED NEONATE

- History and examination
- Serum bilirubin level
- Risk assessment based on total serum bilirubin, history and examination
- Physiological or pathological
- Investigate as needed
- Decide need to follow up or intervene.

TREATMENT

In an ideal situation, treatment guidelines should be based on epidemiological data collected from a local population. In India, in view of paucity of any national database on neonatal jaundice, American Academy of Pediatrics (AAP) guidelines (2004) for NNH management have been followed for the last many years. These guidelines do not address treatment of newborns born less than 35 weeks of gestation.

Recently published guidelines by National Institute for Health and Clinical Excellence (NICE) in 2010 are more inclusive, as they have evaluated data from diverse sources, including AAP 2004 guidelines and few Indian studies also. These guidelines are applicable to neonates born from 23 weeks' gestation onward, till term. There are graphs available for each gestation outlining phototherapy and exchange thresholds from birth itself. Management of jaundice appearing within first 24 hours of life has been addressed clearly.

Tables 3 and 4 and algorithm 1 represent the adaptations from NICE guidelines 2010 for the management of neonatal jaundice.

TABLE 3: Guidelines for treatment of jaundice in preterm neonates 27–32 weeks

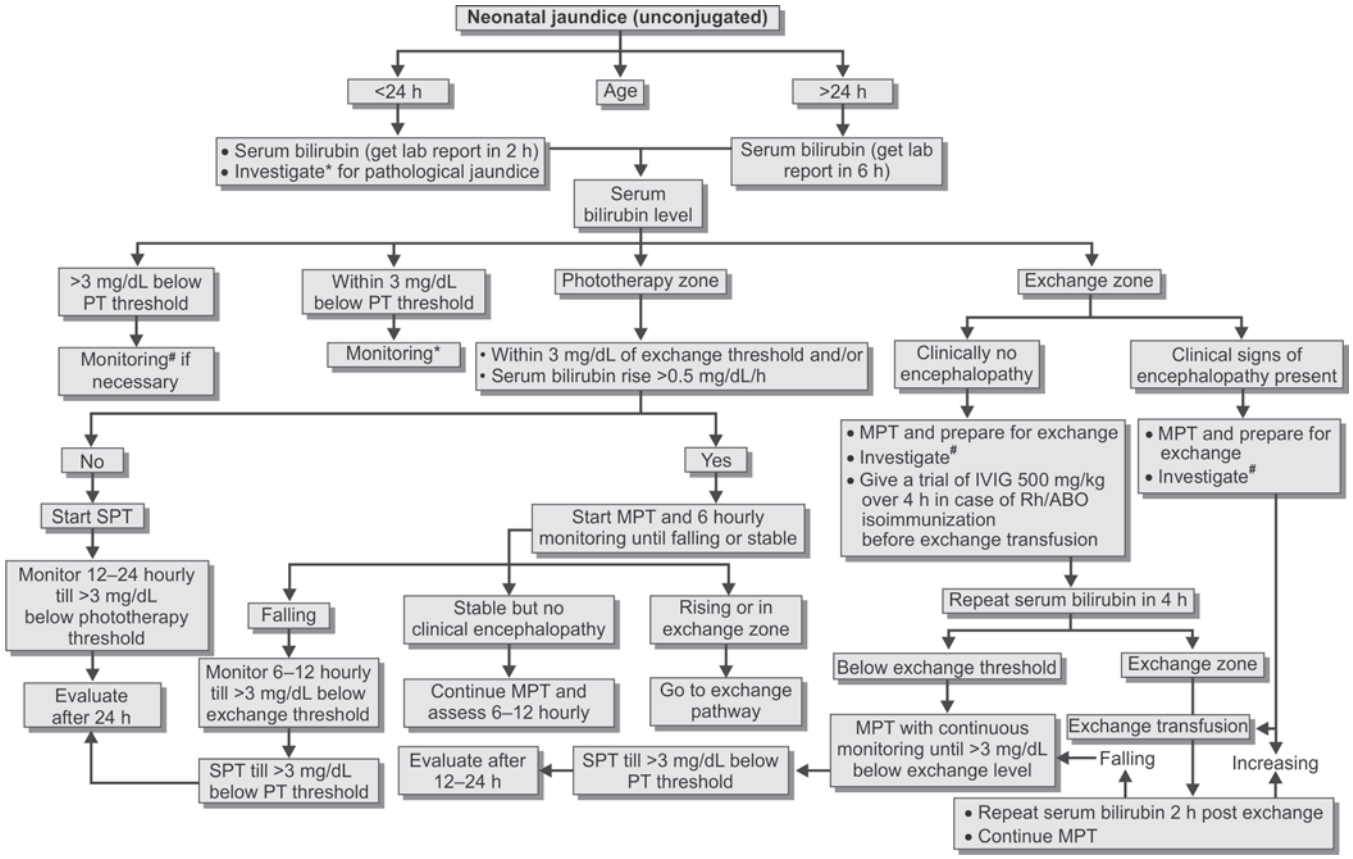
Postnatal age (h)	27 weeks		28 weeks		29 weeks		30 weeks		31 weeks		32 weeks	
	Photo	Exchange	Photo	Exchange	Photo	Exchange	Photo	Exchange	Photo	Exchange	Photo	Exchange
0	2.3	4.7	2.3	4.7	2.3	4.7	2.3	4.7	2.3	4.7	2.3	4.7
6	2.9	5.6	2.9	5.6	3.2	5.8	2.9	5.8	3.2	5.8	3.2	5.8
12	3.5	6.7	3.8	6.7	3.8	6.7	4.1	6.7	4.1	7.0	4.1	7.0
18	4.1	7.3	4.4	7.6	4.4	7.6	4.7	7.9	4.7	8.2	5.0	8.2
24	4.7	8.5	5.0	8.5	5.3	8.8	5.6	9.1	5.8	9.4	5.8	9.4
30	5.6	9.4	5.8	9.4	6.1	9.6	6.1	9.9	6.4	50.2	6.7	50.5
36	6.1	10.0	6.4	11.0	6.7	10.8	7.0	11.1	7.3	11.4	7.6	12.3
42	6.7	11.0	7.0	11.0	7.6	11.7	7.9	12.3	8.2	12.6	8.5	12.9
48	7.6	12.0	7.9	12.0	8.2	12.9	8.5	13.2	9.1	11.5	9.4	14.0
54	8.2	13.0	8.5	13.0	9.1	14.0	9.4	14.3	9.9	14.0	10.7	15.2
60	8.8	14.0	9.4	15.0	9.9	14.9	10.2	15.5	10.8	15.8	11.1	16.4
66	9.4	15.0	9.9	15.0	11.0	15.8	11.1	16.4	11.4	17.0	12.0	17.5
72	9.9	16.0	11.0	16.0	11.0	17.0	11.7	17.5	17.3	18.1	12.9	18.7

TABLE 4: Guidelines for treatment of jaundice in neonates 33 to more than 38 weeks

Postnatal age (h)	33 weeks		34 weeks		35 weeks		36 weeks		37 weeks		>38 weeks	
	Photo	Exchange	Photo	Exchange	Photo	Exchange	Photo	Exchange	Photo	Exchange	Photo	Exchange
0	2.3	4.7	2.3	4.7	2.3	4.7	2.3	4.7	2.3	4.7	5.8	5.8
6	3.2	5.8	3.2	5.8	3.2	5.8	3.5	5.8	3.5	5.8	7.3	8.8
12	4.1	7.0	4.4	7.0	4.4	7.3	4.7	7.3	4.7	7.6	8.8	11.7
18	5.3	8.2	5.6	8.2	5.3	8.5	5.6	8.8	5.8	8.8	10.2	14.6
24	6.1	9.4	6.1	9.6	6.4	9.9	6.7	9.9	7.0	10.2	11.7	17.5
30	7.0	10.5	7.0	11.1	7.3	11.1	7.6	11.4	7.9	11.7	12.4	20.5
36	7.9	11.7	8.2	12.3	8.5	12.4	8.8	12.9	9.1	13.2	11.2	23.4
42	8.8	11.2	8.8	13.5	9.6	14.0	9.9	14.0	10.2	14.6	11.9	26.1
48	9.6	14.3	10.2	14.6	10.5	15.2	10.8	15.5	11.1	10.2	14.6	26.3
54	10.5	15.8	11.1	15.8	11.7	16.4	12.0	17.9	12.6	17.5	15.3	26.3
60	11.7	17.0	12.3	17.5	12.6	17.8	13.2	18.4	11.5	18.7	16.1	26.3
66	12.6	18.1	13.2	18.7	13.5	19.3	14.0	19.6	14.6	20.2	16.8	26.3
72	13.5	19.3	14.0	19.9	14.6	20.5	15.2	21.1	15.8	21.6	17.5	26.3
78	13.5	19.3	14.0	19.9	14.6	20.5	15.2	21.1	15.8	21.6	18.2	26.3
84	13.5	19.3	14.0	19.9	14.6	20.5	15.2	21.1	15.8	21.6	19.0	26.3
90	13.5	19.3	14.0	19.9	14.6	20.5	15.2	21.1	15.8	21.6	19.7	26.3
96	13.5	19.3	14.0	19.9	14.6	20.5	15.2	21.1	15.8	21.6	20.5	26.1

ALGORITHM 1

Management of unconjugated neonatal hyperbilirubinemia



PT, phototherapy; SPT, single phototherapy; MPT, multiple phototherapy; IVIG, intravenous immunoglobulin.

*Monitoring pattern: 24 h/exchange zone—6–12 hourly; rest 12–24 h or later as per postnatal age and risk factors.

#Investigsations: blood groups of mother and baby; DCT, Hb/PCV, retics smear for hemolysis if indicated; sepsis profile, G6PD and the thyroid profile if indicated.

Clinical Pearl

- While interpreting National Institute for Health and Clinical Excellence charts, following conversion needs to be applied: 1 mg/dL of serum bilirubin = 17.1 μm/L of bilirubin.

KEY POINTS

- ☞ All neonates being discharged from hospital should be examined for jaundice. Based on risk assessment, a follow-up plan needs to be decided and explained to the parents clearly
- ☞ Use total bilirubin for all decisions. Do not subtract conjugated bilirubin
- ☞ Appropriate feeding, hydration, blood sugar level, and electrolyte balance must be maintained for babies requiring treatment
- ☞ A neonate presenting in exchange range or suspected to be having bilirubin encephalopathy is a medical emergency. Treatment should be started without any delay.

SUGGESTED READINGS

1. Available from: https://www.nice.org.uk/guidance/cg98/evidence.
2. Evidence Based Clinical Practice Guidelines by National Neonatology Forum, India, October 2010.
3. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications. Pediatrics. 2009;124:1193-8.
4. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297-316.
5. Martin RJ, Fanaroff AA, Walsh MC. Fanaroff and Martin's Neonatal-perinatal Medicine Diseases of the Fetus and Infant. 8th ed.; 2006.
6. Narang A, Gathwala G, Kumar P. Neonatal jaundice: an analysis of 551 cases. Indian Pediatr. 1997;34:429-32.
7. Taeusch HW, Ballard RA, Gleason CA, editors. Avery's Diseases of Newborn. 8th ed.; 2005.

CHAPTER 12

Hypoglycemia

Sailesh G Gupta

INTRODUCTION

There is no universal definition for hypoglycemia. The normal range of blood glucose (BG) is variable and depends upon factor like birthweight, gestational age, body store, feeding status, as well as the presence or absence of the disease.

Operational threshold has been defined as that concentration of plasma or whole BG at which clinician should consider intervention based on the currently available literature. Operational threshold has been defined as BG level less than 40 mg/dL (plasma glucose level <45 mg/dL).

SCREENING OF BABIES (WHO ARE AT RISK)

- Preterm infants
- Small for gestational age
- Large for gestational age
- Infant of diabetic mother
- Sick infants (e.g., sepsis, birth asphyxia, shock, polycythemia, etc.)
- Infants on intravenous fluids and total parenteral nutrition
- Mother receiving drugs like, β-blocker, oral hypoglycemic, and received intrapartum glucose infusion.

SCREENING SCHEDULE

Screening schedule is given in table 1

TABLE 1: Screening schedule

Condition	Timing
Infant of diabetic mother	2, 6, 12, 24, 48, and 72 h
Other at risk neonates	2, 6, 12, 24, 48 (or until glucose values become normal)
Babies on IVF and TPN	6 hourly for the first 72 h then once/twice a day

IVF, intravenous fluids; TPN, total parenteral nutrition.

METHODS OF GLUCOSE ESTIMATION

Important point in BG estimation is whole blood sugar is 10–15% lower than the plasma glucose. Glucose oxidase and glucose electrode method are two most commonly used method for BG estimation in laboratory which are accurate and reliable. Samples should be analyzed quickly as BG values drops by 14–18 mg/dL/h of storage.

MANAGEMENT OF SYMPTOMATIC HYPOGLYCEMIA

- All symptomatic hypoglycemia infants should be treated with intravenous fluids
- A bolus of 2 mL/kg of 10% dextrose is given intravenously after sending a lab sample for confirmation of diagnosis
- Following a bolus of 10% dextrose continuous glucose infusion should be started at glucose infusion rate (GIR) of 6 mg/kg/min
- Blood glucose should be checked 15–30 minutes after giving intravenous 10% dextrose bolus. If it stays greater than 50 mg/dL then decrease frequency of monitoring from every hour to 4–6 hourly
- If BG is less than 50 mg/dL then GIR should be increased in the increment of 2 mg/kg/min every 15–30 minutes until BG is greater than 50 mg/dL or GIR reaches 12 mg/kg/min
- After BG values stabilized for greater than 50 mg/dL for at least 24 hours, then only tapering of GIR should be started at 2 mg/kg/min every 6 hourly with BG monitoring. It should be accompanied by concomitant increase in oral feeds. Once GIR of 4 mg/kg/min is achieved and infant is tolerating oral feeds and BG is greater than 50 mg/dL then only glucose infusion should be stopped.
- Do not stop glucose infusion abruptly as it can cause rebound hypoglycemia. Maximum 12.5% dextrose can be given through peripheral line due to risk of thrombophlebitis.

MANAGEMENT OF ASYMPTOMATIC HYPOGLYCEMIA

Often low blood glucose level (BGL) may not manifest clinically and maybe without any symptoms. Asymptomatic hypoglycemia is defined as a condition with BGL of <45 mg/dL (confirmed in laboratory) with the infant not manifesting clinical features. Unanimous opinion does not exist for the need to treat asymptomatic infants with low BGL. Management of asymptomatic hypoglycemia is summarized in table 2.

TABLE 2: Management plan of infants with asymptomatic hypoglycemia

Condition	Timing
Blood sugar 20–45 mg/dL	Try oral feeds (expressed breast milk or infant formula) and repeat BGL after 1 hr: • If BGL >45 mg/dL, then provide 2 h oral feeds and measure BGL 6 h for 48 h. Aim to maintain BGL between 50 mg/dL and 120 mg/dL • If BGL <45 mg/dL, start IV dextrose infusion and manager as per protocol for symptomatic hypoglycemia
Blood sugar <20 mg/dL	Start IV Dextrose at 6 mg/kg/min. Subsequently manage as symptomatic hypoglycemia

BGL, blood glucose level.

MANAGEMENT OF REFRACTORY HYPOGLYCEMIA

Definitions

Unable to achieve normal BG despite giving glucose infusion at 12 mg/kg/min or hypoglycemia remains for more than 7 days then it's considered to be refractory hypoglycemia.

Important causes

- Hyperinsulinemic states
- Congenital hypopituitarism
- Adrenal insufficiency
- Metabolic disorders like galactosemia, fatty acid oxidation defects, organic acidemias, etc.

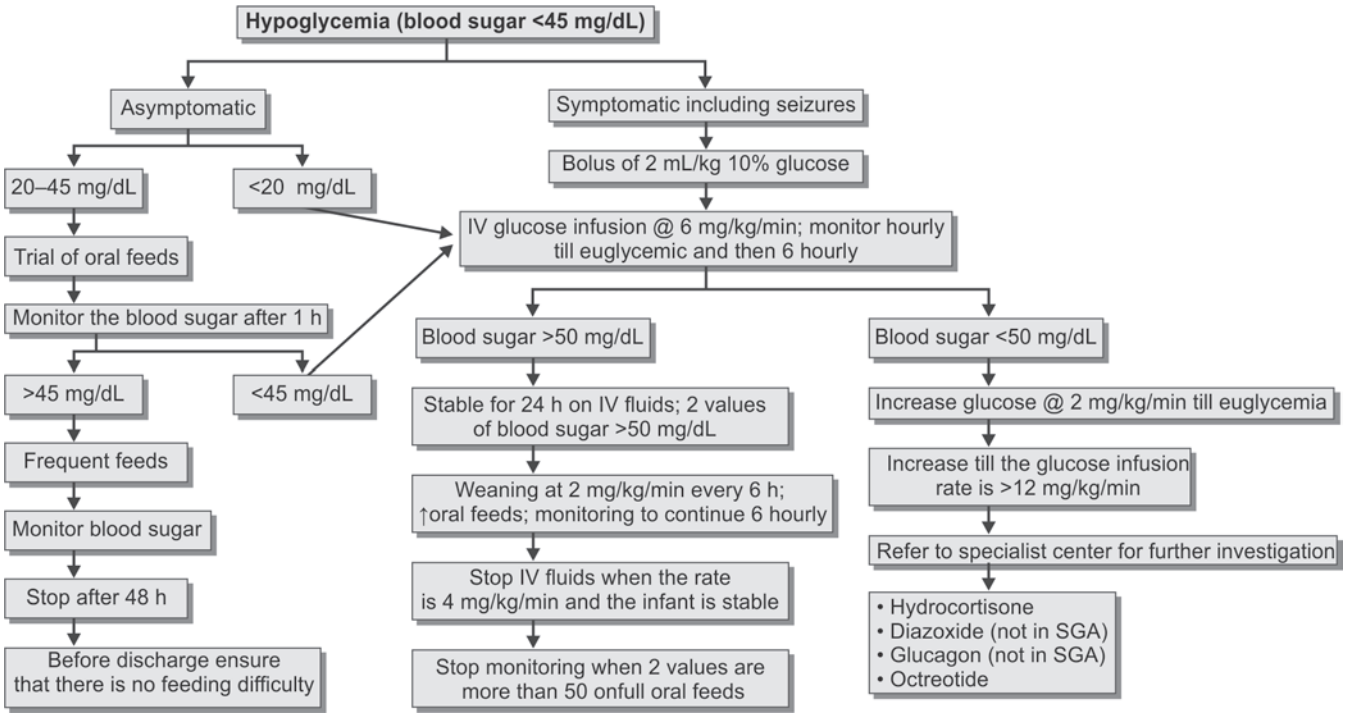
Critical Sample in Management of Refractory Hypoglycemia

- Serum insulin level
- Serum cortisol
- Serum ammonia
- Serum ketone bodies
- Serum lactate.

Other secondary investigations can be done according to the etiology suspected.

ALGORITHM 1

Algorithm for management of neonatal hypoglycemia



IV, intravenous; GIR, gluscose infusion rate.

Drugs for the Treatment of Refractory Hypoglycemia

- Hydrocortisone 5 mg/kg/day intravenous or oral in two divided doses
- Diazoxide 10–25 mg/kg/day orally in three divided doses
- Glucagon 100 μg/kg subcutaneous/intramuscular maximum three doses
- Octreotide 2–10 μg/kg/day subcutaneous two to three times a day.

KEY POINTS

- ☞ A BGL <40 mg/dL or plasma GL <45 mg/dL is considered the operational threshold for management of Hypoglycemia in a Newborn
- ☞ Newborns 'at risk' for Hypoglycemia should be screened clinically and by measurement of BGL to diagnose asymptomatic and symptomatic hypoglycemia
- ☞ All symptomatic hypoglycemia should be treated with Intravenous bolus of 10% dextrose followed by dextrose infusion at the rate 6 mg/Kg/min, and frequent monitoring of BGL. For BGL <50 mg/dL, the infusion rate is increased by 2 mg/Kg/min, until an infusion rate of 12 mg/Kg/min is reached. The dextrose infusion should be tapered gradually only after BGL stabilizes above 50 mg/dL for 24 hours. Abrupt cessation of infusion can cause rebound hypoglycemia
- ☞ Hypoglycemia without clinical manifestations should be treated with IV dextrose infusion if BGL <25 mg/dL. With BGL >25 mg/dL, oral feeding of milk is followed 30 min later, by BGL measurement. If BGL >45 mg/dL, oral feeding and 6 h BGL monitoring are done. If BGL <45 mg/dL, a dextrose bolus of 10% at 2 ml/kg is given and followed up with management as for symptomatic hypoglycemia
- ☞ Inability of achieve BGL >50 mg/dL after dextrose infusion rate of 12 mg/Kg/min, or hypoglycemia lasting over a week is labeled as refractory. Causes should be explored, and treatment may include the use of drugs appropriate to the cause of refractory hypoglycemia.

SUGGESTED READINGS

1. Cornblath M, Ichord R. Hypoglycemia in neonates. Semin Perinatol. 2000;24: 136-49.
2. Cornblath M, Schwartz R. Outcome of neonatal hypoglycemia. Br Med J. 1999; 318:194.
3. Mitanchez D. Glucose regulation in preterm newborn infants. Horm Res. 2007; 68:265-71.

CHAPTER 13

Neonatal Seizures

Sanjay Wazir

INTRODUCTION

Neonatal seizures represent one of the major challenges for the clinician working in nursery because of difficulty in diagnosis and lack of effective evidence based treatment scheme. Incidence of neonatal seizures is inversely proportional to the birthweight with incidence of approximately 60 per 1,000 at less than 1,500 g and 3 per 1,000 at more than 2,500 g at birth.

RISK FACTORS FOR NEONATAL SEIZURES

Maternal

- Advancing maternal age more than 40 years
- Preexisting/gestational diabetes mellitus
- Intrapartum evidence of fetal distress
- Placental abruption, cord prolapse, prolonged second stage
- Maternal pyrexia, chorioamnionitis.

Infant

- Lower gestational age
- Low birthweight
- Post-term more than 42 weeks
- Male sex.

Clinical Pearl

- Half of the seizures in newborns are subclinical and one-third of seizures do not have an electroencephalogram correlate.

ETIOLOGY OF NEONATAL SEIZURES (TABLE 1)

First four causes constitute approximately 85% of all causes of neonatal seizures. It is important to find out the cause as the prognosis is dependent on the etiology of seizure.

TABLE 1: Etiology of neonatal seizures based on timing after birth

Age	Etiology
First 24 h	• Hypoxic ischemic encephalopathy • Meningitis/sepsis • Subdural/subarachnoid/interventricular hemorrhage intrauterine infection • Trauma • Pyridoxine dependency • Drug effect/withdrawal
24–72 h	• Meningitis/sepsis • In premature infants: intraventricular hemorrhage • In full-term infants: infarction, venous thrombosis • Cerebral dysgenesis
72 h to 1 week	• Above causes • Inborn errors of metabolism • Hypocalcemia • Familial neonatal seizures
1 week to 4 weeks	• Above causes • Herpes simplex virus

1. Hypoxic ischemic encephalopathy
2. Intracranial infections: bacterial, viral, fungal, intrauterine
3. Cerebral malformations
4. Intracranial hemorrhage
5. Metabolic: hypocalcemia, hypomagnesemia, hypoglycemia, hypo- or hypernatremia
6. Bilirubin encephalopathy
7. Drug withdrawl: chronic maternal use of drugs
8. Inborn errors of metabolism: nonketotic hyperglycinemia, pyridoxine-dependent epilepsy, folinic acid-responsive seizures, pyruvate dehydrogenase deficiency, glucose transporter deficiency, biotinidase deficiency, Leigh disease, sulfite oxidase deficiency

9. Epilepsy syndromes: benign idiopathic neonatal convulsions, benign familial neonatal seizures, benign nonfamilial (idiopathic) neonatal seizures, early infantile epileptic encephalopathy with burst suppression pattern (Ohtahara syndrome), early myoclonic encephalopathy.

Clinical Pearl

- Sixty percent of the causes of seizures are due to hypoxic ischemic encephalopathy and 20% are related to stroke.

TYPES OF SEIZURES

Types of seizures are given in table 2.

TABLE 2: Types of seizures

Apnea	Pedaling
Subtle	• Eye deviation (term) • Blinking, fixed stare (preterm) • Repetitive mouth and tongue movements • Apnea pedaling, tonic posturing of limbs
Tonic	• Maybe focal or generalized • Tonic extension or flexion of limbs (often signals severe intracranial hemorrhage in preterm infants)
Clonic	• Maybe focal or multifocal • Clonic limb movements (synchronous or asynchronous, localized or often with no anatomic order to progression) • Consciousness maybe preserved • Often signals focal cerebral injury
Myoclonic	• Focal, multifocal, or generalized • Lightning-like jerks of extremities (upper > lower)

DIFFERENTIAL DIAGNOSIS OF MOVEMENT DISORDERS IN NEONATES

Differential diagnosis of movement disorders in neonates is given in table 3.

INVESTIGATIONS

- Clinical history and examination
- Blood sugar
- Serum calcium and magnesium
- Blood gas
- Urea and electrolytes
- Blood culture
- Cerebrospinal fluid
- Electroencephalogram (EEG): Obtain EEG if possible
- Ultrasonography.

ANTIEPILEPTICS AND THEIR DOSES

List of antiepileptics and their doses is given in table 4.

TABLE 3: Differential diagnosis of movement disorders in neonates

Phenomenon	Characteristics
Jitteriness	• Rhythmic character with equal forward and backward movement • Can be restrained and is stimulus sensitive • No eye movements
Benign sleep myoclonus	• Myoclonic activity confined to sleep • Occurs in the first few weeks of life • Spontaneous resolution by 2–3 months • No autonomic movements or eye movements
Hyperekplexia (stiff baby syndrome)	• Triad of generalized stiffness while awake, nocturnal myoclonus and exaggerated startle reflex • Resolved by manual flexion of the neck or hips • Clonazepam is helpful
Nonconvulsive apnea	• Not associated with eye movements • Tachycardia is not seen
Sandifer syndrome	• Caused by acid reflux • Intermittent paroxysmal spells of generalized stiffness and opisthotonic posturing • Usually occur within 30 min of meal
Neonatal dystonia	• Fixed contraction of muscles • Usually in severe brain lesion or in drug overdose like metoclopramide

TABLE 4: List of antiepileptics and their doses

Drug	Loading dose	Maintenance dose
Phenobarbital	20 mg/kg IV maximum 40 mg/kg	3–5 mg/kg per 24 h IV or PO
Phenytoin	20 mg/kg IV (infusion rate 1 mg/kg/min)	3–4 mg/kg per 24 h IV
Midazolam	0.05 mg/kg IV (in 10 min)	0.15 mg/kg/h
Lidocaine	2 mg/kg IV	• 6 mg/kg/h IV • After 24 h of treatment: 4 mg/kg/h • After 36 h: 2 mg/kg/h • After 48 h: Stop
Clonazepam	0.15 mg/kg IV repeat 1x or 2x	0.1 mg/kg per 24 h
Pyridoxine	50–100 mg	50–100 mg

IV, intravenous; PO, per os.

Clinical Pearl

- The data regarding the efficacy of older antiepileptics is not very convincing but newer drugs have hardly any; hence, phenobarbitone remains the first choice in neonatal seizures.

PROGNOSIS

Dependent on the cause of seizures, e.g., in case of late-onset hypocalcemia, the outcome is 100% normal and in case of cerebral malformation, nearly all would have a bad prognosis. Some of the outcomes are listed in table 5.

Predictive Variables

Multiple rather than single factors appear to be most accurate in predicting outcome. However, all these variables ultimately are related to the degree of brain injury at the time of seizure occurrence, and, in turn, the seizure etiology.

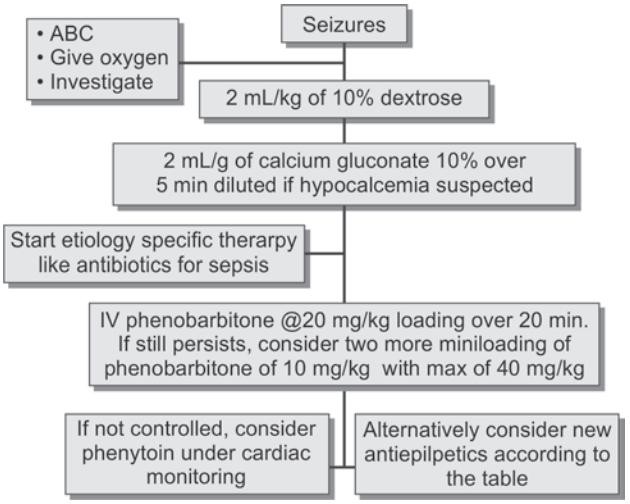
- Features of the interictal EEG from one or serial recordings
- Features of the ictal EEG
- Seizure burden, including the number of sites of seizure onset and seizure duration
- Status epilepticus
- Neurologic examination at the time of seizures
- Number of drugs required to treat seizures
- Findings on neuroimaging
- Conceptional age (term versus preterm)
- Birthweight.

TABLE 5: Long term outcome of neonatal seizures

Outcome	Incidence (%)
Early death	20–30
Developmental delay	55
Mental retardation	20–40
Cerebral palsy	25–40
No neurological abnormalities	22–35
Postnatal epilepsy	20–30

ALGORITHM 1

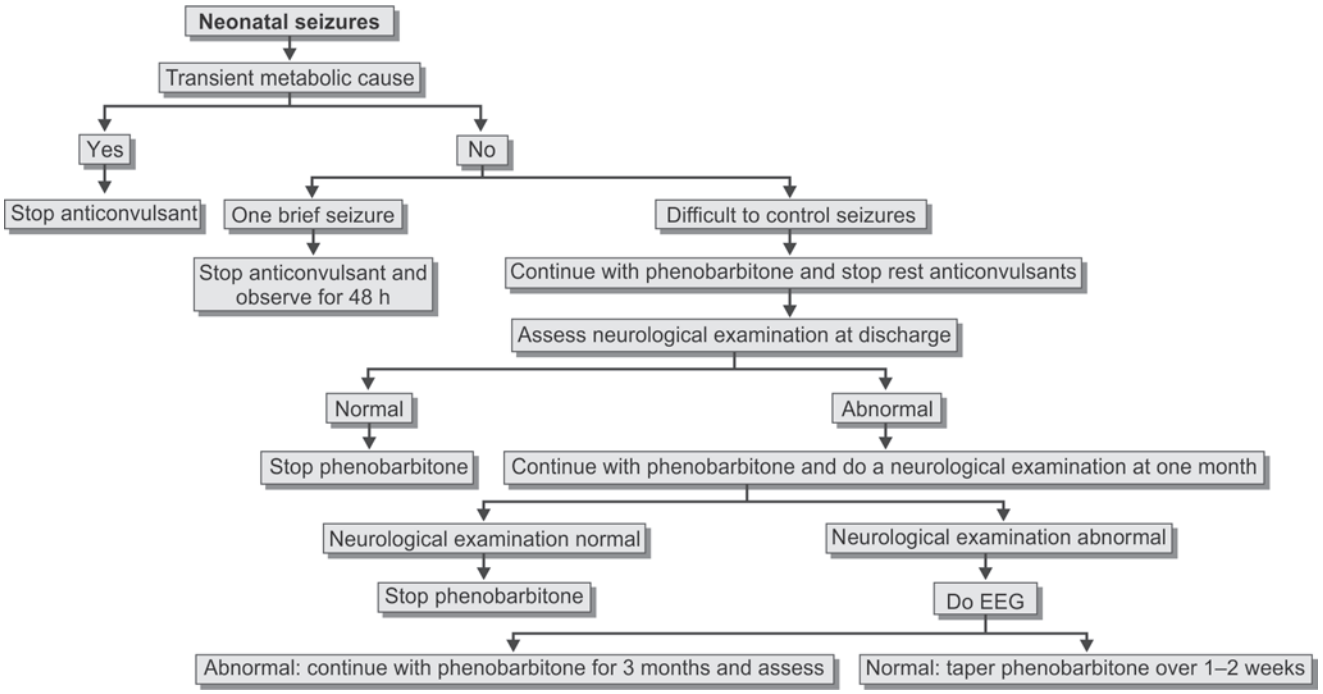
Treatment for neonatal seizures



ABC, airway, breathing, and circulation.

ALGORITHM 2

Weaning protocol for neonatal seizures



EEG, electroencephalogram.

KEY POINTS

- ☞ Neonatal period is the most common time in one's life to get seizures
- ☞ Preferably, all neonatal seizures should have an EEG record available to differentiate between the nonepileptic phenomenon and seizures
- ☞ Antiepileptics may have toxic effects on the brain; hence, one should try to stop as soon as possible
- ☞ Further studies are needed regarding new and more efficacious treatments and their impact on the outcome of different neonatal seizure types.

SUGGESTED READINGS

1. Clancy RR. Summary proceedings from the neurology group on neonatal seizures. Pediatrics. 2006;117(3 Pt 2):S23-7.
2. Glass HC, Sullivan JE. Neonatal seizures. Curr Treat Options Neurol. 2009; 11(6):405-13.
3. Okumura A. The diagnosis and treatment of neonatal seizures. Chang Gung Med J. 2012;35(5):365-72.
4. Zupanc ML. Neonatal seizures. Pediatr Clin North Am. 2004;51(4):961-78.

CHAPTER 14

Neonatal Sepsis

Rahul P Bhamkar, Anjali Kulkarni

INTRODUCTION

Neonatal sepsis is the commonest cause of mortality and morbidity in newborns in our country. It can be divided into two categories based on the onset.

CLASSIFICATION

Etiology-wise, sepsis can be classified as bacterial and fungal sepsis.

- Bacterial sepsis: presents both as early onset sepsis (EOS) and late onset sepsis (LOS)
- Fungal sepsis: presents commonly as LOS.

The difference between early and late onset sepsis is given in table 1.

TABLE 1: Classification of sepsis

Early onset sepsis (<72 h)	Late onset sepsis (>72 h)
• Caused by organisms acquired before or immediately after birth (vertical infection) • Predominantly respiratory presentation	• Caused by organisms acquired from hospital or community • Varied presentation

RISK FACTORS FOR SEPSIS

Risk factors for sepsis are given in table 2.

ORGANISMS IN NEONATAL SEPSIS

According to the National Neonatal Perinatal Database data 2002–2003, *K. pneumoniae* was the commonest (30.1%), followed by *S. aureus* (16.2%), *E. coli* (13%) and *Pseudomonas* sp. (9.3%). The organisms are similar in both EOS and LOS in Indian scenario according to this report.

TABLE 2: Risk factors for sepsis

Early onset sepsis	Late onset sepsis
Maternal factors • Prolonged rupture of membranes >18 h* • Intrapartum maternal fever >38°C within 15 days* • Foul smelling liquor* • Chorioamnionitis* • Unclean vaginal examination • Maternal leukocytosis (WBC >15000) • Prolonged rupture of membrane >12 h • Frequent (>3) per vaginal examination in labor • Vaginal positive swab for group B streptococcus Fetal factors • Fetal distress: sustained fetal tachycardia >160/min* • APGAR <5 • Low birth weight (<1500 g) • Prematurity <34 weeks	• Neonatal intensive care unit admission • Poor hygiene • Low and very low birthweight babies • Poor cord care • Prematurity • Bottle feeding • Invasive procedure • Superficial infection (pyoderma, umbilical sepsis) • Fungal sepsis: exposure to broad-spectrum antibiotics causing alteration of normal flora

*Major risk factors

SIGNS AND SYMPTOMS ASSOCIATED WITH NEONATAL SEPSIS

Early Signs

- Respiratory distress that ranges from mild tachypnea to respiratory failure
- Increase in ventilatory support in the mechanically ventilated patient
- Lethargy or hypotonia
- Increase in apnea
- Feeding intolerance
- Temperature instability

- Hypotension or evidence of poor perfusion
- Increase in heart rate

Late Signs

- Sclerema
- Shock
- Disseminated intravascular coagulation (DIC)
- Pulmonary hemorrhage.

Clinical Pearl

- Since the signs of neonatal sepsis are very nonspecific, any acute deterioration in a neonate should be assumed to be because of septicemia in Indian scenarios unless there are definite indications of alternative pathology.

DIAGNOSTIC WORKUP

- Complete blood count: leukocytosis (>20,000) or leukopenia (<6,000), persistent thrombocytopenia
- Immature to total neutrophil ratio: increase in immature to total white cell ratio greater than 0.3 is 85% sensitive and specific, particularly for EOS
- C-reactive protein: rises approximately 12 hours after onset of sepsis and returns to normal within 2–7 days. Greater than 1 mg/dL indicates sepsis. Sensitivity 85% and specificity 90%. C-reactive protein has low negative predictive value in EOS
- Procalcitonin: greater than 0.25–2 ng/L suggests sepsis; greater than 2 ng/mL, strong suspicion of sepsis
- Blood culture: gold standard in diagnosis till date
- Chest X-ray if respiratory distress
- Lumber puncture: should be performed when index of suspicion of meningitis is high in EOS and in all cases of LOS.

Clinical Pearls

- Blood culture should always be obtained before starting antibiotic therapy, but inability to obtain blood culture should not delay starting of treatment.
- Neutropenia in face of confirmed sepsis indicate that baby is extremely unwell.

TREATMENT

Supportive Care

- Oxygen/ventilation
- Volume expansion/maintaining blood pressure with crystalloids, colloids, use of inotropes
- Treatment of anemia, thrombocytopenia, DIC
- Temperature maintenance
- Treatment of hypoglycemia/hyperglycemia/hypocalcemia

Specific Treatment

All babies with presence of risk factors and/or with signs and symptoms of sepsis should be screened for sepsis and blood culture should be collected. Pending blood culture report babies should be judiciously started on antibiotics.

Antibiotics

For practical purpose, antibiotics can be classified as:

- First-line antibiotics: ampicillin plus gentamicin
- Second-line antibiotics: third or fourth generation cephalosporin/piperacillin plus tazobactum plus amikacin
- Third-line antibiotics: carbapenams plus amikacin
- Fourth-line antibiotics: polymyxin/colistin/vancomycin/linezolid.

Choice of antibiotics should be judiciously decided (Table 3). For suspected LOS, it is justified to start directly on second-line antibiotics. In EOS if high vaginal swab positive, neonate should be treated with specific antibiotics as per culture and sensitivity report. If mother is positive for group B streptococcus then double dose of ampicillin should be used.

Clinical Pearl

- Consideration of fungal sepsis should be given for very low birthweight babies, especially with central lines who deteriorate on antibiotics. Fluconazole prophylaxis in such babies has shown to reduce the incidence of invasive fungal sepsis. In babies with pending culture report, it is justified to start antifungal treatment..

TABLE 3: Antimicrobial dosage with spectrum and schedule

Antibiotic/antifungal	Spectrum	Dose
Ampicillin	*Listeria monocytogenes*, *E. coli*, *Enterococcus*, group B streptococcus	• Mild/moderate infection: 100 mg/kg/dose • Meningitis: 400 mg/kg/day (interval: Table 4)
Cefotaxime	Gram-negative enteric bacteria, meningitis	• 50 mg/kg/dose (interval: Table 4)
Ceftriaxone*	Gram negative bacteria and gonococcal infection	• Sepsis: 50 mg/kg (Table 4) • Meningitis: 80–100 mg/kg
Cefepime	Covers both Gram-positive and -negative organism especially *P. aeruginosa*	• <28 days: 30 mg/kg/dose 12 hourly • >28 days: 50 mg/kg/dose 12 hourly • Meningitis: 50 mg/kg/dose 8 hourly
Piperacilline + tazobactum	Gram-positive, Gram-negative anaerobic, e.g., *Enterococcus*, *Proteus*	• 50–100 mg/kg/dose (interval: Table 4)

Continued

Continued

Antibiotic/antifungal	Spectrum	Dose
Amikacin	Gram-negative enteric bacteria, e.g., *Serratia*	• <29 weeks ○ 0–7 days: 18 mg/kg/dose 48 hourly ○ 8–28 days: 15 mg/kg/dose 36 hourly ○ >29 days: 15 mg/kg/dose 24 hourly • 30–34 weeks ○ 0–7 days: 18 mg/kg/dose 36 hourly ○ >8 days: 15 mg/kg/dose 24 hourly • >35 weeks: ○ 15 mg/kg/dose 24 hourly
Gentamicin	Gram-negative bacteria	• <32 week ○ 4 mg/kg/dose 36 hourly • >32 week ○ 4 mg/kg/dose 24 hourly
Carbapenems	Multiresistant *Klebsiella pneumoniae*, *Enterobacteriaceae*, anaerobes	• 20–25 mg/kg/dose (interval: Table 4)
Colistin	*Pseudomonas aeruginosa*	• 50,000–75,000 units/kg/day divided 8 hourly
Vancomycin	Methicillin-resistant *S. aureus*	• <29 week ○ 0–14 days: 10–15 mg/kg/dose 18 hourly ○ >14 days: 10–15 mg/kg/dose 12 hourly • 30–42 week ○ 0–14 days: 10–15 mg/kg/dose 12 hourly ○ >14 days: 10–15 mg/kg/dose 8 hourly • >42 weeks ○ 10–15 mg/kg/dose 6 hourly
Linezolid	Methicillin-resistant *S. aureus* refractory to vancomycin	• <34 weeks: 10 mg/kg/dose 12 hourly • >34 weeks: 10 mg/kg/dose 8 hourly
Fluconazole	*Candida* spp.	• Prophylaxis: 3 mg/kg/dose twice weekly • Therapeutic: ○ <29 week: – 0–14 days: 6 mg/kg/dose 48 hourly – >14 days: 6 mg/kg/dose 24 hourly ○ >30 weeks – 0–7 days: 6 mg/kg/dose 28 hourly – >7 days: 6 mg/kg/dose 24 hourly
Liposomal amphotericin B	Fluconazole-resistant *Candida* spp.	• 2.5–7 mg/kg/day as continuous infusion over 1 h 24 hourly

*Not recommended for use in neonates with hyperbilirubinemia, concurrent administration with calcium-containing product contraindicated.

TABLE 4: Dosing interval chart

Gestational age	Postnatal age	Interval
<29 weeks	0–28 days >28 days	12 h 8 h
30–36 weeks	0–14 days >14 days	12 h 8 h
>37 weeks	0–7 days >7 days	12 h 8 h

Clinical Pearl

- Irrational use of antibiotics should be avoided in neonatal intensive care unit. Clinically evaluate and consider other clinical diagnosis in the absence of positive laboratory parameters and symptomatic baby.

Management of Early Onset Sepsis

Management of early onset sepsis is represented in algorithm 1. Asymptomatic neonate with minor risk factors should be observed, pending blood culture and septic screen and treatment should be started if baby becomes symptomatic or screening results are positive, whereas neonates with major risk factors should be started on antibiotics pending the sepsis screen results. All symptomatic neonates where alternative diagnosis is not possible should be started on antibiotics.

Clinical Pearl

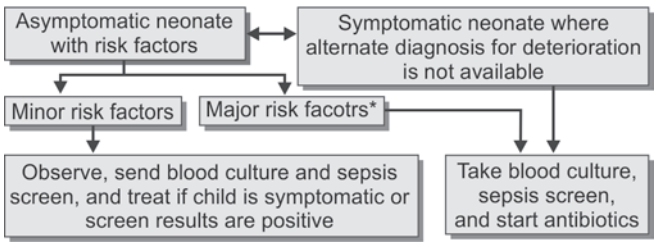
- About 90% of the early onset sepsis would present with respiratory involvement.

Management of Late Onset Sepsis

Management of late onset sepsis is represented in algorithm 2. All severely symptomatic infants should be started on anti-

ALGORITHM 1

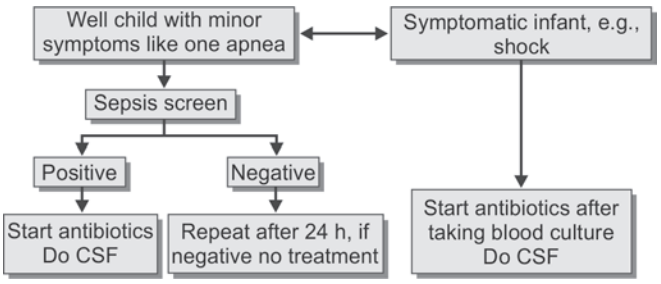
Management of early onset sepsis



*Lumber puncture, all symptomatic infant except in premature baby with RDS

ALGORITHM 2

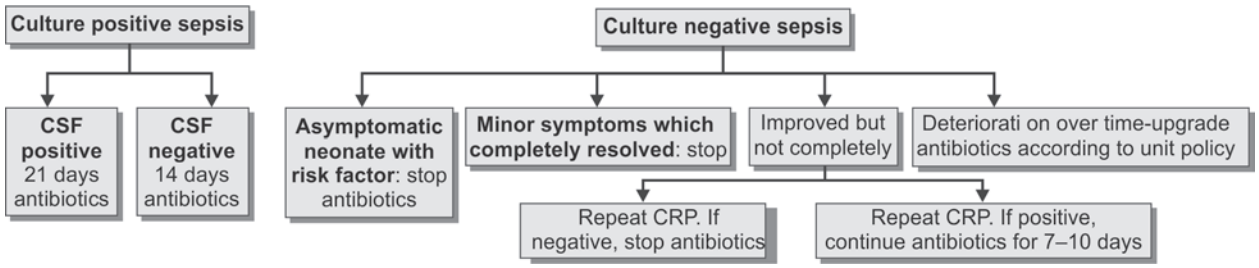
Management of late onset sepsis



CSF, cerebrospinal fluid.

ALGORITHM 3

Stopping antibiotics



biotics pending sepsis screen, blood culture, and cerebrospinal fluid examination and culture reports. Babies with minor symptoms should be started on treatment based on the sepsis screen results.

Clinical Pearls

- A sepsis screen is not warranted in neonates with a high probability for sepsis. Instead, these neonates should be directly started on antibiotics pending blood culture
- Lumbar puncture should be done in all cases of late onset sepsis.

Stopping Antibiotics

Guidelines for stopping antibiotics are illustrated in algorithm 3. Duration of antibiotics depends upon clinical condition of the infant and organism identified. If septic screen and blood culture is negative and baby is asymptomatic or symptoms resolved, antibiotics can be stopped after 48 hours. If blood culture is negative and clinical suspicion is high, repeat blood culture and CRP; continue antibiotics for 7–10 days till infective indices have normalized. For proven sepsis with normal cerebrospinal fluid findings, treatment should be at least 10–14 days and for meningitis, treatment should be for 21 days. For fungal sepsis, treatment duration is 3–6 weeks or 21 days after first negative blood culture.

Adjunctive Therapies in Sepsis

The following treatments have been tried with varying results but there is no evidence-based recommendation for any of these.

- Intravenous immunoglobulin, pentoxifylline (immunomodulator)
- Colony-stimulating factor
- Blood exchange transfusion

KEY POINTS

- Sepsis is the commonest cause of mortality and morbidity in the neonatal period
- We should have a high index of suspicion for diagnosis, and antibiotics must be used judiciously where required along with the appropriate supportive therapy.

SUGGESTED READINGS

1. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics. 1998;102:E41.
2. Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 9th ed. Maryland Heights, Missouri: Elsevier; 2010.
3. Kliegman RM, Stanton BM, Geme JS, Schor NF, Behrman RE, editors. Nelson Textbook of Pediatrics. 19th ed. Maryland Heights, Missouri: Elsevier; 2011.
4. Neonatology Clinical Guidelines. King Edward Memorial Hospital, Perth, Western Australia. Feb 2010.
5. Remington JS, Klein JO. Infectious Diseases of the Fetus and Newborn Infant. 7th ed. Maryland Heights, Missouri: Elsevier; 2010.
6. Segar JL, Patel CA, Tierney SB. Recommended Antimicrobial Dosage Schedules for Neonates. Available from: https://www.uichildrens.org/uploadedFiles/UIChildrens/Health_Professionals.
7. Singh SA, Dutta S, Narang A. Predictive clinical scores for diagnosis of late onset neonatal septicemia. J Trop Pediatr. 2003;49:235-9.
8. Young TE, Magnum B. Neofax: A manual of drugs used in neonatal care. 23rd ed. Columbus, Ohio: Ross Laboratories; 2010.

CHAPTER 15

Approach to Congenital Heart Disease

Dinesh K Chirla, Preetham K Poddutoor

INTRODUCTION

Congenital heart disease (CHD) is found in 7–8 per 100 live births. It may occur as an isolated defect or in association with other malformations such as esophageal atresia, anorectal malformation, exomphalos, and skeletal defects.

About 10–15% have complex lesion with more than one cardiac abnormality and 10–15% have noncardiac abnormality. The most common congenital anomalies are given in table 1.

Clinical Pearl

- The nine most common congenital anomalies account for 80% of all lesions.

Congenital heart disease is particularly common in chromosomal disorders and with some maternal conditions. A neonate should be suspected and evaluated for CHD in the following conditions (Table 2 and Algorithm 1).

Newborn with CHD presents if there is:

- Unfavorable transitional circulation where the circulation is parallel instead of being in series
- Obstruction of series circulation and patent ductus arteriosus closes
- Fall in pulmonary vascular resistance and shunting and mixing occurs.

Initial evaluation would include assessment of perfusion, oxygen saturation, pulses, and blood pressure measurements.

TABLE 1: The most common congenital heart lesion

Acyanotic	Outflow obstruction	Cyanotic
VSD 30%	Pulmonary stenosis 7%	Tetralogy of Fallot 5%
PDA 12%	Aortic stenosis 5%	TGA 5%
ASD 7%	Coarctation of aorta 5%	AVSD 2%

TGA, transposition of the great arteries; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; PDA, patent ductus arteriosus.

TABLE 2: Causes and frequency of congenital heart disease

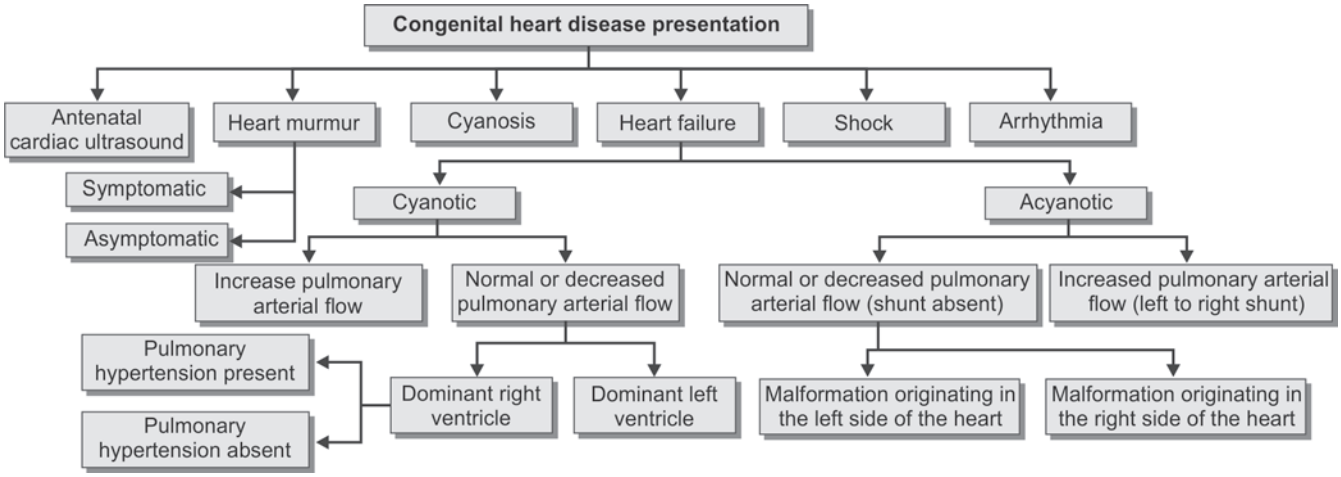
Causes	Frequency (%)	Common cardiac abnormalities
Chromosomal disorder		
Trisomy 21	30–40%	Atrioventricular septal defect, VSD
Trisomy 18 and 13	60–80%	Complex (VSD, PDA)
Turners (45XO)	15%	Aortic valve stenosis, coarctation of aorta
Chromosome 22q deletion	—	Aortic arch anomalies, tetralogy of Fallot
Maternal drugs		
Warfarin therapy	5%	Pulmonary valve stenosis, PDA
Fetal alcohol syndrome	25%	ASD, VSD, tetralogy of Fallot
Maternal disorders		
Rubella infection	30–35%	Peripheral pulmonary stenosis, PDA
Systemic lupus erythematosus (SLE)	35%	Complete heart block
Diabetes mellitus	2%	Increased incidence overall (VSD, transposition, hypertrophied septum)

VSD, ventricular septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus.

ANTENATAL DIAGNOSIS

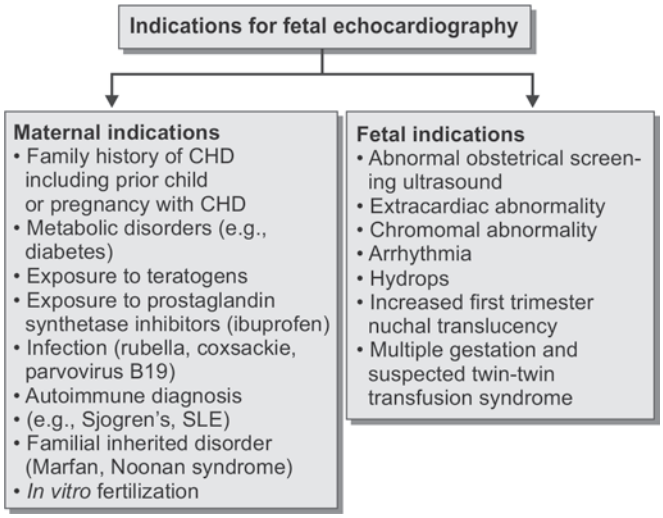
Checking the anatomy of fetal heart has become a routine part of the fetal anomaly scan (targeted imaging for fetal anomalies) at 18–20 weeks in most of the fetal medicine units. If an abnormality is detected, detailed fetal echocardiography is performed by pediatric cardiologists (Algorithm 2). Unfortunately, these services are available only in few tertiary

ALGORITHM 1



ALGORITHM 2

When to do fetal echocardiography



CHD, congenital heart disease; SLE, systemic lupus erythematosus.

units or perinatal centers in India. Depending on diagnosis, some choose termination of pregnancy in complex CHD; majority can continue with pregnancy and have neonates management planned antenatally.

Clinical Pearl

- Neonates with duct-dependent lesion are likely to need treatment in the first 2 days.

Pathologic Murmurs

The intensity and quality of the murmur and associated findings differentiate innocent murmurs from those associated with heart disease.

The following features of murmurs are associated with structural heart disease:

- Murmur intensity grade 3 or higher
- Harsh quality
- Pansystolic duration
- Loudest at upper left, upper right sternal border, or apex
- Abnormal S2.

Clinical Pearl

- The features of an innocent murmur can be remembered as the four S's: Soft, Systolic, aSymptomatic, and left Sternal edge.

Cyanosis

Much more threatening than a murmur is the presence of cyanosis. Peripheral cyanosis may occur when a neonate is cold or unwell from any cause. Central cyanosis is seen on tongue. Cyanosis without pulmonary disease is almost invariably the result of a serious cardiac abnormality. Clinically, it is sometimes difficult to identify cyanosis differentiating between cardiac and pulmonary cyanosis see (Table 3); always check oxygen saturation with pulse oximetry. Those with left-sided obstructive lesions present with inadequate systemic perfusion and shock, whereas those with right-sided lesions present with cyanosis because of inadequate blood reaching the lungs. In neonatal period, cardiac cyanosis may be caused by:

- Reduced pulmonary blood flow
  - Critical pulmonary stenosis
  - Tetralogy of Fallot
  - Tricuspid atresia/Ebstein's
- Poor mixing/separate parallel systemic and pulmonary circulation
  - Transposition of great vessels
- Common mixing of systemic venous and pulmonary venous blood
  - TAPVR, truncus arteriosus, double outlet ventricle.

TABLE 3: Clinical features helpful in distinguishing respiratory from cardiac cyanosis

	Respiratory cyanosis	Cardiac cyanosis
History	Prematurity, meconium liquor/below cords, risk of infection	Family history of congenital heart disease
Respiration	Marked respiratory distress	Little or no respiratory distress unless shocked or metabolic disorders
Cardiovascular examination	Normal	May have clear signs
Response to oxygen	Cyanosis likely to improve	Cyanosis unlikely to improve dramatically
Chest X-ray	Obvious respiratory pathology Normal cardiothoracic ratio	No respiratory pathology, abnormal heart shadow or lung vasculature may be seen
Electrocardiogram	Normal	May be normal, may be helpful
Blood gases	Hypercapnia	Hypo- or normocapnia
Heart rate	++	+++
Respiratory rate	+++	++
Grunt	++	0/+
Murmur	0	0/+/++/+++
Congestive heart failure	0	0/+/++/+++
Abnormal pulses	0	0/+
Response to O_2	+++	0/+

Note that all categories have overlap between respiratory and cardiac causes.

The diagnosis of cyanotic CHD can be confirmed by hyperoxia test if detailed echocardiography is not available.

Heart Failure

Heart failure in neonatal period usually results from left heart obstruction, e.g., coarctation of aorta. If the obstruction is severe then arterial perfusion is predominantly via arterial duct (right to left flow) so called duct-dependent systemic circulation.

Congenital Heart Disease: Presenting as Cardiac Failure

- Neonate—obstructed systemic circulation (duct-dependent): presents with shock
  - Hypoplastic left heart syndrome
  - Critical aortic valve stenosis
  - Severe coarctation of aorta
  - Interruption of aortic arch
- Infants
  - Ventricular septal defect
  - Atrioventricular septal defect
  - Large patent ductus arteriosus.

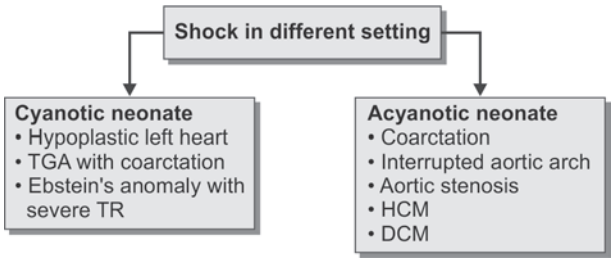
Shock

A variety of mechanisms can lead to cardiogenic shock in newborns with duct-dependent CHD when the ductus arteriosus closes (Algorithm 3):

- In left heart obstructive lesions (e.g., hypoplastic left heart syndrome, critical aortic stenosis, coarctation of the aorta, and interrupted aortic arch), systemic perfusion is lost
- In right-sided obstructive lesions (e.g., total anomalous pulmonary venous connection, tricuspid atresia and mitral atresia), restricted pulmonary blood flow results in reduced systemic blood flow, which may result in shock

ALGORITHM 3

Neonate with cardiogenic shock



TGA, transposition of the great arteries; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy.

- In lesions with parallel pulmonary and systemic circulations (e.g., transposition of the great arteries with intact ventricular septum), mixing between the two circulations is decreased, leading to hypoxia and metabolic acidosis, which results in failure and shock
- Cardiogenic shock must be differentiated from other causes of shock, such as sepsis. In newborns who present with shock, cardiomegaly is a helpful finding indicating a cardiac etiology.

SYSTEMATIC ASSESSMENT OF THE INFANT WITH SUSPECTED CONGENITAL HEART DISEASE

History

- Birth details (peripartum asphyxia)
- Maternal illness or drug ingestion, anticonvulsant, warfarin, lithium
- Family history.

Symptoms in Baby

- Cyanosis
- Poor feeding
- Breathlessness
- Excess weight gain.

Examination

- Color (cyanosis or pallor), oxygen saturation
- Respiratory rate
- Heart rate
- Peripheral pulses:
  - Inequality of volume between right and left brachial pulse
  - Weak femoral pulses
  - Pulses weak or bounding
- Cardiac impulse (right or left ventricular prominence)
- Heart sounds
- Murmur: timing, nature, duration, loudness, site, and radiation
- Hepatomegaly
- Edema
- Peripheral perfusion and temperature
- Blood pressure of all four limbs.

Diagnosis

If CHD is suspected, a chest X-ray and electrocardiography should be performed. Echocardiography combined with Doppler ultrasound will be able to diagnose all causes of CHD. Cardiac catheterization is seldom needed.

Clinical Pearl

- A normal chest X-ray and electrocardiography does not exclude congenital heart disease.

Specific Treatment

Individual treatment options for common acyanotic congenital heart diseases are given in table 4 and those with outflow obstruction in a well child are given in table 5 and for a sick child in table 6. The principles of management of congenital heart disease are given in algorithm 4 and 5, and the management of heart failure is given in algorithm 6.

TABLE 4: Acyanotic heart disease : Left-to-right shunts

Lesion	Symptoms	Signs	Management
ASD-secundum	None	Ejection systolic murmur	Catheter device closure (3–5 years)
AVSD-partial	None, heart failure	Fixed split S2	Surgery at 3 years
VSD-small (80–90%)	None	Pansystolic murmur	None
VSD-large (10–20%)	Heart failure	Active precordium	Diuretics, captopril, surgery at 3–6 months
PDA-term	None	Continuous murmur	Coil or device closure
PDA-preterm	None, heart failure	Systolic murmur + bounding pulses	Fluid restriction, brufen or indomethacin, surgical closure

ASD, atrial septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect.

TABLE 5: Outflow obstruction in the well child

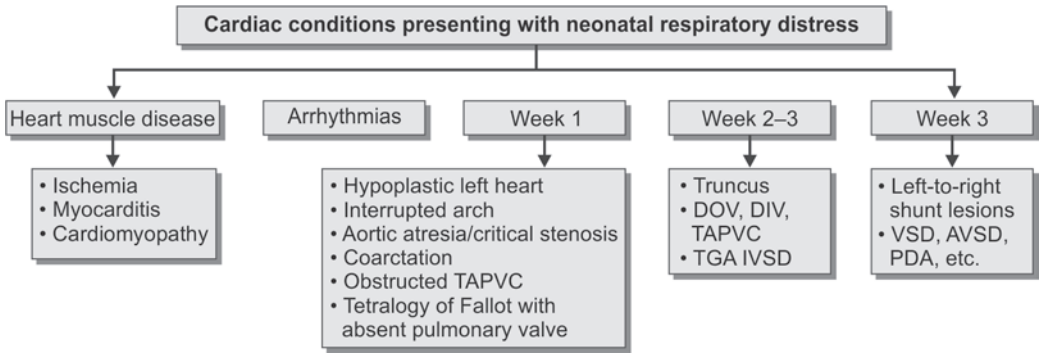
Lesion	Signs	Management
Aortic stenosis	Murmur, upper right sternal edge, carotid thrill	Balloon dilatation
Pulmonary stenosis	Murmur, upper left sternal edge, no carotid thrill	Balloon dilatation
Coarctation of aorta	Systemic hypertension, radiofemoral delay	Surgery

TABLE 6: Left heart outflow obstruction in the sick child—duct-dependent lesion

Lesion	Signs	Management
Coarctation of aorta and prostaglandin	Heart murmur, heart failure	Maintain ABC, immediately start
Interrupted aortic arch	Weak or absent femoral pulses	
	Blood pressure arms > leg	
Hypoplastic left heart syndrome	Circulatory collapse	Maintain ABC, immediately start PGE
	All peripheral pulses weak or absent	Surgery (complex) Norwood

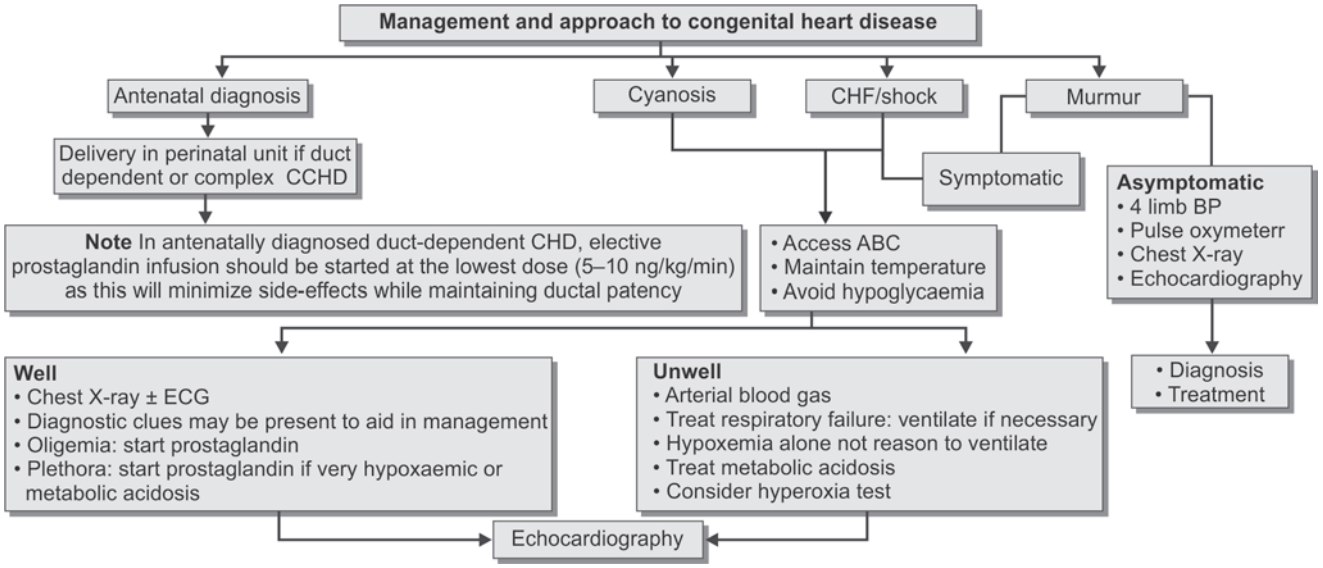
ABC, airway, blood, circulation; PGE, prostaglandin E.

ALGORITHM 4



TAPVC, total anomalous pulmonary venous connection; DOV, double outlet ventricle; DIV, double inlet ventricle; TGA, transposition of the great arteries; IVSD, inlet ventricular septal defect; AVSD, atrioventricular septal defect; PDA, patent ductus arteriosus.

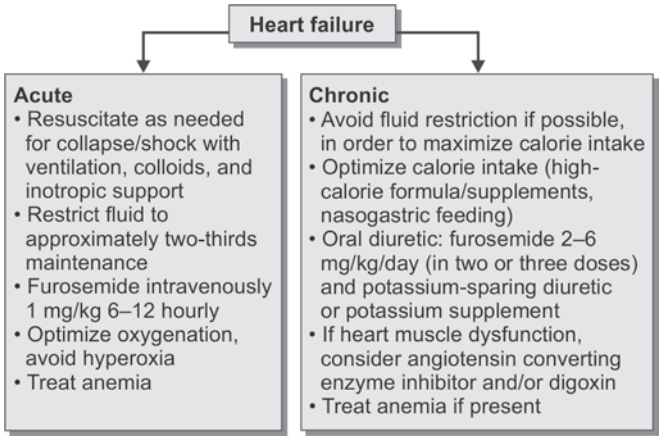
ALGORITHM 5



CHF, congestive heart failure; CCHD, critical congenital heart disease; ABC, airway, breathing, circulation; BP, blood pressure; ECG, echocardiogram.

ALGORITHM 6

Management of heart failure



KEY POINTS

- Congenital heart disease may present as a neonatal emergency
- Acyanotic left-to-right shunts are the commonest anomalies
- Congenital heart disease is an important differential diagnosis in a neonate presenting with respiratory distress
- Occasionally, congenital heart disease may be asymptomatic; hence, it is essential to check saturation and blood pressure in all four limbs in all the newborns prior to discharge.

SUGGESTED READINGS

1. Dolbec K, Mick NW. Congenital Heart Disease. Emerg Med Clin N Am. 2011;29:811-27.
2. Yee L. Cardiac emergencies in the first year of life. Emerg Med Clin N Am. 2007;25:981-1008.
3. Yates R. Cardiovascular disease. Rennie & Roberton's Textbook of Neonatology; 2012.

CHAPTER 16

First Golden Hour Management of Preterm

Naveen Bajaj

INTRODUCTION

The term "golden hour" has been taken from the adult trauma treatment arena in which the best time frame to prevent irreversible internal damage and optimize the chance of survival is the first hour of management. Neonates especially very low birth weight (VLBW) and preterm babies of less than or equal to 32 weeks of gestation are highly vulnerable to many disease in the first hours of life when adaptation is critical and timing of care affects survival and long-term outcome. Delivery room management that focuses on adaptation of these infants, as well as early interventions in first hour of life that improve long-term outcomes, emphasize the importance of this 'golden hour'" of care in this extremely vulnerable population of preterms and VLBW babies.

SPECIAL CONSIDERATIONS IN PRETERM NEONATES

- Poor thermal control
- Poor energy stores
- Poor respiratory drive
- Surfactant deficiency
- Susceptibility to intraventricular hemorrhage and periventricular leukomalacia
- Often born after a complication of pregnancy like antepartum hemorrhage, intrauterine growth restriction, infection, etc.
- Stressed family.

AIM OF GOLDEN HOUR

- To optimize the survival free of disability in preterm infants (≤32 weeks) and VLBW by providing optimal interventions in the first few hours of life
- To undertake all nursing and medical procedures as quickly and with as little disturbance to the infant as possible, usually within 1 hour of admission.

Clinical Pearl

- Consistencies in golden hour stabilization practices improve neonatal outcome in preterm and very low birth weight babies.

BASIC PRINCIPLES

- Lung protection
- Brain protection
- Minimize damage to other organs
- Early nutrition.

Techniques included in the golden hour stabilization practices are:

- Thermoregulation
- Resuscitation as per Neonatal Resuscitation Program guidelines
- Respiratory management
  - Oxygen targeting
  - Administering positive end-expiratory pressure (PEEP)
  - Continuous positive airway pressure (CPAP) ventilation
  - Nasal ventilator strategies to an infant in the delivery room to reduce intubations
  - Early identifications of those infants who need surfactant and mechanical ventilation
- Fluid and nutrition
- Treatment and prevention of infections
- Developmentally supportive care
- Family centered care.

Clinical Pearl

- Thermoregulation, respiratory, and nutrition practices constitute the most important aspect of first golden hour.

PRINCIPLES OF GOLDEN HOUR CARE (FIGURE 1 AND ALGORITHM 1)

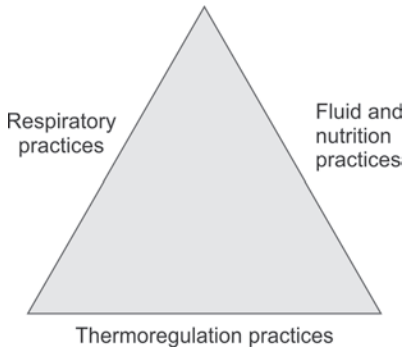


Fig. 1 : The golden hour triad

Thermoregulation

Thermal instability has a detrimental effect on infants' transition to extrauterine life.

Delivery Room Practices

- Maintain delivery room temperature greater than 25–26°C
- Radiant warmer on 30 minutes prior to delivery
- Prewarmed blankets/hat
- Polyethylene bag in less than 29 weeks of gestation
- Heated and humidified gas during resuscitation and transport (preferable)
- Transport in a prewarmed incubator.

Neonatal Intensive Care Unit (NICU) Practices

- Radiant warmer/incubator on 30 minutes prior to expected arrival of baby

ALGORITHM 1

Golden hour management in preterm

Prior to delivery (–30 to 0 min)

Maternal history
- Antenatal steroids
- High risk factors
- Gestational age
- Antenatal counseling

Personnel
- ≤28 weeks: consultant + fellow/registrar + neonatal nurse
- >28 weeks: fellow/registrar + neonatal nurse

Allocation of roles

Prepare resuscitation equipments
- Warmer on
- Prewarm linen
- Check pulse oximeter
- Check oxygen and airsupply
- Plastic bag/bat
- Check T piece, ET, mask, laryngoscope
- Gather surfactant, feeding tube

Organize and prepare NICU equipments and drugs
- Set incubator/warmer temp
- Set up pulse oximeter and multimonitor
- Set up lines trolley
- Set up ventilator
- Gather surfactant, caffein and antibiotics

At delivery (0–10 min)

Start APGAR timer

Thermoregulation
- Place under warmer
- <29 weeks: wrap in plastic bag and do not dry

- Attach pulse oximeter probe
- Initiate resuscitation, if required with 30–60% FiO_2

- Cord blood gases
- Delay cord clamping for 45–60 s

- <26 weeks: intubate and prophylactic surfactant
- ≥26–28 weeks: nasal/mask CPAP (5–6 cm H_2O)
- >28 weeks: CPAP if any sign of respiratory distress
- Titrate FiO_2 to the desired SpO_2 (see Table 1)

Communication
- Talk to NICU staff
- Call parents and discuss

Transport to NICU
- In transport incubator
- on oxygen/CPAP/MV depending upon the need of the baby

In NICU (10–60 min)

Thermoregulation
- Place in warmer/incubator (incubator preferred in <28 weeks)
- Attached skin probe
- Keep plastic bag until insertion of lines

Respiratory support
- CPAP alone
- Early rescue surfactant therapy (INSURE) followed by CPAP
- Mechanical ventilation (patient triggered ventilation)

Vascular access
- UVC/UAV: <28 weeks
- PICC/peripheral IV: 28–32 weeks
- Cardiovascular support if required
- Fluids and Starter TPN

Medication
- Vitamin K
- Caffeine loading dose in infants on CPAP/MV
- Antibiotics if indicated

Communicate parent
- Prognosis
- Length of stay
- Long term developmental problems
- Documentation and note

NICU, neonatal intensive care unit; ET, endotracheal tube; FiO_2, fraction of inspired oxygen; CPAP, continuous positive airway pressure; SpO_2, pulse oxygen saturation; MV, mechanical ventilation; UVC, umbilical venous catheter; UAV, umbilical arterial catheter; PICC, peripherally inserted central catheter; TPN, total parenteral nutrition.

- On admission to NICU, weigh infant in the polyethylene bag
- Use incubator in less than or equal to 28 week baby, and remove bag on admission regardless of admission temperature
- If using radiant warmer and admission temperature less than 37°C, leave in bag until procedures such as line insertion is completed and then remove bag. If using radiant heat source and admission temperature is greater than or equal to 37°C, remove bag. Place a skin temperature probe to avoid extremes in temperature.

Clinical Pearl

- In extreme preterms, additional measures like use of polythene bag in delivery room and transportation of infant in incubator is desired to prevent hypothermia in early hour.

Respiratory Support (Algorithm 2)

Goals of treatment is to use the least amount of intervention necessary to support normal gas exchange while minimizing lung injury by early intervention, optimizing lung recruitment by using high PEEP and avoiding lung overdistention (low tidal volume 5–6 mL/kg).

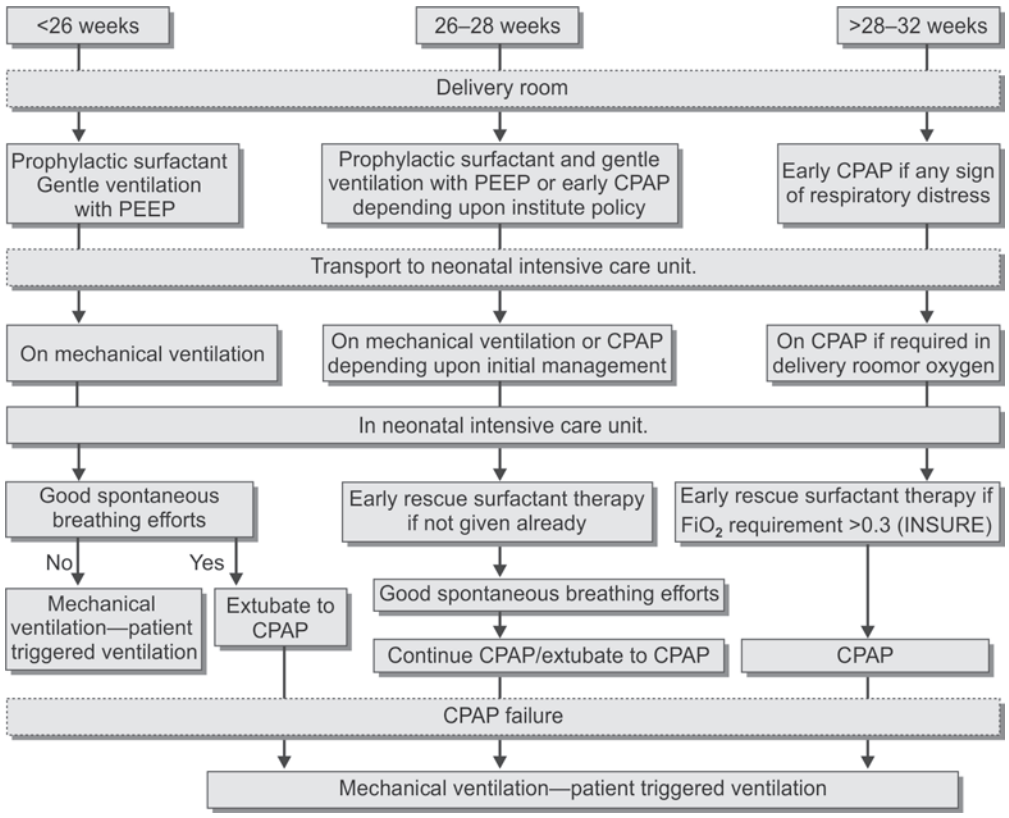
- Use air/oxygen blender for resuscitation
- Use pulse oximetry and target saturations to guide to inspired oxygen concentration
- Intubation and prophylactic surfactant is the best supported approach to the initial respiratory management of the most preterm infants of less than 26 weeks
- Infants of greater than or equal to 26–28 weeks may be best managed with prophylactic surfactant and rapid extubation to nasal CPAP or early elective nasal CPAP with selective surfactant treatment depending upon institution policy
- More mature preterm infants of greater than 28 weeks may be best managed with early elective nasal CPAP with selective surfactant treatment, If a preterm infant is managed initially with nasal CPAP, surfactant is given if fraction of inspired oxygen (FiO_2) requirement increases to 0.30–0.40 with X-ray showing respiratory distress syndrome
- Acceptable oxygen saturations in preterm newborns in delivery room are given in table 1
- In NICU, maintain pulse oxygen saturation SpO_2 88–92%
- Acceptable arterial blood gas: pH = 7.25–7.35; partial pressure of arterial carbon dioxide ($PaCO_2$) = 40–50 mmHg; partial pressure of arterial oxygen (PaO_2) = 50–70 mmHg.

Clinical Pearl

- Prophylactic/early surfactant and nasal continuous positive airway pressure practices are aimed to minimize lung injury.

ALGORITHM 2

Golden hour respiratory practices



PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen.

TABLE 1: Acceptable oxygen saturations in preterm newborns in delivery room

Time from birth in minutes	Acceptable right wrist or hand saturation
1	60
2	65
3	70
4	75
5	80
10	85

Fluids and Nutrition

The goal is to prevent hypoglycemia but also fluid overload.

- Start fluids 60–100 mL/kg depending upon the gestational age
- Start D10% with amino acids [total parenteral nutrition (TPN) starter bag] as the first fluid
- Prevent hypoglycemia and hyperglycemia
- Monitor electrolytes and correct acidosis
- Avoid volume overload
- If hypotensive, start dopamine after one fluid bolus of 10 mL/kg
- Start trophic feeds as early as possible.

Developmentally Supportive Care

- Considerable stress response has been associated with normal birth and high risk (preterm) neonates may be particularly susceptible to stressors because of frequent painful procedures and constant exposure to noxious sensory inputs which are auditory, visual, tactile, and chemosensory in nature in NICU.
- Sound
  - Minimize unnecessary conversation
  - Keep voices low
  - Silence or keep alarms at low volume
- Light
  - Use lowest light level necessary
  - Shield baby's eyes
- Chemosensory
  - Allow alcohol based swabs to dry away from nose
- Tactile
  - Receive baby in bag or warmed, soft blanket
  - Dry and handle gently
  - Use "nesting"
  - Minimize pain
  - Umbilical lines/peripherally inserted central catheter line
  - Premedication for intubation
  - Sucrose for painful procedures
  - Skin-to-skin with parent if possible.

Family Involvement

Birth of a high risk neonate is highly anxiety-provoking for families.

- Provide neonatology consultation or repeat consultation before the birth of the infant
- Establish contact between the family and members of the
- Neonatal intensive care unit team and/or other support individuals before the birth of the infant
- Maintain infant-family contact throughout the admission process
- Ensure that the family is fully informed of their infant's condition
- Welcome the family to the NICU.

Clinical Pearl

- Parental stress needs to be addressed by the treating physician.

INVESTIGATION

Take blood tests from umbilical arterial catheter or peripheral line once inserted and record amount of blood withdrawn.

- Blood glucose
- Arterial blood gas
- Complete and differential blood counts
- Blood culture, C-reactive protein
- Blood group Consider coagulation screen if severe chorioamnionitis/sepsis
- X-ray chest.

KEY POINTS

- ☞ Golden hour is critical short period of time at birth where appropriate interventions (or the lack thereof) can make a difference in neonatal mortality and morbidity
- ☞ Thermoregulation, neuroprotection, respiratory, and nutrition practices constitute the most important aspect of first golden hour care
- ☞ Strong communication, teamwork, clinical skills and evidence-based practices are essential in delivering best care to these high risk neonates consistently
- ☞ Parental counseling is important in allaying the anxiety and stress of the family.

SUGGESTED READINGS

1. Davis PG, Lemyre B, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2001;3:CD003212.
2. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2012;3:CD000510.
3. Stevens TP, Blennow M, Myers EH, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev. 2007;4:CD003063.
4. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362(21):1970-9.
5. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362(21):1959-69.
6. Vaucher YE, Peralta-Carcelen M, Finer NN, Carlo WA, Gantz MG, Walsh MC, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. N Engl J Med. 2012;367(26):2495-504.

CHAPTER 17

Perinatal Hypoxia

Ashish Jain, Veeraraja B Sathenahalli

INTRODUCTION

Perinatal hypoxia/asphyxia is a common major health problem causing morbidity and mortality in neonates. According to National Neonatal-Perinatal Database, perinatal hypoxia is the most common cause of stillbirth accounting up to 45% of cases and is one among the three leading causes of neonatal mortality. This denotes the magnitude of this serious clinical condition. Cautious monitoring and management of a neonate with perinatal hypoxia is an area of importance. Guidelines on clinical approach and management may help in improving the outcome. The management of perinatal hypoxia is evolving day by day with better understanding of its pathophysiology.

DEFINITIONS

The definitions of perinatal hypoxia vary from context to context. Thus, there is no single definition of perinatal hypoxia.

National Neonatal-Perinatal Database defines perinatal hypoxia/asphyxia as moderate when there is slow/gasping breathing or an Apgar score of 4–6 at 1 minute and severe if no breathing or an Apgar score of 0–3 at 1 minute of age.

American Academy of Pediatrics and American College of Obstetrics and Gynecology require presence of all of following criteria to define perinatal asphyxia:

- Profound metabolic or mixed acidemia (pH <7.0) in umbilical cord blood
- Persistence of low Apgar scores less than 3 for more than 5 minutes
- Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities)
- Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart, and intestine).

Clinical Pearl

- No definition of perinatal asphyxia is complete, all the definitions have limitations. The definition which is feasible and sensitive should be used.

CLINICAL EVALUATION

Subsequent to the resuscitation of the baby, the post-asphyxiated newborn should undergo a detailed clinical evaluation, as this neonate is prone for multiorgan dysfunction as perinatal hypoxia virtually affects every organ system. Further management and outcome varies on the severity of organ dysfunction. There are several scoring systems that have being used. A scoring system that can be specifically followed for that setting should be used. Some of the scoring system would need an electroencephalography (EEG) and other investigations on the baby. The most commonly used systems are:

- Sarnat and Sarnat staging system—a descriptive staging system
- Levene staging system—a simpler, practical staging system
- Thompson scoring system.

The babies who have mild stage of the disease (Thompson score <10) are almost free of any neurodevelopmental sequelae, however, the babies with moderate and severe stage of encephalopathy (Thompson score >10 and >15) may have a neurodevelopmental impairment in 25% and 95% of cases, respectively. A non-progressing score is also reassuring and has a better outcome; hence the serial examination is important on day to day basis for the first 7 days.

Clinical Pearls

- Staging/scoring system is vital in management of hypoxic-ischemic encephalopathy. Blood gas and electroencephalogram should be done wherever the facility is available
- These systems though vital in management, a single time finding should not be used as criteria to prognosticate parents about baby. It is suggested to serially follow up and prognosticate about the baby accordingly.

MONITORING

Neonates with moderate and severe encephalopathy are to be shifted to neonatal intensive care unit (NICU) for further

TABLE 1: Suggested monitoring in moderate to severe cases of perinatal asphyxia

Organ system	Possible dysfunctions	Monitoring recommended
Temperature	Temperature dysregulation	Continuous monitoring of temperature, avoid hyperthermia of any degree
CNS	HIE, intracranial hemorrhage, seizures, long-term neurological sequelae	Staging system of HIE, aEEG monitoring where facilities are available
Cardiac	Myocardial dysfunction, valvular dysfunction, rhythm abnormalities, congestive cardiac failure	Heart rate, ECG monitoring, SpO2 monitoring, invasive BP monitoring when required
Renal	Hematuria, acute tubular necrosis, renal vein thrombosis	Urine output measurement, urine routine examination, renal parameters, and serum electrolytes
Pulmonary	Delayed adaptation, respiratory failure, meconium aspiration, surfactant depletion, primary pulmonary hypertension	ABG monitoring, regular adjustments and monitoring of the ventilator settings
GI tract	Necrotizing enterocolitis, hepatic dysfunction	Abdominal girth monitoring, see for aspirates if distention present
Hematological	Thrombocytopenia, coagulation abnormalities	Complete blood counts with platelets and PT, especially if bleeding
Others	Metabolic acidosis, hypoglycemia, hypocalcemia, hyponatremia	Regular monitoring of the blood sugar, calcium, and electrolyte

HIE, hypoxic ischemic encephalopathy; CNS, central nervous system; aEEG, amplitude-integrated electroencephalography; ECG, electrocardiogram; SpO_2, pulse oxygen saturation; BP, blood pressure; ABG, arterial blood gas; GI, gastrointestinal; PT, prothrombin time.

TABLE 2: Levene staging system for hypoxic ischemic encephalopathy

Features	Mild	Moderate	Severe
Consciousness	Irritable	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain spontaneous respiration

management. However, neonates with mild encephalopathy should be monitored at regular intervals for signs of advanced stages of hypoxic ischemic encephalopathy (HIE). The clinical features of HIE vary over time. The window period between these stages can be used for therapeutic intervention. Strict clinical monitoring will help in management of these neonates. Perinatal hypoxia affects virtually every organ system mainly renal, central nervous system and cardiac. The clinical features of organ dysfunction should be looked for. Organ system dysfunction seen in perinatal hypoxia is given in table 1.

MANAGEMENT

The management is mainly supportive and comprises of cardiac, respiratory, metabolic, and neurological support in the form of maintaining optimum saturation, perfusion, blood sugar, calcium levels, and control of seizures.

Delivery Room Management

Maintain appropriate temperature, airway, and serially record Apgar score. Collect umbilical arterial cord blood for analysis. A neonate with moderate to severe hypoxia is resuscitated as per the Neonatal Resuscitation Program guidelines and transferred to NICU for further management. A neonate with mild hypoxia is transferred to mother's side and monitored frequently for the next 48–72 hours for development of any features of HIE (Table 2).

Management in Neonatal Intensive Care Unit

Management of moderate to severe hypoxia consists of clinical, lab monitoring at regular intervals, and maintaining the physiology, viz., temperature, oxygenation, fluid, and electrolyte status. Any complications like seizures are promptly managed. Clinical parameters like heart rate, respiratory rate, pulse oxygen saturation (SpO_2), temperature, blood pressure, capillary refill time, urine output, and neurological examinations for the signs of HIE should be monitored at regular intervals. Laboratory parameters to be monitored include blood sugar, blood gas, urine osmolality, serum electrolytes, and renal function tests at regular intervals. Other parameters like electrocardiogram, and chest X-ray should be done in clinically indicated babies.

Important management guidelines for care in NICU are discussed below.

Supportive Therapy

- Maintain normal temperature and avoid hyperthermia
- Maintain adequate ventilation and oxygenation. The oxygen saturations should be targeted between 90 and 95%.

TABLE 3: Thompson score

Signs	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	None	<3 per day	> 2 per day	Refractory
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	–
Grasp	Normal	Poor	Absent	–
Suck	Normal	Poor	Absent ± bites	–
Respiration	Normal	Hyperventilation	Brief apnea	IPPV
Fontanel	Normal	Full, not tense	Tense	–

LOC, level of consciousness; IPPV, intermittent positive pressure ventilation.

Assisted ventilation should be provided in case of apnea or respiratory distress causing inadequate respiration. Permissive hypercarbia is allowed

- Maintain fluid and electrolyte status by judicious use of fluids. Where tissue perfusion is poor, consider fluid bolus and inotrope support (dopamine and dobutamine). Dobutamine is a better choice as the peripheral vascular resistance in these babies is already high. Restricted fluid administration as a routine is not advised as it may predispose the baby to hypotension. Restrict fluid only if there is hyponatremia (sodium <120 mg/dL) due to syndrome of inappropriate antidiuretic hormone secretion and in cases of acute renal failure. Hypoxia may cause injury to heart affecting its contractility. This can be assessed using echocardiography and managed accordingly
- Maintain normal metabolic milieu by frequent monitoring of blood sugar. Serum calcium is monitored regularly. It is recommended to administer calcium in maintenance dose to all severely hypoxic for 2 days so as to maintain calcium in normal range
- Seizures are serious manifestation of HIE (Stage II HIE). Hypoxic seizures usually occur in the first 12–24 hours. These may be subtle or evident prominently. Electroencephalogram recording will help to identify subclinical seizures. Any metabolic disturbances like hypoglycemia, hyponatremia, and hypocalcemia should be corrected.

Specific Therapy

Treatment of seizures: phenobarbitone is the initial drug of choice. Loading dose of 20 mg/kg followed by 2 additional boluses of 10 mg/kg if seizures continue. Maintenance dose of 3–5 mg/kg/day is started after 24 hours. Monitor for respiratory depression during loading doses.

Phenytoin is added to seizures uncontrolled by phenobarbitone. Loading dose is 15–20 mg/kg and maintenance dose is 4–8 mg/kg/day.

Benzodiazepines are third-line drugs. Lorazepam is advised in doses of 0.05–0.1 mg/kg/dose intravenously. In refractory cases, consider use of investigations like EEG, cranial ultrasonography, computed tomography scan, and magnetic resonance imaging brain to evaluate for neural injuries.

Long-term seizure management: it is based on clinical exam and EEG. If clinical exam and EEG are normal, anticonvulsant can be weaned. If on more than one anticonvulsant, the last anticonvulsant is weaned first. If any of the two are found to be abnormal, then the anticonvulsant is continued for 1 month and baby reassessed at 1 month. Newborns with neurological deficit/sequelae and abnormal EEG are at risk of recurrent seizures and may require long-term anticonvulsant therapy.

- Cardiac support: fluid bolus and inotrope are advised to maintain adequate perfusion
- It is advised to withhold feeds until all parameters are stable
- Hematologic, hepatic, and pulmonary derangements are managed accordingly.

Therapeutic Hypothermia

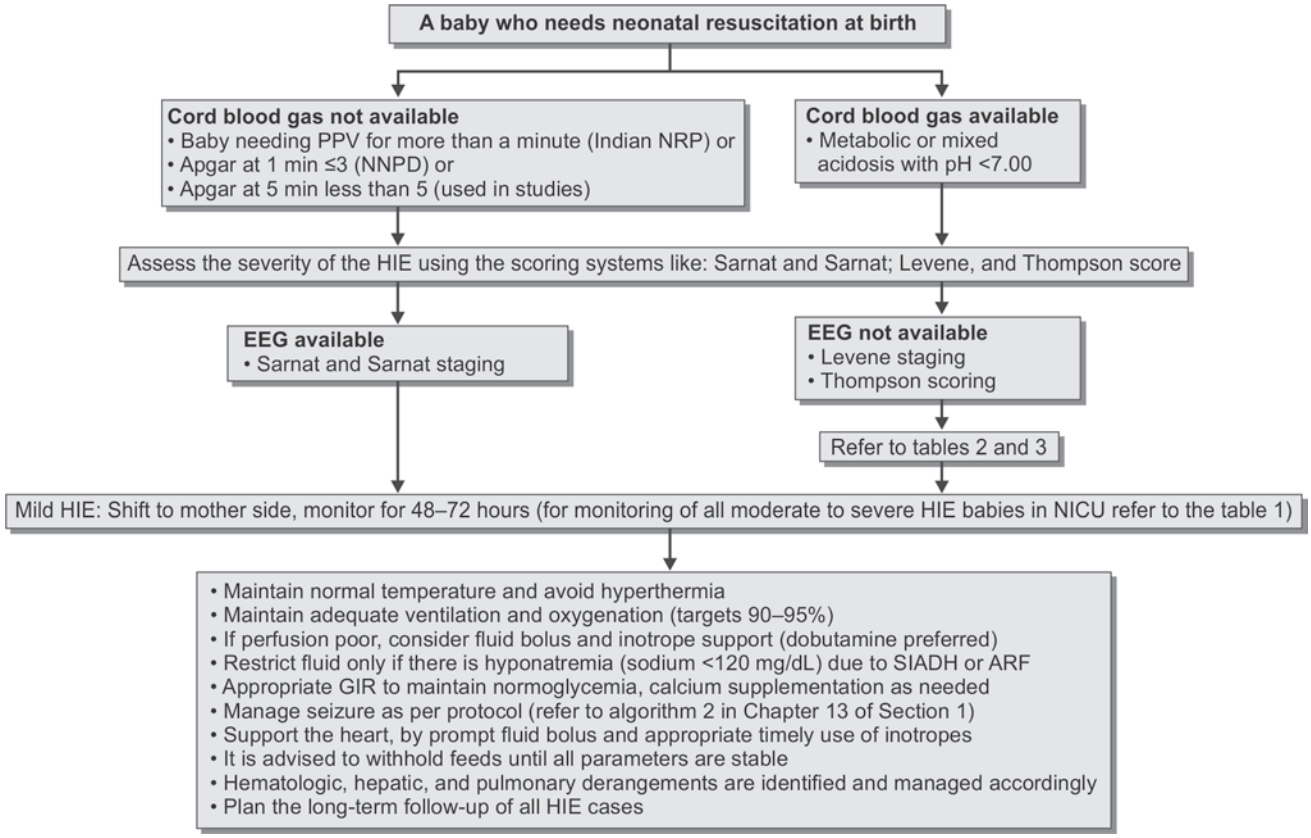
This is now emerging as a novel therapy in babies with perinatal asphyxia to prevent the death and neurodevelopmental impairment. This mode is used in infants of 36 weeks gestation or more with moderate to severe encephalopathy. It consists of moderate use of therapeutic hypothermia (33–34°C) within 4 hours of life. It has shown reduction in combined outcome of mortality or major neurodevelopmental sequelae within 6 hours of life and continued for 72 hours of age.

Clinical Pearls

- Metabolic cause should be ruled out while managing seizures in a neonate with perinatal hypoxia
- Monitoring and management of multisystems is a key factor in prognosis of the baby.

ALGORITHM 1

Algorithm for management of an asphyxiated baby



PPV, positive pressure ventilation; NRP, Neonatal Resuscitation Program; NNPD, National Neonatal-Perinatal Database; HIE, hypoxic ischemic encephalopathy; EEG, electroencephalography; NICU, neonatal intensive care unit; SIADH, syndrome of inappropriate antidiuretic hormone secretion; ARF, acute renal failure; GIR, glucose infusion rate.

KEY POINTS

- ☞ Good antenatal care and prompt neonatal resuscitation are essential for prevention of perinatal hypoxia. However, in the event of a baby suffering from hypoxia at birth, adequate supportive care and specific management can reduce the mortality and long-term morbidity provided there is least possible delay in starting the treatment
- ☞ A system of staging like Levene staging system, a practical and easy to use system or others, like Thompson score, should be used in every case for better management and prognostication
- ☞ Therapeutic hypothermia is an emerging mode of therapy in the management of an asphyxiated baby with better long-term outcome
- ☞ The early prediction of the complications and supportive management forms the cornerstone in the management of a baby with perinatal asphyxia.

SUGGESTED READINGS

1. Blackmon LR, Stark AR; American Academy of Pediatrics Committee on Fetus and Newborn. Hypothermia: a neuroprotective therapy for neonatal hypoxic ischemic encephalopathy. Pediatrics. 2006;117;942-8.
2. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;1:CD003311.
3. Levene MI. The asphyxiated newborn infant. In: Levene MI, Lilford RJ , editors. Fetal and neonatal neurology and neurosurgery. Edinburgh: Churchill Livingstone; 1995. pp. 405-25.
4. National Neonatal Perinatal Database report (National Neonatology Forum, India); 2003.
5. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and encephalographic study. Arch Neurol. 1976;33:696-705.
6. Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, et al. The value of a scoring system for hypoxic ischemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr. 1997;86;757-61.

CHAPTER 18

Teen Pregnancy and Contraception

Prema Raghunathan

INTRODUCTION

Adolescents compromise about 26% of Indian population. According to National Family Health Survey-3, 16% of women in age group 15–19 years have at least one child ever born. Only 8% of women and 15% of men know about emergency contraception. Among this, a significant number is contributed by married adolescents in India, most other teens have sexual relationships due to peer pressure or impulsivity. Teen pregnancies are higher in India than even in United Kingdom (UK), United States (US). The rate of birth among adolescents in US is about 13% of all births. Adolescents have limited education on sexuality, even if they are sexually active.

The increasing rates of teen pregnancies and abortion causes increased medical expenditure as most of these pregnancies are unplanned. They are also mostly seen in underprivileged society. Teen pregnancies push an adolescent to become school dropout, face lot of stress, and can succumb to psychological trauma. Hence, clinicians caring for adolescents should step in to provide sexual education (safe sex) and contraceptive counseling as part of reproductive health.

CONTRACEPTION

Contraception counseling is an important aspect of teen care. The first step is to identify adolescent who are sexually active (maintain confidentiality) and the ones who follow abstinence. The caregivers, parents, adolescent specialist should support adolescents who follow abstinence as "abstinence is the best method of contraception". If the teen is sexually active, contraceptive counseling should be given to understand the adolescent's perception and misperception about contraceptives, risks of unprotected intercourse, educate regarding real risks, and contraindications for various methods available. Once the contraceptive method is chosen by the adolescent, the provider must discuss the common side effects, realistic expectation for failure, a contingency plan for that possibility, and strategies for close follow-up.

American College of Obstetricians and Gynecologists stipulate that a routine pelvic examination with Pap smear be initiated 3 years after onset of sexual activity and annual screening for sexually transmitted infections (STIs).

The various contraceptive methods are broadly classified into hormonal (Table 1), nonhormonal (Table 2), and emergency contraception. The nonhormonal methods are barrier methods, spermicides, and intrauterine devices (IUDs). The hormonal methods are combination pills or progesterone-only pills.

Nonhormonal Methods

Barrier Method

Condoms: it prevents sperms from being deposited in the vagina (Fig 1). The advantages are:

- There are no major side effects
- Risk of STIs reduced (acquired immunodeficiency syndrome and human papillomavirus)
- Low cost, easy availability
- Little need for advanced planning.

A female condom is second choice over male condom due to its complexity of properly using device, its low typical efficacy rate, and lack of studies on effectiveness in STIs. Diaphragm and cervical caps are messy and less used by teenagers.

Spermicides

These are available as foam, cream, films, or effervescent vaginal suppositories containing nonoxynol-9. They must be placed in vaginal cavity shortly before intercourse.

Combination Methods

Use of condom by male and spermicidal foam by female adolescent is extremely effective and failure rate is 2%.

Hormonal Methods

Estrogenic substances in combination with a progestin or a progestin alone are used in these methods. The mechanism

TABLE 1: List of hormonal contraceptives

Methods	Available as	Potential Side effects	Comments
Commonly used methods			
Oral contraceptive pills	• Mala D • Mala N	Breakthrough bleeding, nausea, headaches, breast tenderness	• Decreased burden: Menstrual blood loss dysmenorrhea, acne • Pelvic inflammatory disease
Progestin only	Mini pills	Irregular bleeding, breast, tenderness, depression	Used among breast feeding teens
Contraceptive injections-progestin-only injection	• Depo-Provera–3 monthly • NET-EN-2 monthly	• Weight again • Acne • Depression • Irregular bleeding or amenorrhea	Not used for more than one year, preferred among married teens
Rarely used methods			
Vaginal ring	NuvaRing	Vaginal irritation and discharge	Decreases dysmenorrhea, acne, pelvic inflammatory disease
Transdermal patch	Weekly	Allergic reaction at skin site, breast tenderness, breakthrough bleeding	Not freely available in India
Implant	Implanon	Weight gain, local insertion complications	• High efficacy • Acceptability, Decreases dysmenorrhea

TABLE 2: List of nonhormonal methods

Commonly used methods		
Methods	**Potential Side effects**	**Comments**
Male condom	Latex allergy	• Prevents sexually transmitted diseases and human immunodeficiency virus risk • Failure rate reduced if used with other hormonal contraceptive method
Female condom	Vaginal discomfort	Not available in India, needs proper education for perfect use
Intrauterine device copper-containing	Excessive menstrual blood loss	Nonhormonal, used among parous teens
Spermicides	urinary tract infections, Allergy to ingredients	Should be used by teenage girls along with partner using condoms for maximum contraception

Fig. 1: Female condoms

of action of both (the hormones) estrogen and progesterone combination and progesterone-only pills is to prevent luteinizing hormone (LH) surge and as a result to inhibit ovulation, they also thicken cervical mucous in such a way that prevents sperm penetration. They also cause stromal edema, regression of endometrial glands, and produce static endometrial hypoplasia. These hormones are steroidal contraceptives, can be used orally, parenterally or as devices: intrauterine and vaginal. The oral combination pills typically contain ethinyl estradiol and a progestin. The typical failure, i.e., pregnancy rates are under 1 per woman years of use. Exogenous estrogen use can cause serious side effects rarely like thrombophlebitis, myocardial infarction, hepatic adenoma, and carbohydrate intolerance. The more commonly seen adverse effects are nausea, weight gain, acne in certain progestin pills which can be reduced by using estrogen containing pills which suppresses activity of sebaceous glands. The advantage, of estrogen are relief of dysmenorrhea, short menstrual cycle; estrogen containing pills have higher levels of cardioprotective high density lipoproteins. A few extended cyclic pills are being released which can cause amenorrhea for 3 months to 1 year. However, the major disadvantages of those pills is compliance as adolescents do not take pills every day and may lead to increased failure rates and breakthrough bleeding. The recommendations for missing pills are given in box 1. The most commonly used pill in India is Mala-D (norethisterone acetate + ethinyl estradiol), Mala-N (norgestrel

+ ethinyl estradiol) which is also supplied by Government of India. Other oral contraceptive pills (OCPs) are Ovral-L, Novelon, Femilon, and Loette.

Other combination methods are transdermal patch (Fig. 2) and vaginal contraceptive ring. The transdermal patch releases 20 μg ethinyl estradiol and 150 μg norelgestromin daily. This method is not popular among adolescents as patch can get partial or fully detached. The vaginal contraceptive ring (NuvaRing) is a flexible, transparent, colorless ring which is inserted into vagina by self and remains for 3 weeks where it releases 15 μg of ethinyl estradiol and 120 μg of etonogestrel/day.

In situations where estrogens are contraindicated, progestin-only pills can be used. These are called "mini pills" and are less reliable in inhibiting ovulation, compliance is poor among adolescents. The injectable progestin, medroxy-progesterone acetate, is highly effective as deep intramuscular (IM) injection 150 μg (Depo-Provera). Bone mineral density loss which is reversible side effect should be kept in mind. The progestin-only drug can also be used as subcutaneous implant.

Box 1: Guidelines for missed OCPS

OCP–missed pill rules

- If the teen has missed taking OCP ask her to resume her usual pill taking schedule as early as possible. (she may take two pills on the same day)
- If pills are missed in week 1 (Days 1–7), emergency contraception should be considered
- If the missed pills are in week 3 she should omit the pill free interval
- Abstinence or condoms should be used as backup method if the following number of pills are missed
  - Two for twenty (if two or more 20 μg ethinyl estradiol pills are missed)
  - Three for thirty (if three or more 30–35 μg ethinyl estradiol pills are missed
- Emergency contraception: if you have had unprotected sex in the previous 7 days and you have missed two or more pills (i.e., more than 48 hours late) in the first week of a pack, you may need emergency contraception.

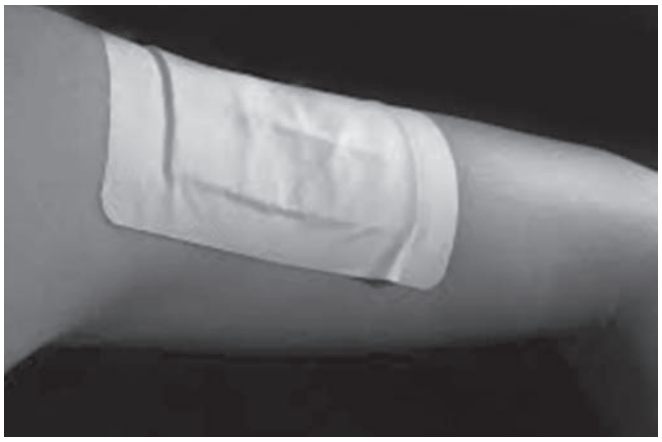


Fig. 2: Transdermal patch

Contraindications of Combined Hormonal Contraceptives

Absolute contraindications (class 4 in the World Health Organization classification)

- Pregnancy
- Undiagnosed genital bleeding
- Breast cancer
- Past or present circulatory disease
- Thrombophilia
- Pill induced hypertension
- Migraine with aura
- Active liver disease
- Systemic lupus erythematosus
- Hemolytic-uremic syndrome
- Thrombotic thrombocytopenic purpura.

Relative contraindications (class 2 or 3 in the World Health Organizationclassification)

- Smoker aged over 35 years
- Hypertension (blood pressure >140/90 mmHg)
- Diabetes
- Hyperprolactinemia
- Gallbladder disease
- Migraine without aura
- Osteosclerosis
- Sickle-cell disease.

Clinical Pearl

- Abstinence is the best contraception for teens.

Emergency Contraception

Pregnancy risk with unprotected intercourse (in midcycle) is 20–30%. The risk can be reduced if emergency contraception is used within 72 hours; these emergency contraceptive pills are combination of ethinyl estradiol and norgestrel/levonorgestrel. This helps by disrupting luteal phase and hormone pattern, makes cervix unstable, and unsuitable uterine lining for implantation. They also blunt LH surge and impair ovulation in midcycle. The important side effects are nausea and vomiting.

Potential Indications for Use of Emergency Contraception

- Lack of contraceptive use during coitus
- Mechanical failure of male condom (breakage, slippage, or leakage)
- Dislodgment, breakage, or incorrect use of diaphragm, cervical cap, or female condom
- Failure of spermicide tablet or film to melt before intercourse
- Error in practicing withdrawal (coitus interruptus)
- Missed combined oral contraceptives (any two consecutive pills)

- Missed progestin-only oral contraceptive (one or more)
- Expulsion or partial expulsion of an IUD
- Exposure to potential teratogen (such as isotretinoin or thalidomide while not using effective contraception)
- Late injection of injectable contraceptive (>2 weeks delay of a progestin-only formulation, such as depot medroxyprogesterone acetate)
- Two or more days delay in starting new vaginal ring or patch cycle
- Rape.

INTRAUTERINE DEVICES

Intrauterine devices are small flexible plastic objects introduced in uterine cavity through cervix. They contain copper (Cu) or progesterone. Cu-T 380A IUD renders endometrium unsuitable for implantation, the levonorgestrel IUD acts by thickening of cervical mucosa, inhibiting sperm survival and suppresses endometrium (Fig. 3). This method of contraception is used among teens who are highly sexually active but they should take measures to prevent STIs (Algorithm 1).

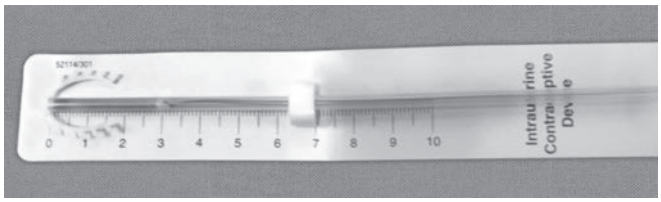
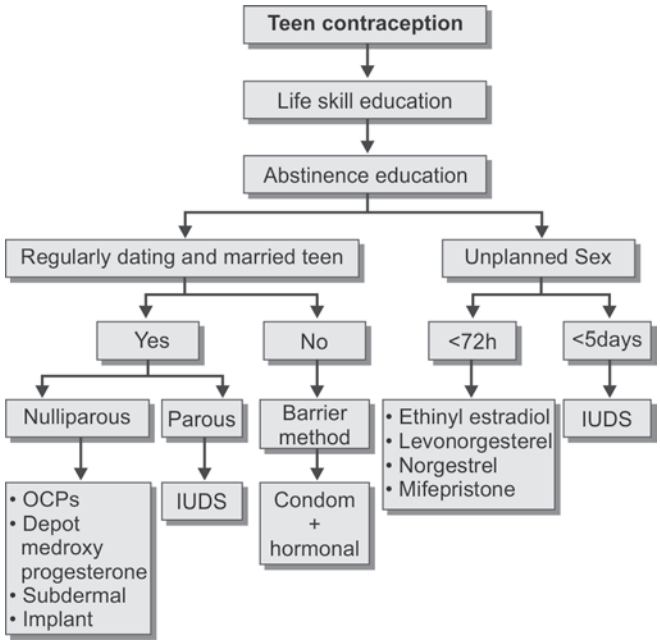


Fig. 3: Intrauterine devices

ALGORITHM 1

Approach to teen contraception



IUDs, intrauterine device; OCPs, oral contraceptive pills.

ADOLESCENT PREGNANCY

By providing good education including sexual education to our teens, counseling them regarding abstinence, and providing life skills, teen pregnancies can be avoided. Still there are lots of pregnancies being reported. As one sector of them could be early marriages from rural population and sexual abuse. Among Indian studies, teenage pregnancy varies from 5.1% to as high as 21.12%.

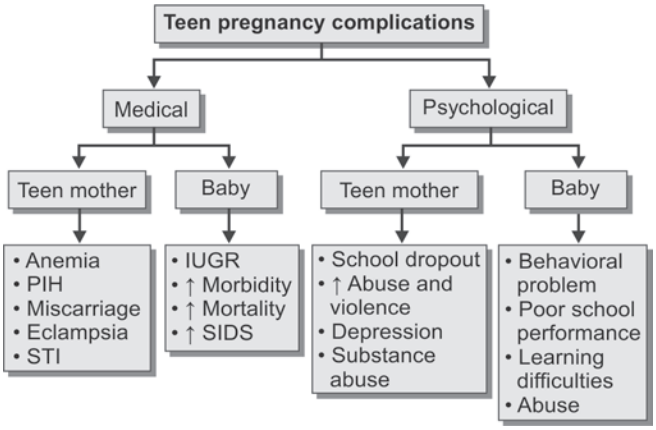
The adolescent caregivers should always suspect pregnancy when there is secondary amenorrhea as most teens may be reluctant to give history of sexual activity. The methods to diagnose pregnancy are urine pregnancy test, which is sensitive by 5 days of missed cycles by 98%. Ultrasound scan detects pregnancy and can also rule out an ectopic pregnancy.

The next step after diagnosing is addressing psychosocial, emotional, and medical aspects. The options of elective termination of pregnancy or raising the child by friends/family/option of adoption can be given to family.

Complications due to teen pregnancy could be medical or psychosocial (Algorithm 2). Most teen pregnancies do not have major medical complications. The pregnancy termination rate is about 33% in Indian statistics. Miscarriages/stillbirth rate is about 15%. Teen mothers have higher rate of anemia, pregnancy induced hypertension, eclampsia, poor weight gain, increased STIs, increased abuse, violence, and depression. The babies of teen mothers have behavioral problems in preschool years, poor scholastic performance, learning difficulties; these could be attributed to poverty, negative parenting styles, and higher possibilities of abuse and neglect.

There are lot of educational programs for youth in various countries to educate teens about abstinence, contraception, STIs; this education and life skills training

ALGORITHM 2



PIH, pregnancy induced hypertension; STI, sexually transmitted infection; IUGR, intrauterine growth retardation; SIDS, sudden infant death syndrome.

given at schools and adolescents clinics, health clinics, and/or, youth organizations have to be geared up to tackle this problem in India.

KEY POINTS

- ☞ Adolescents need sexual education
- ☞ Encourage and support abstinence
- ☞ Provide contraceptive counseling for sexually active teens
- ☞ Encourage dual protection for pregnancy and sexually transmitted infections.

SUGGESTED READINGS

1. Parthasarathy A, Nair MK, Menon PS, Bhave SY. Bhave's Textbook of Adolescent Medicine, 1st edition. New Delhi, India: Jaypee Brothers Medical Publishers; 2006.
2. Brooks RL, Shrier LA. An update on contraception for adolescents. Adolesc Med. 1999;10(2):211-9.
3. Brown RT, Braveman PK. Contraception and adolescents. Adolesc Med Clin. 2005;16(3):15-16.
4. Greydanus DE, Senanayake P, Gains MJ. Reproductive health: an international perspective. Indian J Pediatr. 1999;66(3):415-24.
5. World Health Organization (WHO). (2000). Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. [online] Available from extranet.who.int/iris/restricted/bitstream/10665/61086/1/WHO_RHR_00.02.pdf. [Accessed November, 2015].

CHAPTER 19

HEEADSSS Assessment of the Adolescent Child

Piyali Bhattacharya

Young people are resources to be developed, not problems to be solved.

Pittman

INTRODUCTION

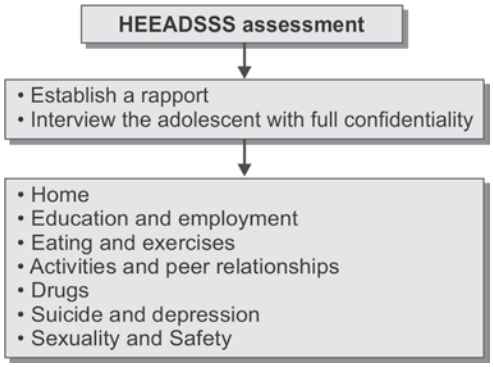
The HEEADSSS (Home, Education and employment, Eating and exercise, Activities and peer relationships, Drugs, Suicide and depression, Sexuality and Safety) assessment is a screening tool for conducting a comprehensive psychosocial history and health risk assessment of an adolescent (Algorithm 1). It provides an ideal platform for a preventive health check and information about the young one's functioning in key areas of their life.

BUILD A RELATIONSHIP

- Confidently welcome the adolescent

ALGORITHM 1

Algorithm depicts points for interviewing and risk assessment in an adolescent child



HEEADSSS, Home, Education and employment, Eating and exercise, Activities and peer relationships, Drugs, Suicide and depression, Sexuality and Safety.

- Respond openly to adolescent's initial reactions and feelings
- Give clear introductions: yourself, your role, what you will be doing and why, e.g., "to get a better understanding of different areas of your life and how these might affect your health, I would like to ask you a few questions if it is okay with you"
  - Reassure the young person about confidentiality. However, three exceptions must be made clear to the young person and their caregivers:
    1. Harm to self
    2. Harm to others
    3. Others harming you.
  - Start with less sensitive areas of a young person's life and move towards more sensitive areas using a "third person" approach, e.g., "Some young people of your age are starting to experiment with drugs or alcohol (or sex). Have any of your friends tried these? How about yourself?"
  - Perform a risk assessment and screen for specific risk behaviors which occur in clusters.

INTERVIEWING THE ADOLESCENT

Home

- How is it at home at the moment? Who lives with you? Where do you live?
- Do you have your own space? Who do you get along best with? Could you talk to them if you were worried about anything? Is there anyone new at home? Has someone left recently?
- Have you moved recently?
- Have you ever had to live away from home? (Why?)
- Have you ever run away? (Why?)
- Is there any physical violence at home?

Education and Employment

- What are your favorite subjects and least favorite subjects at school?
- How are your grades? Any recent changes? Have you changed schools in the past few years?
- Have you ever had to repeat a class? Have you ever had to repeat a grade? What are your future education/employment plans/goals? Are you working? Where? How long?
- Tell me about your friends at school. Is your school a safe place?
- Have you ever been suspended? Expelled? Have you ever considered dropping out?
- How well do you get along with the people at school or work?
- Do you feel connected to your school? Do you feel as if you belong?
- Are there adults at school you feel you could talk to about something important? (Who?)

Eating and Exercise

- Has your weight changed recently? Are you worried about it? Have you ever dieted?
- How much exercise do you get? How much exercise do you get in an average day/week?
- What do you think would be a healthy diet? How does that compare to your current eating patterns?
- Do you worry about your weight? How often?
- Do you eat in front of the television? Computer? What would it be like if you gained/lost 10 pounds?

Activities and Hobbies

- What do you do to relax? What do you and your friends do for fun? (With whom, where, and when?)
- What do you and your family do for fun? (With whom, where, and when?)
- Do you participate in any sports or other activities?
- Do you regularly attend a club, or other organized activity?
- Do you have any hobbies?
- Do you read for fun? (What?)
- How much television do you watch in a week? How about video games? What music do you like to listen to?

Drugs, Alcohol, and Tobacco

- Lots of teenagers try smoking/alcohol, have you ever tried it?
- Have you been offered drugs? Is it hard for you to say no in this situation?
- Is there any history of alcohol or drug problems in your family? Does anyone at home use tobacco?
- Do you ever drink or use drugs when you are alone?

Sex and Relationships

- Have you ever been in a romantic relationship? Tell me about your dates
- Have any of your relationships ever been sexual relationship? Are your sexual activities enjoyable?
- Are you interested in boys? Girls? Both?
- Have you ever been forced or pressured into doing something sexual that you did not want to do?
- Have you ever been touched sexually in a way that you did not want?
- Have you ever been raped, on a date or any other time?
- How many sexual partners have you had altogether?
- Have you ever been pregnant or worried that you may be pregnant? (females)
- Have you ever gotten someone pregnant or worried that that might have happened? (males) What does the term "safe sex" mean to you?
- What do you know about contraception?

Suicide and Depression

- Do you feel sad or down more than usual? Do you find yourself crying more than usual? Are you "bored" all the time? Are you having trouble getting to sleep?
- Does it seem that you have lost interest in things that you used to really enjoy? Do you ever feel so down that life is not worth living?
- Do you find yourself spending less and less time with friends? Would you rather just be by yourself most of the time?
- Have you ever thought a lot about hurting yourself or someone else?
- Have you ever had to hurt yourself (e.g., by cutting yourself) to calm down or feel better?
- Have you started using alcohol or drugs to help you relax, calm down, or feel better?

Safety and Abuse

- Have you ever been seriously injured? Do you always wear a seatbelt in the car?
- Have you ever ridden with a driver who was drunk or high? When? How often?
- Do you use safety equipment for sports and/or other physical activities (e.g., helmets for biking or skateboarding)?
- Is there any violence in your home? Does the violence ever get physical?
- Is there a lot of violence at your school? In your neighborhood? Among your friends?
- Have you ever been physically or sexually abused? Have you ever been raped, on a date or at any other time? (If not asked previously)
- Have you ever been in a car or motorcycle accident? (What happened?)
- Have you ever been picked on or bullied? Is that still a problem?
- Have you gotten into physical fights in school or your neighborhood? Are you still getting into fights?
- Have you ever felt that you had to carry a knife, gun, or other weapon to protect yourself? Do you still feel that way?
- All communication should be with: open-ended questions, affirmations, reflective listening and summary statements (OARS).

WRAPPING UP THE SESSION

At the end of the HEEADSSS assessment, the pediatrician should compliment the young person on their strengths and areas in their life where they are doing well. He should:

- Identify areas for intervention and prevention
- Identify and discuss any issues of concern psychosocial health
- Identify the overall level of risk of the young person and specific risk factors in their lives, as well as protective factors and strengths
- Identify areas for intervention and follow-up
- Provide health education about particular health issues or risk behaviors.

The HEEADSSS assessment is not simply an information gathering exercise; listen carefully to the young person's verbal and nonverbal responses. Adolescents may present with minor complaints but exploring beyond the presenting complaint may detect underlying health concerns and risk factors, thereby providing timely intervention and preventive education.

PRINCIPLES OF INTERVENTION

- Allow time to finish, provide a brief summary, give opportunity for questions
- Discuss options and help the adolescent make choices
- Based on the level of risk: decrease risk factors or increase protective factors
- Possible foci: environment and social context, family, individual.

A pediatrician must seek a collaborative approach and facilitate access to psychological and specialist counseling services once a problem has been identified.

Clinical Pearl

- Specific risk behaviors usually occur in clusters. Risk assessment, therefore, must be done continuously throughout the whole interview of the adolescent in order to identify associated factors.

SUGGESTED READINGS

1. Goldenring JM, Rosen DS. Getting into adolescent heads: an essential update. Contemp Pediatr. 2004;21:64-90.
2. Sanci L. Adolescent Health Care Principles. Melbourne, Australia: The Centre for Adolescent Health, The Royal Australian College of General Practitioners; 2001.
3. SERU. Improving Young People's Access to Health Care Through General Practice: A Guide for General Practitioners and Divisions of General Practice. Melbourne, Australia: Access SERU, Department of General Practice and Public Health, University of Melbourne; 1999.

CHAPTER 20

Adolescent Anemia

Vaishali R Deshmukh

INTRODUCTION

Anemia is a major public health problem in India. It has a special significance in adolescents as it affects final height, cognition, and reproductive health.

Most of the hereditary or congenital anemias present before the age of adolescence (exceptions: congenital dyserythropoietic anemia, milder forms of hemolytic anemia). Since nutritional anemia, especially iron deficiency anemia, is the most commonly found anemia in adolescents in India as well as all over the world, it will be discussed here in detail.

Anemia is not a specific entity. It is a condition, which results from an underlying pathologic process.

Surprisingly, in a gradually developing anemia, hardly any symptoms are apparent until hemoglobin reaches a level of 8 g/dL or lower because, the body adjusts for anemia in the initial stages by various adaptive mechanisms.

The normal lifespan of red blood cells (RBCs) is 110–120 days. Adult RBCs do not have a nucleus. This makes them a better oxygen vehicle but gives them a definite lifespan. Adolescents, beyond the age of 12 years, have hematologic ranges similar to those of adults. At puberty, hemoglobin concentration reaches adult level as a result of effect of androgens on erythropoiesis.

PREVALENCE

According to the World Health Organization Global Database, the prevalence of anemia is very high in India putting it in severe public health problem category.

According to National Family Health Survey-3, the prevalence of anemia in Indian adolescent girls is 56–68% and boys is 56–68% and 30%, respectively.

DEFINITION

Anemia is defined as reduction in the number of RBCs or reduced packed cell volume (hematocrit) or low hemoglobin, all below the lower limit for the age norm.

Clinical Pearl

The World Health Organization Global Database:

- Prevalence of anemia in south-east Asia: 57%
- Global prevalence in school-aged children: 25.4% (305 million)
- Overall prevalence in India: 74.3%.

TABLE 1: The World Health Organization guidelines for severity of anemia

Age	No anemia	Mild	Moderate	Severe
12–14 years	>12 g/dL	11.0–11.9 g/dL	8.0–10.9 g/dL	<8 g/dL
Nonpregnant >15 years girls	>12 g/dL	11.0–11.9 g/dL	8.0–10.9 g/dL	<8 g/dL
Men	>13 g/dL	11.0–12.9 g/dL	8.0–10.9 g/dL	<8 g/dL

Source: Guidelines for treatment of iron deficiency anemia - MoHFW, Govt. of India.

The functional definition of anemia is "an insufficient RBC mass to adequately deliver oxygen to peripheral tissues" (Table 1).

Severe Anemia

Severe anemia is defined clinically as a low hemoglobin concentration leading to cardiac decompensation, that is, to the point that the heart cannot maintain adequate circulation of the blood. There is extreme pallor. If the hemoglobin or hematocrit can be determined, cutoffs of hemoglobin below 7.0 g/dL or hematocrit below 20% should be used to define severe anemia.

Clinical Pearl

- Anemia is caused by either reduced or ineffective production of red blood cells (RBCs), blood loss, or increased destruction of RBCs.

Mechanism of Anemia of Chronic Diseases

In a chronic disease, anemia is caused either due to decreased production or increased destruction of RBCs. The mechanism is as follows:

- Reduced erythropoietin
- Moderate decrease in RBC lifespan
- Increased RBC destruction by the hyperactive reticulo-endothelial system
- Relative failure of bone marrow response
- Defective release of iron from tissues into plasma
- Increased levels of tumor necrosis factor causing suppressed erythroid response.

Etiology of Anemia (Algorithm 1)

Nutritional Anemia

By definition, it is the anemia caused by dietary deficiency of one or more nutrients required for hemoglobin synthesis. The most common deficiency is that of iron followed by folate and vitamin B12. This deficiency is usually compounded by intestinal parasites (helminthiasis) and malaria.

Iron deficiency anemia typically shows three phases with increasing severity:

1. Prelatent phase of iron deficiency: reduced serum ferritin, reduced iron stores without reduction in serum iron
2. Latent phase: iron stores are exhausted but hemoglobin levels are normal. Some symptoms such as fatigue, malaise but no anemia. Increase in total iron binding capacity, reduction in transferrin saturation
3. Iron deficiency anemia: pallor, pica, low hemoglobin, presence of microcytes.

Other Causes of Anemia in Adolescents

Other causes of anemia in adolescents are as follows:

- Thalassemia
- Sickle-cell anemia
- Pernicious anemia
- Hemorrhagic causes
- Chronic disease
- Bone marrow infiltration.

SPECIAL FEATURES OF ANEMIA IN ADOLESCENTS

Various unique factors contribute to the cause and effect of anemia in adolescence.

Clinical Pearl

- The most common anemia in adolescents all over the world is iron deficiency anemia.

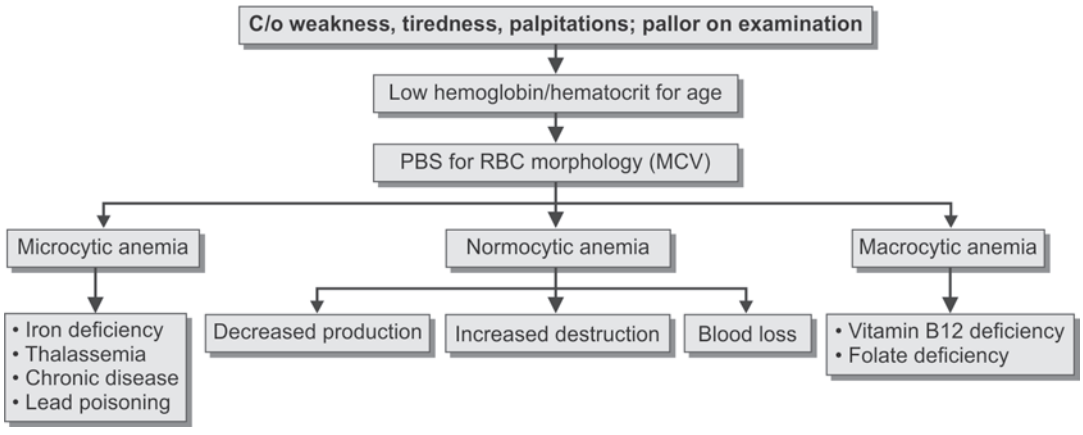
Gender difference between normal ranges of hematocrit starts becoming apparent at adolescence. The sudden growth spurt (the third and the last spurt after intrauterine life and gestation) leads to relative deficiency of nutrients and occult deficiencies become apparent. Hormones like testosterone, which affect erythropoiesis, peak during adolescence.

- In adolescent boys, the rapidly increasing muscle mass demands high amount of iron. In addition, the blood volume increases in short span
- Menstrual losses contribute to iron deficiency in adolescent girls
- In girls, the beginning of menstruation, i.e., menarche, leads to significant loss of blood on a regular basis. The menstrual flow may be heavier in the initial period of menarche. Add to this the increased demand for iron due to rapid growth and the result is significant anemia in adolescent girls. Teenage pregnancy makes the physiological anemia of pregnancy much more severe
- Intergenerational effect of anemia: low maternal hemoglobin and weight is a major cause of intrauterine growth restriction and high maternal mortality
- Changes in thinking patterns and lifestyle lead to food fads, consumption of junk food, and irregular eating habits

  The changing lifestyle and the peculiar temperament of adolescents are responsible for this. They eat a lot of junk food due to irregular timings and peer pressure. The sense of newly acquired freedom and the need to stay away from home necessitates them to eat outside food
- Socioeconomic status of the family, traditional eating habits of the region, the fear of gaining weight, and irregular

ALGORITHM 1

Approach to anemia



PBS, peripheral blood smear; RBC, red blood cell; MCV, mean corpuscular volume; C/o, complaints of.

eating habits are of great importance in development of adolescent anemia
- Adolescents have poor compliance to treatment
- "I do not care" attitude causes difficulty in convincing them of consequences
- Occasional or no visits to doctors prevent early detection.

Clinical Effects of Anemia

- In a gradually developing anemia, patient may remain asymptomatic until hemoglobin reaches a level of 8 g/dL or lower. The symptoms depend upon the magnitude and the rate of reduction in oxygen carrying capacity of blood and the capacity of the pulmonary and the cardiovascular system to compensate for anemia. The symptomatology also reflects the symptoms of the underlying disease
- Normally, the body adjusts for anemia in the initial stages by various adaptive mechanisms. The cardiac output increases to increase the oxygen delivery to the tissues. The production of 2,3-diphosphoglycerate in the RBCs increases leading to reduced affinity of hemoglobin to oxygen. This causes shift of oxygen dissociation curve to the left causing release of oxygen to tissues faster. This is also seen at high altitudes. Production of erythropoietin increases too, leading to stimulation of bone marrow and increased RBC output
- A striking feature of iron deficiency anemia is pica. This desire to consume unusual things is very peculiar to iron deficiency anemia, the reason is not clear, especially seen is pagophagia, i.e., urge to eat unusual amounts of ice
- Skin and mucosa: the hair texture worsens leading to lack of luster, premature graying, and thinning of hair. This effect can be used to counsel the adolescents as this may appeal to them
- Neuromuscular symptoms: headache, vertigo, tinnitus, faintness, lack of concentration, drowsiness, restlessness, muscular weakness; in pernicious anemia, paresthesias
- Behavioral and cognitive problems: iron deficiency adversely affects behavior by impairing cognitive functions, producing noncognitive disturbances, and limiting activity and work capacity

Iron supplementation among iron deficient anemic children benefits learning processes as measured by the school achievement test scores:
- Poor physical growth
- High maternal mortality
- Gastrointestinal: symptoms of underlying disorder (duodenal ulcer, cancer, hiatus hernia).

INVESTIGATIONS (ALGORITHM 2)

- Hemogram with peripheral blood smear (PBS): to determine the severity of anemia, affection of other cell lines, RBC morphology, hematocrit level, and presence of parasites such as malaria
- Reticulocyte count: to assess bone marrow response
- Stool for parasites and occult blood
- Hemoglobin electrophoresis
- Serum bilirubin and serum iron studies
- Investigations to rule out underlying diseases.

MANAGEMENT

Treatment Program (Algorithm 3)

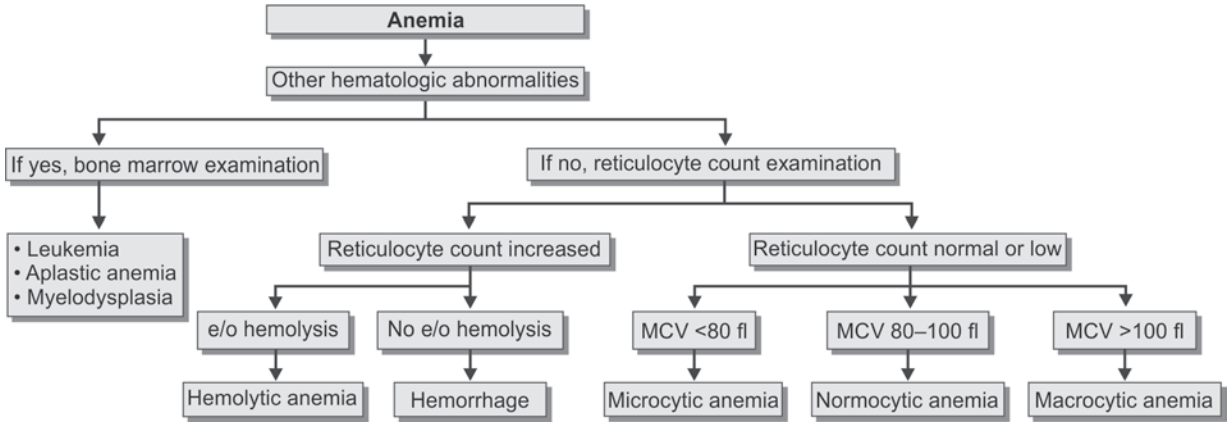
International Nutritional Anemia Consultative Group has recommended the following treatment program:
- Mild anemia: 60 mg of elemental iron daily for 3 months after which hemoglobin estimation is done
- Moderate anemia: it is investigated for complete blood count, PBS, malarial parasites, and stool for occult blood and treated in the same way as mild anemia
- Severe anemia: investigate and treat with 120 mg iron + 400 μg folic acid daily for 3 months.

Indications for Blood Transfusion

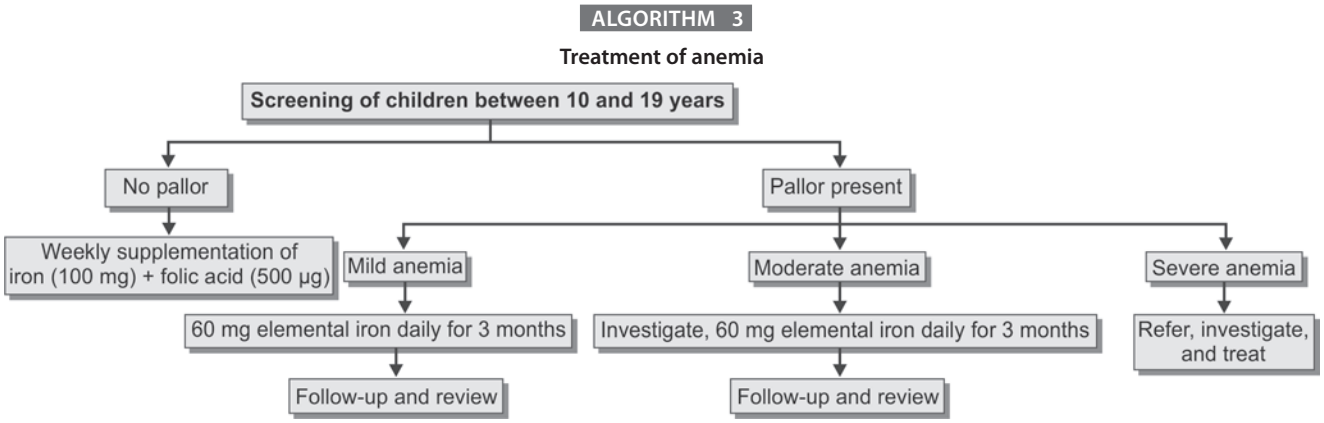
- All children with hemoglobin less than or equal to 4 g/dL

ALGORITHM 2

Diagnosis of anemia



MCV, mean corpuscular volume; e/o, evidence of.



- Children with hemoglobin 4–6 g/dL with complications, such as dehydration, shock, impaired consciousness, heart failure, deep and labored breathing, very high parasitemia (>10% of RBC)
- If packed cells are available, give 10 mL/kg over 3–4 hours preferably. If not, give whole blood 20 mL/kg over 3–4 hours with close monitoring and diuretics.

Prevention (Fig. 1)

Due to its prevalence across all age groups all over the world, prevention plays a major role in the management of iron deficiency anemia

- Increased awareness about the magnitude of anemia and its far-reaching consequences among the masses will go a long way to reduce its incidence
- School and college based awareness programs to reduce consumption of junk food and to encourage healthy dietary habits
- Food based interventions: fortification of commonly consumed food, such as salt, milk, or *atta* with iron
- Screening for anemia in adolescents and other high risk groups to tap cases of anemia in presymptomatic stage
- Regular supplementation of iron-folic acid tablets to adolescents and pregnant women.

National Iron plus Initiative: this is a proposed lifecycle iron-folic acid supplementation program by Ministry of Health and Family Welfare, where age specific recommendations are made for prophylactic iron and folic acid supplementation to children, adolescents, and pregnant women.

All adolescent boys as well as girls (10–19 years) are given weekly tablets containing 100 mg elemental iron and 500 µg of folic acid along with biannual deworming:

- Diet: increased consumption of food rich in iron, such as animal proteins, green leafy vegetables, jaggery, etc. Using iron pots for cooking
- Biannual deworming of all school-going children with albendazole
- Malaria control
- Treatment of underlying condition
- Reproductive and obstetric interventions: preventing adolescent pregnancies, reducing the total number of pregnancies and increasing the time between pregnancies will contribute to the control of iron deficiency anemia in women. Pregnancy creates a large demand for iron, which is needed to develop the fetus and placenta and to expand a woman's blood volume. Additional iron is lost with blood lost at delivery. When the iron demands of pregnancy are combined with the iron demands of adolescent growth, girls enter adulthood at great risk of iron deficiency.

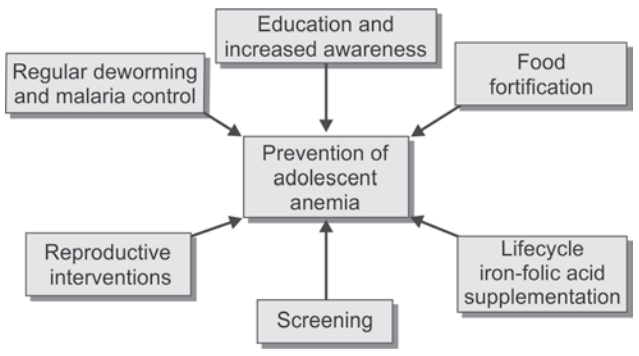


Fig. 1: Prevention of anemia

CONCLUSION

Anemia is a major public health problem in India. In adolescent age group, iron deficiency anemia is the most common anemia. It is of particular significance due to its major effects on growth, development, productivity, maternal mortality, and intergenerational effects. Regular screening, prophylaxis, early detection and treatment, food fortification, and public awareness programs are needed to control iron deficiency anemia.

KEY POINTS

- ☞ Iron deficiency anemia is the most common type of anemia in adolescents all over the world
- ☞ Due to the unique stage of growth, adolescent anemia has a significant impact on growth, cognition, reproduction, and general productivity
- ☞ Prevention is the best method of managing iron deficiency anemia.

SUGGESTED READINGS

1. Means RT, Glader B. Anemia: general considerations. In: Greer JP (Ed). Wintrobe's Clinical Hematology, 12th edition. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 2009. pp. 779-807.
2. de Benoist B, McLean E, Egli I, Cogswell M (Eds). Worldwide Prevalence of Anemia 1993-2005: WHO Global Database on Anaemia. Geneva, Switzerland: World Health Organization; 2008.
3. Kliegman RM, Stanton BM, Geme JS, Schor N, Behrman RE. Nelson's Textbook of Pediatrics, 19th edition. Philadelphia, PA, USA: Saunders-Elsevier; 2011.
4. Parthasarathy A, Nair MK, Menon PS, Bhave SY. Bhave's Textbook of Adolescent Medicine, 1st edition. New Delhi, India: Jaypee Brothers Medical Publishers; 2006.
5. Adolescent Division, Ministry of Health and Family Welfare, Government of India. (2013). Guidelines for Control of Iron Deficiency Anaemia: National Iron plus Initiative (Towards infinite potential in an anaemia free India). [online] Available from www.pbnrhm.org/docs/iron_plus_guidelines.pdf. [Accessed November, 2015].
6. Chellan R, Paul L. Prevalence of iron-deficiency anemia in India: Results from a large nationwide survey. J Population Social Studies. 2010;19(1):59-80.
7. Lozoff B. Behavioral alterations in iron deficiency. Adv Pediatr. 1988;35:331-59.
8. Soemantri AG, Pollitt E, Kim I. Iron deficiency anemia and educational achievement. Am J Clin Nutr. 1985;42(6):1221-8.
9. Işık Balcı Y, Karabulut A, Gürses D, Ethem Çövüt I. Prevalence and risk factors of anemia among adolescents in Denizli, Turkey. Iran J Pediatr. 2012;22(1):77-81.
10. Daniel WA. Hematocrit: maturity relationship in adolescence. Pediatrics. 1973;52(3):388-94.
11. Stoltzfus RJ, Dreyfuss ML (Eds). (1998). Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia. International Nutritional Anemia Consultative Group (INACG). [online] Available from www.who.int/nutrition/publications/micronutrients/guidelines_for_Iron_supplementation.pdf. [Accessed November, 2015].

CHAPTER 21

Academics and Career Choices in Adolescents: Approach in the Pediatric Office Setting

Ira E Almeida

INTRODUCTION

For parents whose health concerns about their wards have been addressed by the pediatrician for so many years, there is no leap of faith in expecting that the same doctor must have something in a bottle or book that addresses their biggest anxiety during their child's adolescence academic performance. Most children enter high school and adolescence at the same time in India—it becomes a time fraught with stress by definition alone. In most government schools, high school is the first time children can fail a grade and have to repeat it—in such schools, government policy mandates that children get promoted to the next grade regardless of competence in taught skills right up to grade VII. It is not surprising that pediatric practices face large numbers of adolescents presenting with academic difficulties. A pediatric practice must stretch its role to point parents and their adolescent children presenting with such difficulties in the correct direction, whether with a direct solution or by referring the child to appropriate assessors.

A seemingly innocuous statement made by a mother "my child does not study well; give him a tonic", can cause a great deal of anxiety in the pediatrician. However, this is not as simple as it sounds. Besides, doctors often feel helpless when the parents ask them to advise career choices for their wards (often they also hope that they will inspire their kids to become doctors).

In the conventional system of education in India, we have those who are academic and those who are not. For those who are academic achievers, the paths that most parents wish for their children are those that will take them to professional courses like medicine and engineering and if not successful, allied fields like physiotherapy, audiology, diplomas in technical courses, etc. are acceptable. For the creative types who fall off this path, many interesting fields like photography, design, advertising, media, communication, and event management are now available.

If the child has made up his mind as to what he/she wants to do, encouraging them to shadow a professional in the field for a day or more can be helpful. If the child is undecided, aptitude testing and workshops on career options are useful.

An approach to help the pediatrician in office practice to guide and refer appropriately with regard to academics and career choices is represented in algorithm 1.

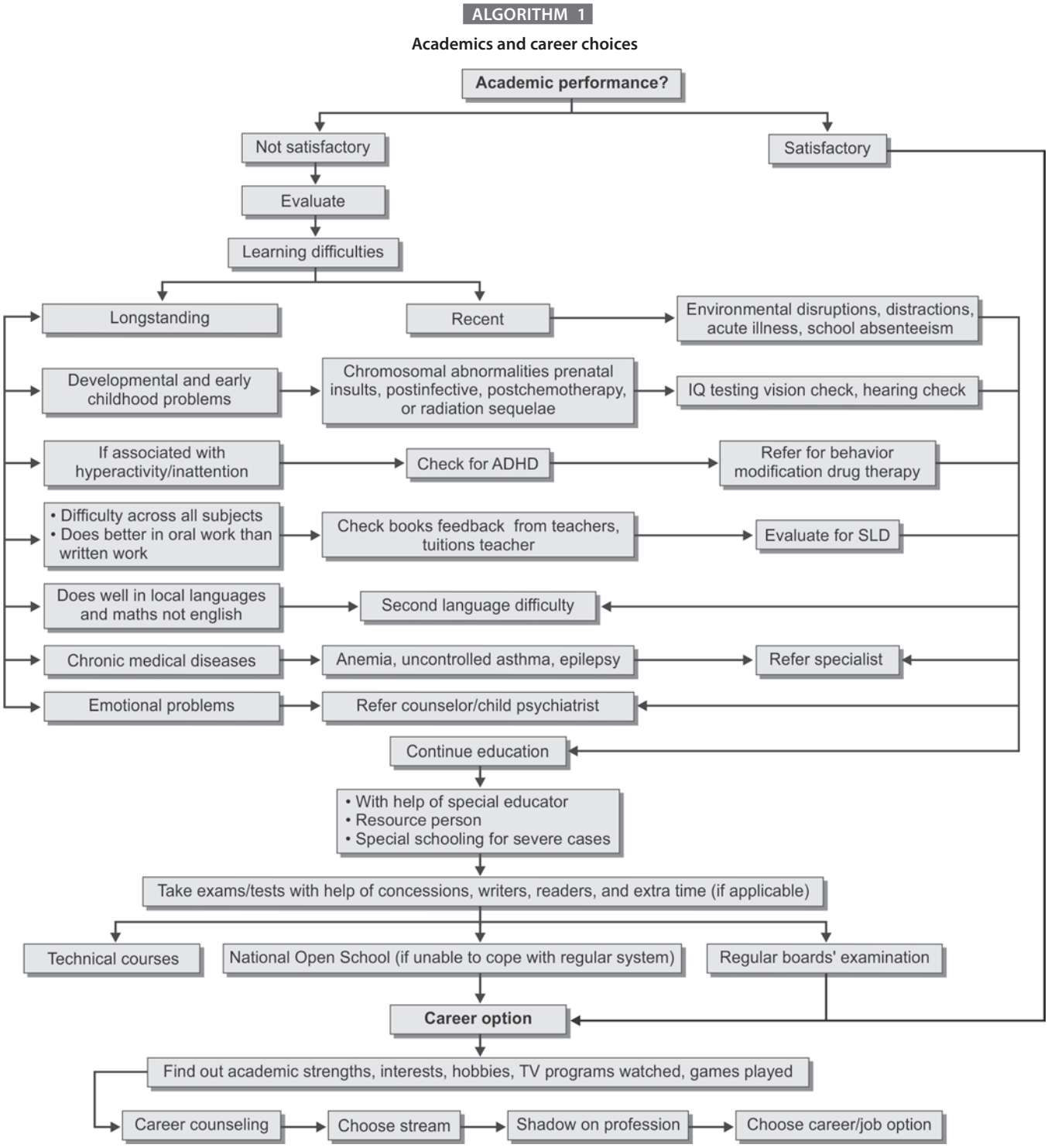
SCHOOL AND PERFORMANCE

The greater difficulty is when the child presents with underachievement. For the pediatrician, one needs to evaluate study skills, examine parental expectations, and check performance reports. Medical problems like hypothyroidism, iron, iodine, or vitamin deficiencies must be looked into. Checking for specific learning disability, attention deficit hyperactivity disorder, emotional problems, physical problems, and substance abuse becomes imperative. Specific learning disability usually presents with the child doing well orally, but doing disproportionally badly in written work. Emotional problems which can affect self-esteem, concentration, and application should be considered. Below normal intelligence could be due to perinatal causes like TORCH [toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes] infections, prematurity, meningoencephalitis, or an underlying chromosomal disorder like Klinefelter's syndrome, Fragile X, Turner's syndrome, etc.

Clinical Pearl

- Anemia in adolescent girls and iodine deficiency in hilly areas are often missed and are easily correctable causes of poor school performance.

Physical problems like visual disability (uncorrected refractive errors, squint, or more serious conditions like chorioretinitis, retinal detachment, etc.), hearing disability, (congenital or acquired) need a thorough evaluation. Children with Down syndrome, mild cerebral palsy, hemiplegic syndromes may also have writing difficulties and would



SLD, specific learning disability; ADHD, attention deficit hyperactivity disorder; IQ, intelligence quotient; TV, television.

benefit from technological alternatives like tablets. Substance abuse should be looked into if there are any tell-tale signs like red eyes, inappropriate use of sunglasses, long sleeves, and unexplained need for pocket money or parental suspicion. An excessive amount of screen time can affect academic performance, especially online addiction to pornography.

COLLEGE AND CAREERS

Career counseling tests may not be always accurate though they may help to clear the confusion in the child's mind and give the parents the satisfaction that they are doing something. Asking the child how they see themselves 10 years from now and

working backwards may help. More often the child knows what they do not want to do, before they know what they want to.

Taking into consideration their interests, personality, life goals, and values besides their academic strengths and aptitude makes it easier to zero in on a career. Most career guidance centers are able to provide information regarding eligibility and entrance procedures for career options both in India and abroad.

Clinical Pearl

- Children with borderline mental retardation should be put in skill programs/apprenticeships as early as possible, i.e., after middle school.

KEY POINTS

- ☞ Be alert to learning difficulties, which should be evaluated and managed promptly, to prevent the child getting into a cycle of low esteem, worthlessness, dropping out of school, and failure
- ☞ Guide parents of children with specific learning difficulties to seek remediation with a special educator. If detected late, accommodation with concessions and the National Open School, are the options
- ☞ The plethora of career choices is confusing. Work with parents to access career information and career guidance centers
- ☞ Be a catalyst in enabling children reach their full potential. Your role could make difference between a child being independent and being isolated, depressed, and unproductive.

SUGGESTED READINGS

1. Karande S, Kulkarni M. Poor school performance. Indian J Pediatr. 2005;72(11): 961-7.
2. Shapiro BK, Gallico RP. Learning disabilities. Pediatr Clin North Am. 1993;40(3):491-505.
3. Elkind D. All Grown Up and No Place To Go: Teenagers in Crisis. MA, USA: Addison-Wesley; 1998.
4. American Psychiatric Association. Diagnostic Criteria for ADHD DSM-4: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA, USA: American Psychiatric Association, 2013.
5. Academic underachievement among the gifted: Students perception of factors that reverse the pattern. Gifted Child Quarterly (NAGC). 2004;36(3):140-6.
6. Klegman RM, Stanton BM, St. Geme J, Schor NF, editors. Neurodevelopment function and dysfunction in the school age child. Nelson Textbook of Paediatrics. 20th ed. Philadelphia: Elsevier; 2016. pp. 192-99.

Websites for Parents

- www.careerchoices.com
- www.talkitover.in
- www.onestepup.in
- www.nos.org
- www.careerage.com
- www.careerplanning.about.com.

CHAPTER 22

Polycystic Ovarian Syndrome and Menstrual Problems in Adolescents

Roli M Srivastava

POLYCYSTIC OVARIAN SYNDROME

The condition "polycystic ovarian syndrome (PCOS)" was first described in 1935 by Dr Stein and Dr Leventhal; hence its original name Stein-Leventhal syndrome is characterized by an imbalance of hormones in women which can affect menstrual periods and ovulation. Women are often very embarrassed by some of the symptoms associated with this condition, such as excessive hair growth, acne, obesity, and the development of small cysts on the ovaries. Because of these distressing symptoms, women may also experience feelings of depression and anxiety. It is one of the most common female endocrine disorders affecting approximately 5–10% of women of reproductive age and is one of the leading causes of infertility. It is a very common problem amongst young women and teenage girls, sometimes even affecting girls as young as 11 years of age. If not treated early, serious health complications, such as diabetes and cardiovascular disease, can develop and so, the management of the PCOS patient often will vary over time as the patient enters different stages of life with different goals. In contrast, because of the long-term health implications of insulin resistance (IR), the importance of lifestyle modification towards weight management and maintaining adequate physical activity should be the one constant in the management of these patients.

DIAGNOSIS IS BY CLINICAL EXAMINATION, ULTRASOUND, AND LABORATORY

Polycystic ovarian syndrome is most simply clinically defined as the presence of:

- Hyperandrogenism (clinically and/or biochemically)
- Chronic anovulation in the absence of specific adrenal and/or pituitary disease.

Hyperandrogenism

Hyperandrogenism may present clinically as hirsutism, acne, and male-pattern alopecia.

- Hirsutism: the growth of coarse hair on a woman in a male pattern (upper lip, chin, chest, upper abdomen, back, etc.)
- Acne: pubertal acne in general is twice as prevalent in adolescent males versus females and males are more likely to have severe disease. Thus, an adolescent female with moderate-to-severe acne should be investigated for PCOS
- Virilization: clitoromegaly, deepening voice, increased musculature, or rapidly progressive hirsutism or alopecia), however, is not a feature of PCOS, but instead of more severe hyperandrogenism.

Chronic Anovulation

It may result in:

- Oligomenorrhea
- Amenorrhea
- Dysfunctional uterine bleeding
- Infertility.

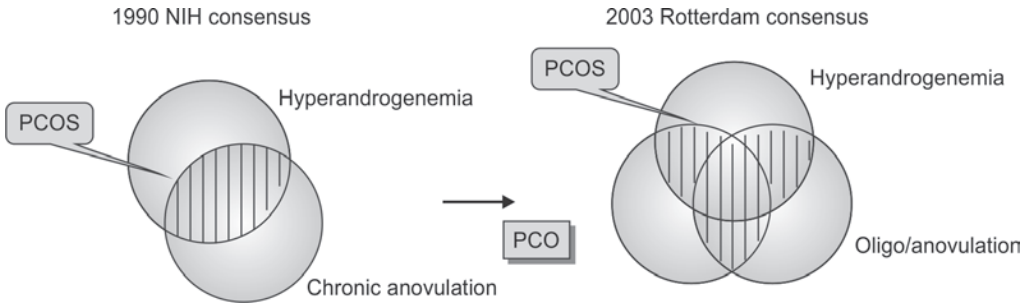
However, around 20% of patients with PCOS may have normal menstrual cycles. Often, menstrual abnormalities are long-standing, even since menarche although primary amenorrhea very rare (Box 1).

POLYCYSTIC OVARIAN SYNDROME DIAGNOSTIC CRITERIA

Polycystic ovarian syndrome includes a wide spectrum of clinical symptoms and signs. Three different diagnostic classifications had been proposed to define this disease till November 2015. The first one was published in 1990, and is known as the "National Institute of Health criteria". Later, in 2003, an expert panel met in Rotterdam and added

Box 1: Clinical features of polycystic ovarian syndrome

- Oligomenorrhea/amenorrhea
- Hirsutism
- Acne
- Acanthosis nigricans
- Obesity
- Male-pattern alopecia



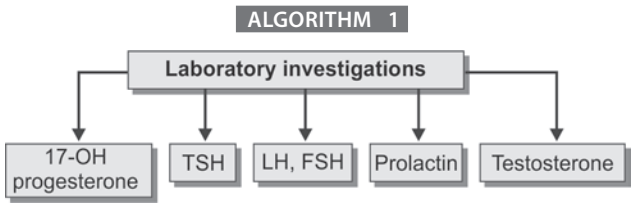
NIH, National Institute of Health;PCOS, polycystic ovarian syndrome; PCO, polycystic ovaries on ultrasound.

Fig. 1: 1990 National Institute of Health consensus versus 2003 Rotterdam consensus

TABLE 1: Polycystic ovarian syndrome diagnostic criteria

NH 1990	Rotterdam 2003	AE-PCOS Society 2006	AACE/ACE and AES Society 2015
• Chronic anovulation • Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies, e.g., congenital adrenal hyperplasia) (Both criteria needed)	• Oligo- and/or anovulation • Clinical and/or biochemical signs of hyperandrogenism • Polycystic ovaries (Two of three criteria needed)	• Clinical and/or biochemical signs of hyperandrogenism • Ovarian dysfunction (Oligo-anovulation and/or polycystic ovarian morphology) (Both criteria needed)	• Chronic anovulation • Hyperandrogenism (clinical/biologic) • Polycystic ovaries (one of the above three criteria)

NIH, National Institute of Health; AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AES, Androgen Excess and PCOS Society.



17-OH progesterone, 17-hydroxyprogesterone; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

to the previous criteria the presence of polycystic ovarian morphology detected by transvaginal ultrasonography (Fig. 1). Then, the Androgen Excess Society, published in 2006, gave the new diagnostic criteria being applied till late and finally latest in November 2015, the American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess Society released new guidelines in the evaluation and treatment of PCOS (Table 1).

As PCOS is an umbrella of various signs and symptoms, certain diseases with nearly same presenting features, especially irregular cycles and androgenic features, have to be ruled out to reach the diagnosis (Algorithm 1).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS (TABLE 2)

Not all women with PCOS have polycystic ovaries, nor do all women with ovarian cysts have PCOS; although a pelvic ultrasound is a major diagnostic tool, it is not the only one. The diagnosis is straightforward using the Rotterdam criteria, even when the syndrome is associated with a wide range of symptoms. The number of follicles and ovary volume are both important in the ultrasound evaluation.

RADIOGRAPHIC FEATURES

Ovaries may show sonographic features of polycystic ovaries (Fig. 2), bilateral enlarged ovaries with multiple small follicles: 50%

- Increased ovarian size (>10 cc)
- 12 or more follicles measuring 2–9 mm
- Follicles of similar size
- Peripheral location of follicles: gives a string of pearl appearance
- Hyperechoic central stroma.

PATHOPHYSIOLOGY OF POLYCYSTIC OVARIAN SYNDROME

Polycystic ovaries develop, when the ovaries are stimulated to produce androgens, either through excess of luteinizing

Clinical Pearl

- Polycystic ovarian syndrome (PCOS) should be considered and appropriate assessment should be undertaken before commencement of the oral contraceptive pills in adolescents with irregular periods, i.e., irregular cycles (≥35 days or <21 days), 2 years following menarche. Other causes of irregular cycles, such as thyroid dysfunction or hyperprolactinemia, need to be considered and excluded prior to the diagnosis of PCOS.

TABLE 2: Diagnosis and differential diagnosis

Differential diagnosis	Test	Comments
Hypothalamic amenorrhea: weight loss, exercise, anxiety, chronic illness	Low FSH	LH: FSH >2 is suggestive of PCOS
Pituitary adenoma: galactorrhea may be present	High prolactin	Mild transient hyperprolactinemia: (check for hypothyroidism) prolactin is generally only 50% above the upper limit of normal
Hypothyroidism: cold dry skin, constipation	High TSH	
Late-onset congenital adrenal hyperplasia: rare, mimics PCOS in all regards. The classic forms presents in newborn girls as ambiguous genitalia	High 17-OH progesterone	A morning, fasting, level of <200 ng/dL in the follicular phase excludes late-onset 21-hydroxylase deficiency. Oral contraceptives and glucocorticoids can affect values
Premature ovarian failure	High FSH	
Cushing's syndrome hypertension, purple abdominal striae, prominent dorsal cervical fat pads, and a rounded, plethoric face	High cortisol	Mild elevations can be seen in PCOS values ≥2 times the upper limit of normal (Cushing's syndrome). Oral contraceptive pills should be discontinued before dynamic testing
Adrenal tumor: extensive signs of virilization	Very high TT	TT values may be normal in PCOS. Oral contraceptive pills lower TT, 3 months off OCPs best to get true value. Most testosterone values in PCOS will be ≤150 ng/dL, i.e., mild elevation, testosterone values of ≥200 ng/dL suggest ovarian or adrenal tumor

FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovarian syndrome; TSH, thyroid-stimulating hormone; 17-OH progesterone, 17-hydroxyprogesterone; TT, total testosterone; OCPs, oral contraceptive pills.

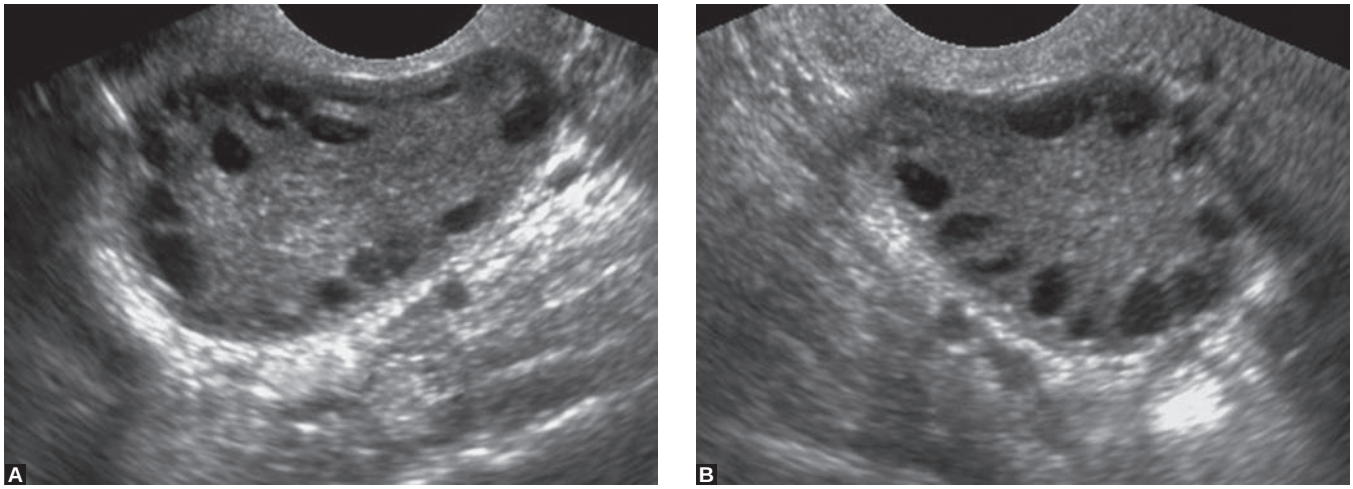


Fig. 2: Characteristic string of pearls sign seen: **A,** left ovary and **B,** right ovary

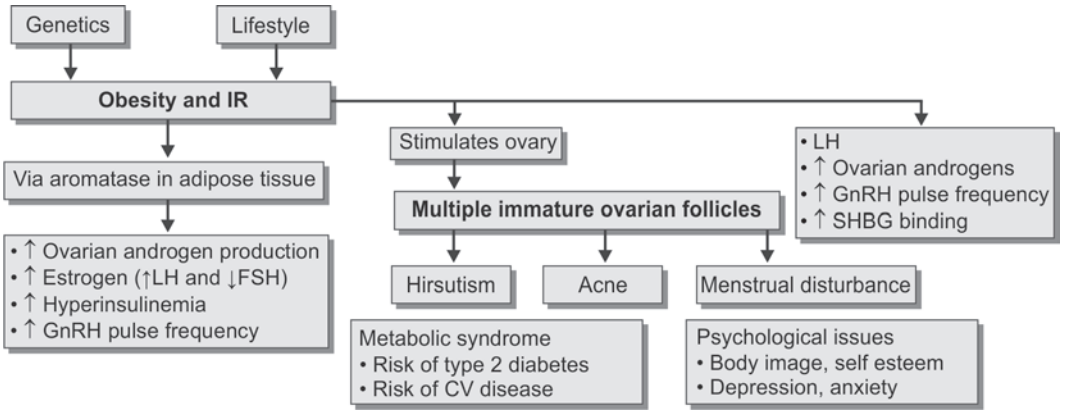
hormone (LH) or through hyperinsulinemia in women whose ovaries are sensitive to this stimulus. Multiple ovarian cysts are seen in ultrasound. These "cysts" are actually immature follicles whose development has arrested at an early-antral stage due to the disturbed ovarian function. Polycystic ovarian syndrome is characterized by a complex set of symptoms, and research to date suggests that IR could be a leading cause. Polycystic ovarian syndrome may also have a genetic predisposition. A majority of patients with PCOS have IR and/or are obese. Their elevated insulin levels contribute to the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS. Adipose tissue possesses aromatase that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese patients creates the paradox of having both excess androgens (which are responsible for hirsutism and virilization) and estrogens [which inhibits follicle-stimulating hormone (FSH) via negative feedback]. Also, hyperinsulinemia increases gonadotropin-releasing hormone (GnRH) pulse frequency, LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation and decreased sex hormone-binding globulin (SHBG) binding; all these steps lead to the development of PCOS. Insulin resistance is a common finding among patients of normal weight as well as those overweight patients (Algorithm 2).

POLYCYSTIC OVARIAN SYNDROME

Health consequences of polycystic ovarian syndrome are given in box 2 and table 3.

ALGORITHM 2

Pathophysiology of polycystic ovarian syndrome



IR, insulin resistance; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; SHBG, sex hormone-binding globulin; CV, cardiovascular.

Box 2: Polycystic ovarian syndrome: health consequences

- Reproductive
  - Infertility
  - Increased risk of miscarriage
  - Increased risk of gestational diabetes/preeclampsia
  - Increased risk of endometrial cancer
- Psychosocial
  - Depression and anxiety
  - Cosmetic concerns (hyperandrogenic symptoms)
  - Increased risk of type 2 diabetes
- Cardiometabolic
  - Diabetes hypertension
  - Dyslipidemia
  - Increased inflammation
  - Increased cardiovascular disease risk
  - Non-alcoholic steatohepatitis
  - Sleep apnea

TABLE 3: The spectrum of features of polycystic ovarian syndrome and associated menstrual problems

Clinical	Endocrinal	Probable complications
Obesity	Increased insulin	Dyslipidemaia
Menstrual disturbance	Decreased sex hormone binding globulin	LDL increased
Oligomenorrhoea	–	HDL increased
Amenorrhoea	–	Triglycerides increased
Regular cycle	–	–
Hyper-androgenism	Testosterone Increased	Diabetese mellitus
Infertility	LH increased	CV Disease, hypertension
Asymptomatic	Prolactin increased	Endometrial carcinoma

LH, luteinizing hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CV, cardiovascular.

MANAGEMENT OF POLYCYSTIC OVARIAN SYNDROME

The overall aims of treatment are to:

- Correct the high androgen levels and adverse metabolic effects
- Restore menstrual regularity
- Manage the cosmetic symptoms and signs
- Restore fertility if desired
- Long-term health: chronic disease prevention
- Diabetes prevention
- Cardiovascular disease risk reduction
- Cancer prevention

The medical management of PCOS can be broken into:

- Chronic management
- Acute management (Algorithm 3).

HIRSUTISM

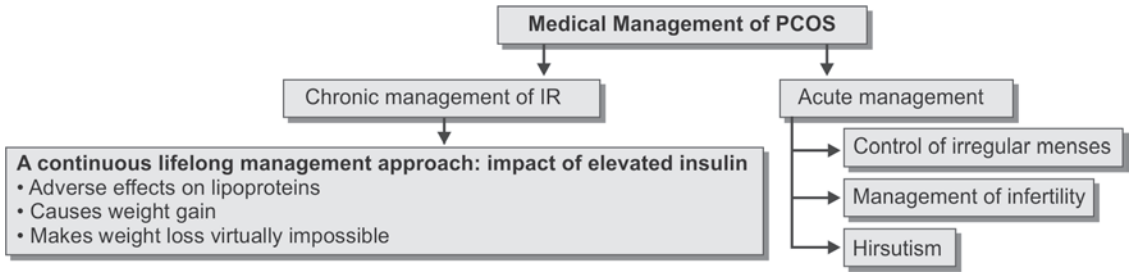
The decision to treat should be based on the patient's perception of the excess terminal hair growth. It can be managed in two ways (Algorithm 5):

- Treatment of hirsutism:
  - Cosmetic: shaving, waxing, electrolysis, etc.
- Medical management of hirsutism:
  - Decreasing the amount
  - Blocking action of androgens.

Mechanical

- Plucking is best avoided as it can lead to folliculitis and scarring
- Shaving is likely to be the cheapest and simplest
- Electrolysis involves electrocoagulation of the hair follicle

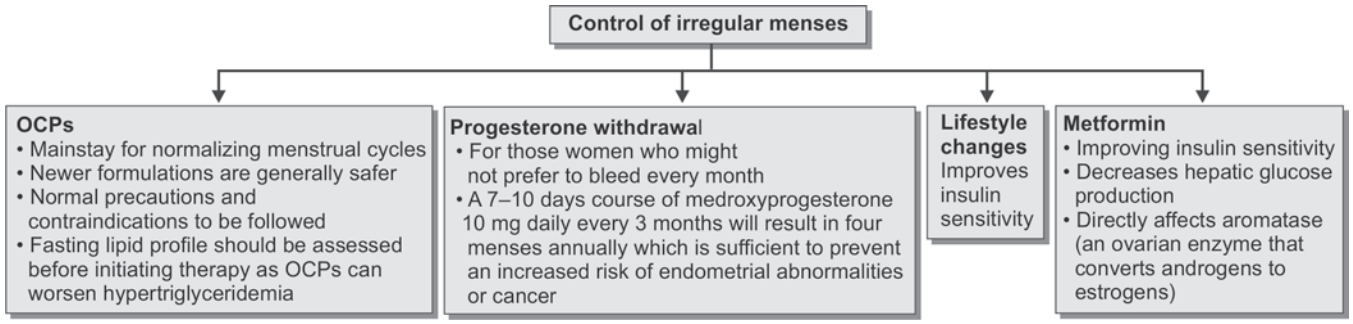
ALGORITHM 3



IR, insulin resistance; PCOS, polycystic ovarian syndrome.

ALGORITHM 4

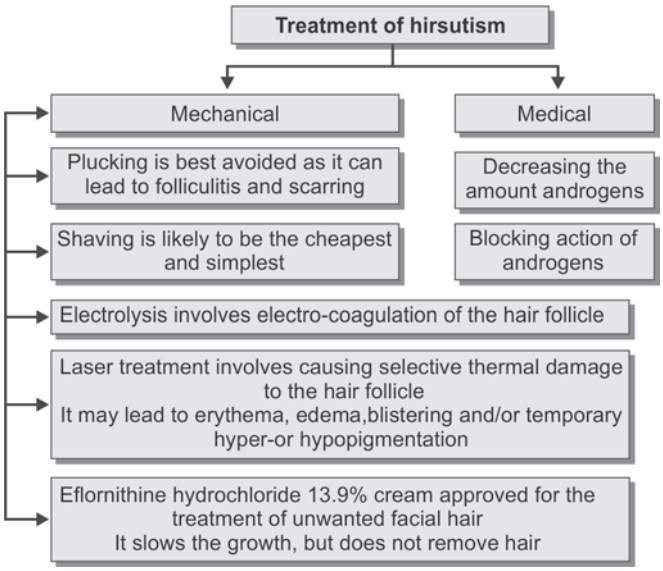
Acute management: Control of irregular menses



OCPs, oral contraceptive pills.

ALGORITHM 5

Management of hirsutism



- Laser treatment involves causing selective thermal damage to the hair follicle. It may lead to erythema, edema, blistering and/or temporary hyper- or hypopigmentation.
- Eflornithine hydrochloride 13.9% cream: approved for the treatment of unwanted facial hair. It slows the growth, but does not remove hair.

Testosterone Production (Algorithm 3)

- Oral contraceptive pills: gonadotropin production (as testosterone is predominantly ovarian in nature and is caused by both LH and by effect of hyperinsulinemia at the ovary and SHBG
- Metformin
- Lifestyle modification/weight loss.

Medical Management of Hirsutism (Algorithm 6)

Testosterone Action

- Antiandrogens (spironolactone):
  - Aldosterone antagonist
  - Antihypertensive agent also has a 67% relative affinity for the testosterone receptors (SHBG by insulin sensitivity):
    - Spironolactone: 50 mg twice a day 6–12 months
    - Increase to 100 mg twice a day if required
    - Side effects: menstrual irregularity, nausea.

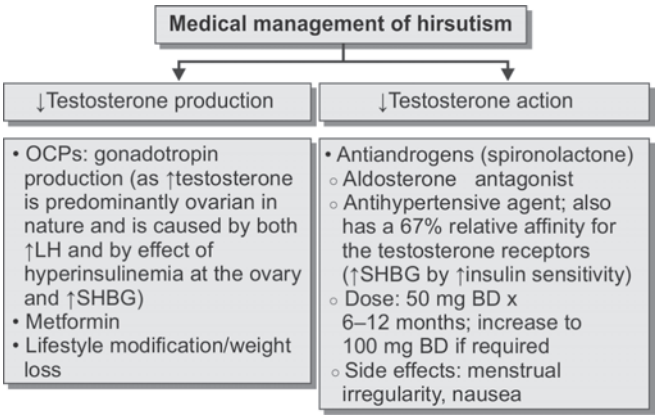
Management of Infertility

It is rarely required in adolescents. It is very difficult to cover its intricacies; therefore, just a brief word on clomiphene, metformin, and lifestyle modifications is being taken up. Polycystic ovarian syndrome accounts for 75% of anovulatory infertility. Additionally, when pregnancies do occur, the first trimester miscarriage rate is as high as 30–50% (Table 4).

TABLE 4: Management of infertility

Clomiphene	Lifestyle modification/weight loss	Metformin
• Obese women do not respond to low doses at the rate of 50 mg dose • The degree of obesity correlates with the dose of clomiphene needed to induce ovulation • The higher doses may cause side effects and can increase the rate of multiple gestations, given in combination with metformin	• Lifestyle modification needs to be stressed • 3–6 month trial of aggressive lifestyle modification may be a prudent first step before considering an insulin sensitizer	• Start at 500 mg twice a day and increased to thrice a day if ovulation did not occur by 6 weeks, and add clomiphene 6 weeks later • Use improves the outcome of other infertility therapies • Improves fertilization and pregnancy rates • In the setting of infertility, metformin therapy should likely be continued for as long as fertility efforts are ongoing, even if it "fails" initially • Reduces risk of early pregnancy loss; no birth defects occurred

ALGORITHM 6



DIABETES RISK AND LONG-TERM MANAGEMENT OF INSULIN RESISTANCE IN POLYCYSTIC OVARIAN SYNDROME

Most PCOS patients are inherently IR with the obesity seen in many, with a substantial proportion of patients have abnormalities on the oral glucose tolerance test.

Lifestyle modification:

- 20 minutes of brisk walking
- Daily metformin is found to be useful for significant improvement in insulin sensitivity; causes reduction in the development of type 2 diabetes mellitus.

Cardiovascular Risk Factors and Disease in Polycystic Ovarian Syndrome

- Prevalence of diagnosed hypertension or higher ambulatory blood pressure in PCOS

Signs of insulin resistance	Best test for insulin resistance
• Upper-body obesity • Acanthosis nigricans • However, only 35–50% of polycystic ovarian syndrome patients are obese	• Best test for insulin resistance is 2 hour oral glucose tolerance test • Interpretation: ◦ Impaired glucose tolerance:140–199 mg/dL ◦ Diabetic: ≥200 mg/dL

- The pattern of dyslipidemia in PCOS is in keeping with IR, increased triglycerides, low high density lipoprotein cholesterol.

Assessment of Cardiometabolic Risk (Fig. 3 and Table 5)

- Screen all PCOS for following: obesity, lack of physical activity, cigarette smoking, dyslipidemia, hypertension and impaired glucose tolerance test
- All women with PCOS should be assessed for excess weight at every visit. Age appropriate and gender appropriate body mass index should be considered.

LIFESTYLE MANAGEMENT FOR WOMEN WITH POLYCYSTIC OVARY SYNDROME

Lifestyle management (single or combined approaches of diet, exercise and/or behavioral interventions) for weight loss, prevention of weight gain, or for general health benefits should be recommended in women with PCOS (Box 3).

Although first-line monotherapy in adolescent age group includes metformin and/or combination therapy with oral contraceptive agents and antiandrogen agents.

It is hoped that early and proper diagnosis, will allow more women to be managed properly for their presenting symptoms (hirsutism, irregular menses, etc.), but also to be educated and managed for the continuing health risk of IR throughout their lives.

Box 3: Lifestyle management

- Face to face, tailored dietary advice, including education, behavioral change techniques and ongoing emotional support should be provided to women with PCOS and a BMI ≥25 kg/m^2 (overweight/obese)
- Exercise recommendations
- 150 min/week or 20 minutes/day
- Of this, 90 min/week should be aerobic activity at moderate-to-high intensity (60–90% of maximum heart rate)

PCOS, polycystic ovarian syndrome; BMI, body mass index.

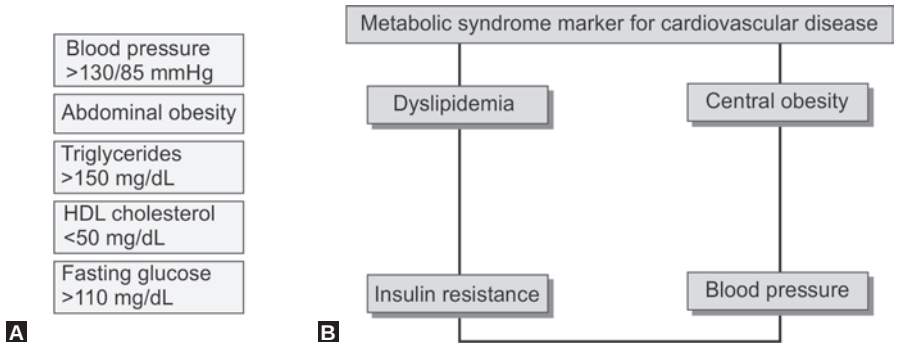


Fig 3: A, Metabolic syndrome and **B,** metabolic syndrome marker for cardiovascular disease

TABLE 5: Assessment of cardiometabolic risk

Diabetes status	Blood pressure monitoring	Lipid profile measurement
Prediabetes and/or type 2 diabetes should be assessed	Blood pressure should be measured	Complete lipid profile
Oral GTT should be performed	Annually: in PCOS with BMI 18.5 kg/m^2	Every 2 years: PCOS with normal lipid profile
Every 2nd year in all women with PCOS	Every visit: in PCOS with BMI ≥25 kg/m^2	Every year: PCOS with abnormal lipid profiles and/or excess weight
Annually: in those with additional risk factors for type 2 diabetes, e.g., features of IR	The ideal daytime blood pressure should not exceed 135/85 mmHg	A lipid profile should include: total cholesterol, LDL-C, HDL-C, and triglycerides

GTT, glucose tolerance test; PCOS, polycystic ovarian syndrome; IR, insulin resistance; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

KEY POINTS

- Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among young women affecting approximately 5–10%
- One of the leading causes of infertility
- There is not a single diagnostic test for PCOS
- Associated with a range of metabolic abnormalities which can lead to long-term health problems
- Lifestyle changes play an important role in management of the syndrome
- Management should be individually tailored for each patient depending on the type of symptoms and clinical features found
- Prevent weight gain and address weight loss if needed as body mass index >30 limits fertility
- About 5–10% weight loss will greatly assist in symptom control
- Women with PCOS have increased risk of endometrial cancer with prolonged amenorrhea; aim for >4 periods/year unless on contraception.

SUGGESTED READINGS

1. Artini PG, Di Berardino OM, Simi G, Papini F, Ruggiero M, Monteleone P, et al. Best methods for identification and treatment of PCOS. Minerva Ginecol. 2010;62(1):33-48.
2. Atiomo WU, Pearson S, Shaw S, Prentice A, Dubbins P. Ultrasound criteria in the diagnosis of polycystic ovary syndrome (PCOS). Ultrasound Med Biol. 2000;26(6):977-80.
3. Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC. PCOS according to the Rotterdam consensus criteria: Change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG. 2006;113(10):1210-7.
4. Dunaif A, Thomas A. Current concepts in the polycystic ovary syndrome. Annu Rev Med. 2001;52:401-19.
5. Farah L, Lazenby AJ, Boots LR, Azziz R. Prevalence of polycystic ovary syndrome in women seeking treatment from community electrologists. Alabama Professional Electrology Association Study Group. J Reprod Med. 1999;44(10):870-4.
6. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Obesity and the polycystic ovary syndrome. Int J Obes Relat Metab Disord. 2002;26(7):883-96.
7. http://e-hmr.org/ViewImage.php?Type=F&aid=264837&id=F2&afn=130_HMR_32_4_197&fn=hmr-32-197-g002_0130HMR
8. http://www.aafp.org/afp/2006/0415/p1374.html
9. http://www.jarrettfertility.com/PCOS%20patient%20handout.pdf
10. http://www.managingpcos.org.au/pcos-evidence-based-guidelines/algorithms
11. http://www.managingpcos.org.au/pcos-evidence-based-guidelines/algorithms
12. Rebar R, Judd HL, Yen SS, Rakoff J, Vandenberg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. J Clin Invest. 1976;57(5):1320-9.
13. Sheehan MT. Polycystic ovarian syndrome: diagnosis and management. Clin Med Res. 2004;2(1):13-27.
14. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935;29:181-91.
15. Stein IF, Leventhal ML. Amenorrhoea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935;29:181-91.
16. Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BG, Wong JL, et al. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Aust. 2011;195(6):S65-112.
17. Weissleder R, Wittenberg J, Harisinghani MG, Chen JW, editors. Primer of Diagnostic Imaging. 5th ed. St. Louis, MO: Mosby; 2011.

CHAPTER 23

Approach to a Case of Sexual Abuse in Children/Adolescent

Sushma P Desai

WHAT IS CHILD/ ADOLESCENT SEXUAL ABUSE

Definition of adolescent sexual abuse as provided by many working in the field of child abuse, it is "any sexual behavior directed at the dependent developmentally immature child and adolescent that they do not comprehend fully, to which they are unable to give informed consent. It involves the exposure of a child to sexual contact, activity, or behavior and may include invitation to sexual touching, intercourse, or other forms of exploitation such as juvenile prostitution or pornography".

Clinical Pearl

- Under the law, child sexual abuse is an umbrella term describing criminal and civil offenses in which adult engages in sexual activity with a minor or exploits a minor for the purpose of sexual gratification. It can never be considered normal or socially acceptable behavior.

The World Health Organization defines an adolescent as being between 10 and 19 years.

SEXUAL ABUSE BEHAVIOR DEFINITION

- An adult exposing his/her genitals to or persuading a child or adolescent to do the same
- An adult touching a child or adolescent's genitals or making a child or adolescent touch the adult's genitalia
- An adult involving a child or adolescent in pornography, either by exposing a child or adolescent to create pornographic material
- An adult having oral, vaginal, and anal intercourse with a child or adolescent
- Any verbal or other sexual suggestion made to a child or adolescent by an adult
- An adult persuading a child or adolescent to engage in sexual activity.

If an older adolescent manifest such a behavior to a child it will also constitute child sexual abuse.

Clinical Pearl

- The United Nations Children's Fund: "Child marriage represents the most prevalent form of sexual abuse and exploitation of girls".

AGE OF CONSENSUAL SEX

Age of consensual sex in India is 16 year of age. Age of simple majority is 18 years and legal age of consent for marriage is 21 years in boy and 18 years in girls.

PEDOPHILE

Usually, it has an unidentifiable sexual preference with regard to prepubertal children and will frequent locations that attract children.

INCEST (INTRAFAMILIAL CHILD ABUSE/CHILD INCESTUOUS ABUSE)

Traditionally "incest" is defined as sexual relations between people classed as being too closely related to marry each other.

Clinical Pearl

- Incest between a child/adolescent and a related adult has been identified as the most widespread form of child sexual abuse with a huge capacity for the damage to a child. It leads to serious type of long-term psychological trauma, especially in case of parental incest.

Most often reported form of incest is father-daughter and stepfather-daughter incest, mother/stepmother-daughter form contributes to a small portion of the remaining incest. Sibling incest may also be as common as or more common than other types of incest. Prevalence of parental incest is difficult to assess due to secrecy and privacy. Statistics show that about 30% of all perpetrators are related to the sexual victim, 60% are family acquaintances, and 10% are strangers.

COMMERCIAL SEXUAL EXPLOITATION OF CHILDREN

Commercial sexual exploitation of children is defined as "Sexual abuse by an adult accompanied by remuneration in cash or in kind to the child or to the third person(s). Commercial sexual exploitation of children usually take the form of child prostitution or child pornography and is often facilitated by child sex tourism (also internet child pornography)". It is particularly a problem of developing countries of Asia.

Types

Child sexual abuse includes a variety of sexual offenses, including:

- Sexual assault: an adult uses a minor for the purpose of sexual gratification, e.g., rape (including sodomy) and sexual penetration with an object
- Sexual exploitation: offenses in which an adult victimizes a minor for advancement, sexual gratification, or profit, e.g., prostituting a child and creating or trafficking in child pornography
- Sexual grooming: it defines a social conduct of a potential child sex offender who seeks to make a minor more accepting of their advances, e.g., in an online chat room.

VULNERABLE SITUATIONS (RISK FACTORS)

- Children and adolescents of single parent: due to lack of adequate supervision
- Children and adolescents with low self-esteem: due to failure in academic life. If parents persistently keep comparing them with the achievers; this results in low self-esteem and as rebellion they may involve in sexual activity considering it as an achievement
- Attraction to city life: children and adolescents get induced by middlemen and easy access to money/comforts of life
- Lack of education: children and adolescents due to lack of education lack of being well-informed may get induced to sexual activities by strangers easily
- Children and adolescence education on sex and sexual parts will help them take care of their private parts and sexual life
- Poverty: high risk of getting sexually abused because of poor socioeconomic conditions
- Parental factors: loss of job and substance abuse like alcoholism. Drug addiction
- Mentally and physically: challenged/retarded children and adolescents
- Unloved, uncared children, and adolescent
- Violence in community.

PROFILE OF THE ADULT SEX OFFENDER

- Children and adolescents living in parents homes are more likely to be abused by adults from within the family or known friend circle. In 80% of the cases, the perpetrator is either related or known to the victim
- Children on streets or observation homes are more likely to be abused by strangers
- The offender has a special ability to identify vulnerable children, to use that vulnerability to sexually abuse the child
- The systematically desensitize children to touch
- They use adult authority to isolate the victim from others and enforce their victim's silence including threats, force, bribery, acts of cruelty.

TYPES OF OFFENDERS

There are two groups:

- Situational: does not prefer children, but offend under certain circumstances. They can be:
  - Regressed: typically has a relationship with the adults, but a stressor causes them to seek children as a substitute
  - Morally indiscriminate: all-round sexual deviant, who may commit other sexual offenses unrelated to children
  - Naïve/inadequate: often mentally disabled in some way, finds children less threatening
- Preferential: has true sexual interest in children
  - Mysoped: sadistic and violent, target strangers more often than acquaintances
  - Fixated: little or no activity with own age, described as "overgrown child".

STATISTICS OF CHILD SEXUAL ABUSE IN INDIA

Global prevalence: study in 2009 shows (65 studies from 22 countries) 19.7% of female children and 7.9% male, highest in Africa 34.4%, lowest in Europe 9.2%, Asia 23.9%.

India: the Ministry of Women and Child Development published the *Study on Child Abuse: India 2007*. Its main findings included 53.22% of children reported having faced sexual abuse. About 52.9% were boys and 47.06% girls. Andhra Pradesh, Bihar, Assam, and Delhi reported highest incidence. Children on streets, at work, and in institutional care reported higher incidence. The study also reported 50% of the abusers are known to the child or are in a position of trust and responsibility. Most children had not reported the matter to anyone.

Clinical Pearls

- About 40% of girls and 25% of boys are sexually abused before they reach 16 years of age.
- One-tenth children is being sexually abused at any given point of time.

EFFECTS

Psychological Effects

Clinical Pearl

- About 51–79% of sexually abused children exhibit psychological symptoms.

The child sexual abuse can lead to both long- and short-term harm, including psychopathology in later life. The common effects are anxiety, depression, eating disorders, poor self esteem, somatization, sleep disturbances, dissociative disorder, and posttraumatic stress disorder. Children may manifest regressive disorders like thumb sucking and bed wetting.

Clinical Pearl

- The strongest indicator of sexual abuse is inappropriate sexual knowledge and interest.

The victim may withdraw from school and normal social activities and exhibit learning and behavioral problem, cruelty to animals, attention deficit hyperactivity disorder, conduct disorder, and oppositional defiant disorder.

Adolescent victims show risky sexual behavior. Self-inflicted harm and teenage pregnancy is one of the important effects. Increased rates of crime in sexually abused teen are observed.

Physical Effects

- Injury: depending on age and the size of the child and the degree of force used. Internal laceration, bleeding, and damage to internal organs and even death
- Infection: sexually transmitted infections, human immunodeficiency virus/acquired immunodeficiency syndrome
- Neurological damage: traumatic stress, including stress caused by sexual abuse, causes notable changes in brain functioning and development. Increased likelihood of "ictal temporal lobe epilepsy-like symptoms". Short-term memory impairment and lowering of the score of math scholastic aptitude test.

DIAGNOSIS/DISCLOSURE

- Victims are often unable to speak due to different reasons such as threat, fear, shame, guilt
- Therefore, indirect nonverbal clues, behavioral disturbances, psychosomatic, psychiatric, and seldom physical symptoms are often the only way to recognize sexual abuse
- There is no specific symptom/syndrome
- Most important element of the diagnosis is the disclosure, which depends on our ability to speak with children
- Children need support and stress-reducing resources after disclosure of sexual abuse. Negative social reactions to the disclosure have been found to be harmful to the survivor's well-being.

Clinical Pearl

- Children who receive supportive responses after disclosure have less traumatic symptoms and are abused for a shorter period of time.

- American Academy of Child and Adolescent Psychiatry provides guidelines for what to say to the victim and what to do following the disclosure.

EXAMINATION OF A CASE OF SEXUAL ABUSE

History

- Look for risk factors of victimization/vulnerability for sexual abuse in adolescents like:
  - Female sex
  - Going alone in lonely places at odd times
  - Going to a friend's house for exchanging notes
  - Parties (especially night parties)
  - Dating
  - Crowded places (e.g., buses, trains, fair, etc.)
  - "Immoral" neighborhood
  - Families with a person of personality disorder (sex maniac)
  - Single parent/broken homes
  - Both parents working and child alone at home
  - Children on foster care, i.e., parents or elders are out and some relative/friend is staying at home
  - Drinking/watching pornography/movie with friends
  - Heart breaks, failure, and other situations needing emotional support
  - History of past abuse
- How to identify sex abuse/flag signs for the adolescent specialist:
  - Fear of being bathed
  - Having a great deal of knowledge about sex at a very young age or sexual behavior that seems beyond his or her age
  - Feeling depressed
  - Anxiety, low-self esteem
  - Sudden avoidance to visit a particular place or a particular person, decreased desire of interaction with peers
  - Poor interest in academics
  - Fondling with one's genitalia too often
  - Drug or alcohol abuse.

Physical Examination

- Points to remember:
  - Ensure patient privacy
  - Prepare the child by explaining the examination and showing equipment; this has been shown to diminish fears and anxiety
  - Ask whom he/she would like in the room for support during the examination
- The examination should include:
  - Mental maturity—by asking questions like age, time, etc.
  - Physical maturity—with the help of growth parameters
  - Nutrition status
  - Look—vacant/starry/slating/fearful
  - Mental status—confused/clear/apprehensive
  - Clothing—any evidence struggle/trace evidence like hair and stains of forensic importance
  - Oral hygiene and personal hygiene
  - Physical indicator of sexual assault and injuries
- Indicators of child sexual abuse:
  - Sure indicators:
    - Venereal diseases
    - Pregnancy
    - Presence of semen
    - Gonococcal infection of pharynx, urethra, rectum, vagina
  - Probable indicators:
    - Genital herpes
    - Trichomonas
    - Recurrent urinary tract infection
    - Horizontal hymen opening in relation to age.
  - Near indicators:
    - Abdominal pains
    - Leaking vagina or anus
    - Difficult walking
    - Sudden withdrawal from normal activities
    - Sudden change in appetite
    - Unusual sexual knowledge
    - Mood variation without any obvious reasons
    - Depression or depersonalization
    - Irritation unprovoked or easily induced
    - Suicide attempts or threats
    - Lack of attachment to parents
    - Torn clothing and/or stained with blood or semen
- Detail examination of the genitalia:
  - Genital injuries in adolescents:
    - Scratches over the thigh, genitalia, or body
    - Bruising of the vulva
    - Swelling in the genital area
    - Minor tears in the hymen
    - Minor lacerations
    - Bleeding
    - Laceration of large size in case of age incompatibility
- Sexual abuse signs in sodomy (Table 1).

TABLE 1: Sexual abuse signs in sodomy

Chronic	Recent
Proctitis	Tear
Hypotonic sphincters	Bleeding
Anal fistula	Bruising
Anal and perianal skin changes	Semen
Chondylomata, warts, chancre	Gonorrhea

Age Determination

It has a great medicolegal importance as the justice and punishment to the abuser is directly related to the age of the victim. The age determination of an adolescent can be done from a comprehensive examination of the following four aspects:

1. General physical features
2. Secondary sexual character: Tanner's staging
3. Appearance of teeth: orthopantomogram is helpful
4. Ossification of bones.

Collection of Forensic Samples

The following samples are required to be collected in sexual abuse cases:

- Blood (blood grouping, testing drug intoxication)
- Urine (to test for suspected pregnancy, drug testing)
- Seminal stain (blood grouping)
- Nail scraping (from under the nails, to look for epithelium of the assailant)
- Hair (to look for seminal stain, foreign hair)
- Vaginal swabs (vulva, low vaginal, high vaginal): it is stressed here that it should be made a routine
- Microscopic examination of vaginal slides (motile and immotile sperm).

TREATMENT

The initial approach depends upon following factors:

- Age at the time of presentation
- Circumstances of presentation for treatment
- Comorbid conditions.

The goal of management is:

- To treat current issues
- To prevent future abuse/untoward incidences.

There are three modalities of therapy:

1. Family therapy
2. Group therapy
3. Individual therapy.

Treatment of young children requires strong parental involvement and can benefit from family therapy. Adolescents tend to be more independent, they respond well to individual or group therapy. The modalities also shift during the course of therapy, e.g., group therapy is rarely used in initial stages as the subject matter is very personal and/or embarrassing.

PHARMACOLOGICAL MANAGEMENT

Prophylaxis of Sexually Transmitted Diseases

Incidence of sexually transmitted diseases from sexual assault without prophylaxis is:

- Condyloma: 1 in 4
- Chlamydia: 1 in 10
- Gonorrhea: 1 in 30
- Human immunodeficiency virus: 1 in 1,000
- Syphilis: 1 in 1,000
- Hepatitis B/herpes simplex virus: uncertain.

Gonorrhea and Chlamydia

- Nonpregnant victims:
  - Doxycycline 300 mg orally, stat, followed by 100 mg twice a day for 3 days (patient >8 years old)
- Alternative:
  - Floxacin 400 mg twice a day for 7 days (patient >16 years old)
  - Azithromycin 2 g orally, single dose
- Pregnancy and adolescent victims: erythromycin 1.5 g orally stat, followed by 500 mg four times a day.

Syphilis

Benzathine penicillin 2.4 million units (adults), in children not usually given because of a low incidence of risk of syphilis, instead a follow-up rapid plasma reagent test is done at 6–12 weeks. If seroconversion has occurred therapy is given at that time.

Human Papillomavirus

Not known prophylactic regimen. Human papillomavirus vaccine is recommended for all adolescent girls and quadrivalent vaccine for adolescent boys above age of 9 years.

Human Immunodeficiency Virus

The risk of transmission is very less, risk-benefit ratio should be weighed before giving the drugs.

- Triple-drug therapy including zidovudine, lamivudine (3TC) and famotidine.

Herpes Simplex Virus

- Acyclovir 40 mg/kg.

Trichomonas

- Metronidazole 2 g orally (single dose).

Pregnancy Prophylaxis

Incidence of pregnancy in rape/sexual assault is 1 per 100.

- Levonorgestrel 0.75 mg 2 tablets stat or ethinyl estradiol 0.05 mg 2 tablet stat, followed by 2 tablet after 12 hours.

FOLLOW-UP AND REHABILITATION

- Follow-up care must be given to assess the late complications, especially the psychosocial problems
- Parental support is very important for the rehabilitation. Adolescents can be taken care of at home environment in a better way
- If parents cannot support their adolescent children, especially in rural areas, supportive social and legal networks should be developed for them to prevent suicidal attempts or fall into flesh trade.

PREVENTION

- Adults (parents, families, community, and teachers) must help children through nonthreatening and age-appropriate means to participate in their own protection
- Personal safety curriculum is designed to:
  - Protect children/adolescents from abuse, specifically sexual abuse
  - Empower children/adolescent to take part in their own protection by giving them age appropriate information, skills, and self-esteem
  - Teach children/adolescent that their body belongs only to them and nobody has the right to touch them in a way they do not like or understand, give them knowledge of sexual organs and function
  - Children not to keep secret
  - To be bold to make friends—but when it comes to sex learn to say no
  - Teach children/adolescent that only the offender is to blame for any inappropriate sexual touch
  - Teach assertiveness skills, helping children to stand up for their own right without violating the right of others
  - Build the support system of each child including the family, school, community, and friends.

HOW TO HELP THE SURVIVOR

When a survivor tells us that she/he has been sexually abused, she/he is entrusting you with a part of the life that is painful, frightening, and vulnerable.

The following guidelines can help us honor that trust and assist their healing:

- Believe the survivor
- Be clear that abuse is never a child or young adolescent's fault
- Do not sympathize with the abuser
- Express your compassion
- Validate the survivor's feeling and join with the survivor in validating the damage
- Encourage the survivor to get support
- Seek expert's help if the survivor is suicidal
- Respect the time and space taken to heal
- Resist seeing the survivor as a victim.

SEXUAL ABUSE AND EXISTING LEGAL SYSTEM

- It is necessary to give recognition to child abuse as an offence against innocence and, therefore, the law against child rape needs to be more stringent
- Since sexual abuse of minors has its own characteristics, it needs to be addressed separately from the offence of sexual assault on an adult person
- Ironically, existing rape/sexual abuse laws make no distinction between rape of a minor and that of an adult.

Clinical Pearl

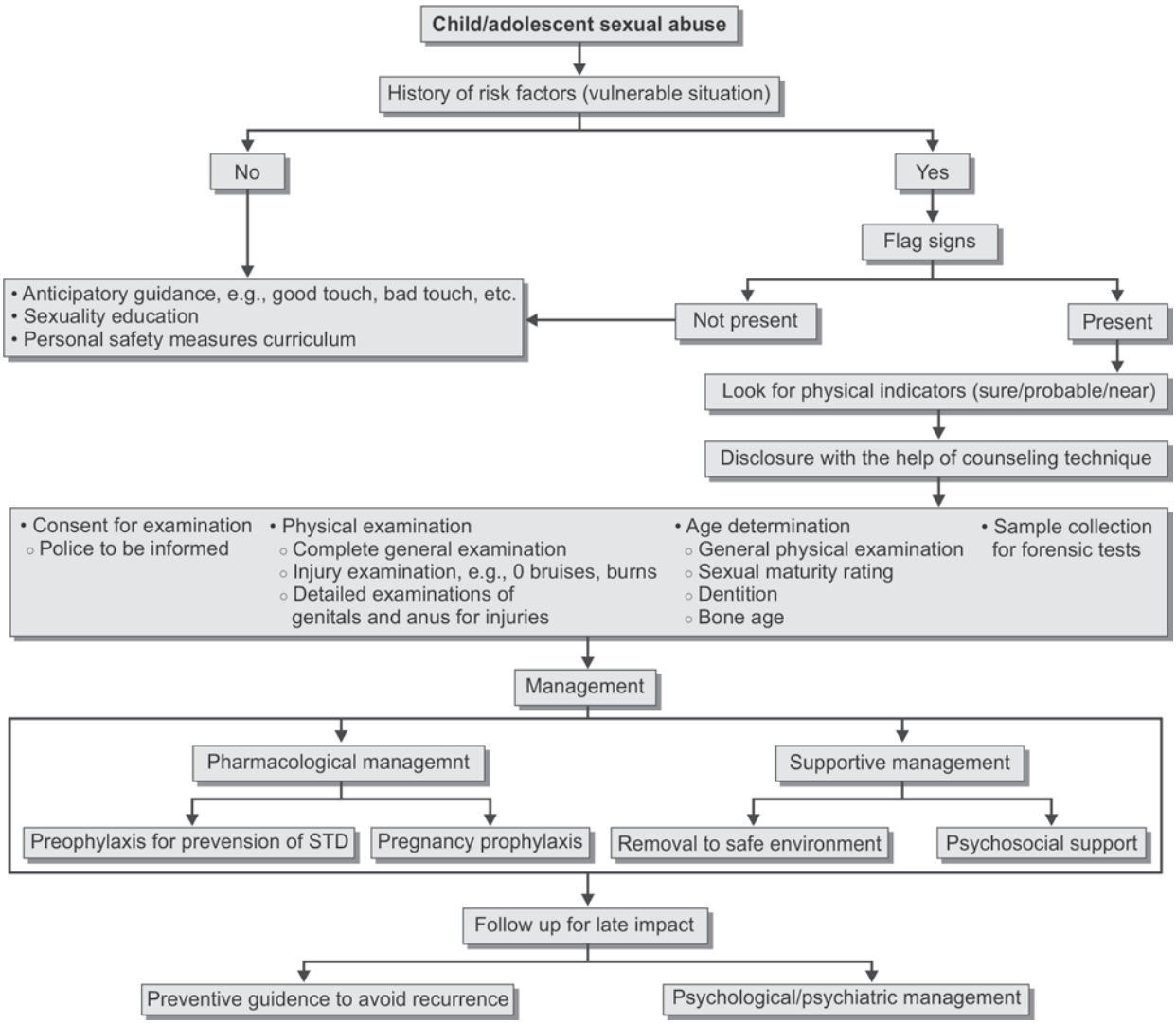
- The "Protection of Children Against Sexual Offense Bill 2011" was passed in the Indian Parliament on May 22, 2012 which came into force from November 14, 2012.

International Law

Child sexual abuse is outlawed nearly everywhere in the world, generally with severe criminal penalties including in some jurisdiction, life imprisonment, or capital punishment. An adult's sexual intercourse with a child below the age of legal consent is defined as statutory rape, based on the principle that a child is not capable of consent and that any apparent consent by a child is not considered to be legal consent. The United Nations Conventions on the Rights of the Child (CRC) is an international treaty that legally obliges states to protect children's rights in November 2008, 193 countries are bound by the CRC, including every member of United Nations except the United States and Somalia (Algorithm 1).

ALGORITHM 1

An algorithmic approach to a case of child/adolescent sexual abuse



KEY POINTS

- ☞ Sexual abuse is rampant and universal as children and adolescents are vulnerable and most often not in a position to voice their protest against the heinous offense against their body/their complains are not taken seriously and many times silenced
- ☞ About 40% of girls and 25% of boys suffer from sexual abuse before they reach 16 years of age. Majority of them are not surfaced
- ☞ Contrary to the common belief, majority of the offenders are known to the victim
- ☞ Child sexual abuse is one of the most fundamental violations of children's human rights which lead to tremendous psychological trauma having many long-term and short-term effects on their overall development adversely affecting them throughout their life
- ☞ As the survivors are often not able to reveal, high index of suspicion based on nonverbal clues, psychosomatic symptoms and seldom physical signs are helpful to come to the diagnosis
- ☞ Important aspects of management are helping the survivor in disclosure with the help of counseling and strong psychosocial support. Pharmacological therapy is aimed at prevention of pregnancy and prophylaxis against sexually transmitted infection
- ☞ There is a great need to find ways to prevent child/adolescent sexual abuse and to ensure the safety from victimization of any form
- ☞ Self-defense training for every girl has an important role in prevention of victimization. Schools have the potential to teach protective behaviors effectively, including teaching the parents
- ☞ There is a need for incorporation of child sexual abuse in Indian Penal Code, including incest, sexual abuse of boys, and nonpenetrative sexual abuse.

SUGGESTED READINGS

1. Aggarwal A. (2000). Age estimation in the living: some medicolegal considerations. [online] Available from: anilaggrawal.com/ij/vol_001_no_002/ug001.html. [Accessed November, 2015].
2. American Academy of Child and Adolescent Psychiatry. (2014). Responding to child sexual abuse. [online] Available from: www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Responding%20To-Child-Sexual-Abuse-028.aspx. [Accessed November, 2015].
3. American Academy of Pediatrics and Adolescent Psychiatry. Factsheet on Child Sexual abuse.
4. American Psychological Association. (2011). Understanding child sexual abuse: education, prevention, and recovery. [online] Available from: www.apa.org/pi/about/newsletter/2011/12/sexual-abuse.aspx. [Accessed November, 2015].
5. Amnesty International USA. United Nations Convention on the Rights of the Child: Frequently Asked Questions. 2008.
6. Child Marriage. Available from: http://www.unicef.org/chinese/protection/files/Child marriage.pdf.
7. Child sexual abuse: consequences and implications. J Paediatr Health Care. 2009;24(6):385-64.
8. Department of child protection, UNICEF, DWCD, Government of India/Manual for Medical Officer dealing with medicolegal cases of victims of trafficking for commercial sexual exploitation and child sexual abuse.
9. Medline plus, US National Library of Medicine. Child Sexual Abuse. 2008-04-02.
10. Parthasarathy A, Nair MK, Menon PS, Bhave SY. Bhave's Textbook of Adolescent Medicine, 1st ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ldt.; 2006.
11. Pereda N, Guilera G, Forns M, Gómez-Benito J. Prevalence of child sexual abuse in community and student samples: a meta-analysis. Clin Psychol Rev. 2009;29(4):328-38.
12. Teicher MH. Scars that won't heal: the neurobiology of child abuse. Sci Am. 2002;286(3):68-75.
13. The Ministry of Women and Child Development, the Government of India. (2007). Study on Child Abuse: India - 2007. [online] Available from: www.savethechildren.in/custom/recent-publication/Study_on_Child_Abuse_India_2007.pdf. [Accessed November, 2015].
14. The sexual exploitation of children. Chart 1: Definition of terms associated with the sexual exploitation of children, University of Pennsylvania, Centre of Youth Policy Studies, US National Institute of Justice; August 2001.
15. Tulir: Center for Treatment of Child Sexual Abuse, Chennai, India.
16. Widom CS. Posttraumatic stress disorder in abused and neglected children grown up. Am J Psychiatry. 1999;156(8):1223-9.
17. World Health Organization (WHO). (2000). Violence and injury prevention: Guidelines for medico-legal care for victims of sexual violence. [online] Available from: www.who.int/violence_injury_prevention/publications/violence/med_leg_guidelines/en/. [Accessed November, 2015].
18. World Health Organization. (2002). Understanding and addressing violence against women: Sexual violence. [online] Available from: apps.who.int/iris/bitstream/10665/77434/1/WHO_RHR_12.37_eng.pdf. [Accessed November, 2015].

CHAPTER 24

Adolescent Depression/ Suicidal Tendency and Its Management

Paula Goel

INTRODUCTION

Every year about 2 million adolescents (1 in every 12) suffer an episode of depression; 1 in 5 adolescents experience depression before they reach adulthood. Depression affects 3.5% of children at any given time, impeding healthy psychosocial development. Diminished self-worth, academic struggles, and difficulties in social relations with family and peers exert a heavy toll on youth who are often unable to communicate the nature of their experience. It is a common and serious problem. It increases the risk for suicide, the third leading cause of death in this age-group.

Often, it leads to more poor academic achievement, greater absenteeism, strained relationships with family and friends, interference with extracurricular activities, and substance abuse. Clinical depression during adolescence represents the strongest risk factor for teenager suicide and is linked to significant psychosocial impairment in adulthood.

Periodic screening of children presenting—for any reason—to primary care physicians can improve clinical recognition of these disorders and result in improved rates of treatment.

The importance of detecting and treating depression in adolescents is being increasingly recognized.

Prevalence is related to age, gender, and social class (about 1% between 10 years and 14 years of age and 25% among late teens).

PREDISPOSING FACTORS

- Biological factors
- Endocrinal factors
- Social factors
- Structural factors in brain
- Environmental factors: socioeconomic status, level of family conflict, abuse or neglect, and parental separation or divorce
- Family history of depression.

CLINICAL FEATURES

Presence of following symptoms for more than 2 weeks (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision):

- Depressed mood: feels sad, empty, bored, appears tearful, irritable mood
- Markedly decreased interest or pleasure in almost all activities most of the day, nearly every day
- Significant weight loss or weight gain with increase or decrease in appetite nearly every day
- Poor sleep, insomnia, or hypersomnia nearly every day
- Psychomotor agitation or retardation almost daily: restlessness, pacing, tapping of fingers, abruptly starting and stopping tasks, meaninglessly moving objects around. Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt nearly daily
- Diminished ability to think or concentrate on academics/ indecisiveness almost daily
- Recurrent thoughts of death or suicidal ideation
- Clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Symptoms persist for more than 2 months or are characterized by morbid preoccupation with feelings of worthlessness, suicidal ideation, psychotic symptoms, marked functional impairment.

Clinical features can also be classified as:

- Affective: depressed mood and feelings of worthlessness or guilt
- Behavioral symptoms: social withdrawal and agitation. Feelings of restlessness, grouchiness, aggression, sulkiness
- Cognitive symptoms or problems in thinking including difficulty in concentration or making decisions, school difficulties
- Somatic symptoms: insomnia or hypersomnia
- Prepubertal children: somatic symptoms

- Adolescents: affective and behavioral symptoms
- Highly intelligent, academically strong children compensate for mood disorders with increased attention to academics
- Comorbidities: conduct disorder, defiant disorder, panic disorder, attention deficit hyperkinetic disorder, anxiety disorders, and disruptive disorders.

The US Preventive Services Task Force now recommends screening adolescents (12–18 years) for major depressive disorder when systems are in place to assure accurate diagnosis, psychotherapy (cognitive-behavioral or interpersonal) and follow-up.

The American Academy of Pediatrics also strengthened their recommendations for mental health screening and counseling in the latest Bright Futures Guidelines.

The Guidelines for Adolescent Depression in Primary Care (GLAD-PC) were published in 2007 and have been updated in 2010. Guidelines for Adolescent Depression in Primary Care provides provide a roadmap for enhancing care. This time tool presents important elements from the 2010 GLAD-PC for the identification, assessment, and treatment of adolescent depression in the office setting.

- Systems must be in place to allow effective triage (safety/placement) for:
  - Identification of high risk cases
  - Screening
  - Assessment and intervention
  - A predetermined "go-to" list of providers and facilities to refer for care when indicated.
- The good news:
  - Screening is simple, effective, and well received by patients, parents, and providers
  - A two-question screening can identify the need for more in depth screening
  - Adolescents prefer to have their depression addressed in primary care
  - Most adolescents see their primary doctor at least annually; an estimated 45% of suicide victims reportedly saw their primary doctor in the month prior to the suicide
  - Most depressed adolescents can be treated in primary care
  - There are effective treatments and guidelines for using them in primary care
- The bad news
  - Only about 1 of 3 adolescents with depression is identified (American College of Preventive Medicine, 2011)
  - Fewer than half of primary care clinicians inquire about depression with adolescents; fewer yet use a standardized instrument to assess depression
  - Fewer than half of adolescents who are diagnosed are treated appropriately
  - Severe cases should be treated by mental health specialists, but there is a severe shortage of child psychiatrists—few of these severe cases are seen by specialists
  - Reimbursement policies are often a disincentive to treating depression in primary care
  - Little coordination typically occurs between primary care and mental health specialties
- The challenge
  - The burden of adolescent depression prevention and management falls squarely on primary care
  - Most pediatricians and family practitioners believe it is their responsibility to identify depression, but relatively few believe it is their responsibility to treat it
  - Most do not feel equipped to manage adolescent depression, and their office systems are not set up to handle it
  - Adolescent depression is different than adult depression due to developmental issues, responses to treatment, issues in psychotherapy, risks of medications, family dynamics
- Steps to integrate care:
  - Assess the practice: adolescent patient load, prevalence of mental health issues
  - Determine the role you want to play and services to provide for adolescent depression
  - Build a network of local resources: therapists, peer counseling, group programs, etc.
  - Determine relation with mental health resources: consultation, colocation, collaboration
  - Provide training where needed: screening/assessing, record keeping, confidentiality (state law), staff roles, insurance coverage including preapprovals or preauthorizations for referrals; counseling/psychotherapy training for designated staff
  - Assure systems are in place to allow effective triage (safety/placement) that includes a "go-to" list of providers and facilities to send patients as needed
  - Follow guideline recommendations
- Guide to the office visit: mental health or emotional issues as chief complaint, or positive screen on Patient Health Questionnaire-2
- Staff: preparation for visit.

IDENTIFY RISK STATUS

- Assistant: Perform chart review to ensure:
  - Forms/assessments to be completed by patient in chart
  - Score instrument in chart for clinician.

ASSESS FOR DEPRESSION

- Review symptom assessment and scoring
- Interview with patient and family/caregiver to identify contributing factors
- Collect collateral information and family history to help distinguish adjustment disorders and family relationship issues
- Assess for safety/suicide risk and appropriate level of care
- Refer to crisis or emergency services if necessary.

DIAGNOSE AND RATE SEVERITY

Provide diagnosis; rate severity: mild, moderate, or severe [based on number of symptoms present].

EDUCATE

- Depression is an illness, not a weakness; very common, no one's fault, usually involves genetic and environmental factors
- Functional impairment in various domains can be manifestations of the illness
- Depression can be a recurrent illness—recovery may take a while
- Key to overcoming depression is staying with the treatment plan long term
- Stress in the parent-child relationship, if present, may be part of the problem
- Ask adolescent about future goals—if none, be wary of suicidal ideation.

INITIAL MANAGEMENT

- Discuss limits of confidentiality
- Emphasize monitoring symptoms, especially changes reflecting increasing suicidal ideation.

Primary Care

- Offer referral for peer/family support, community resources, etc.
- Facilitate parental and patient self-management; provide written materials and websites for more information.

CONSIDER CONSULTATION

With mental health specialist: recommended for severe or complicated depressions, or for interventions not within scope of the pediatric practice:

- Decide to treat in practice or refer to trusted network of mental health providers
- If referred, designate case coordination responsibilities; follow-up plan
- Maintain contact with mental health specialist as long as such treatment continues.

TREATMENT PLAN

If treating in practice:

- Include family: set specific goals for key areas of functioning—home, peer relationships, school and work.

Mild depression:

- Active support and monitoring for 6–8 weeks, contact every 1–2 weeks

Moderate or severe:

- Initiate shared decision discussion about therapy:
  - Psychotherapy and/or antidepressants
  - Review benefits and risks of each option including the black box warning regarding selective serotonin reuptake inhibitors (SSRIs) and suicide risk
- Discuss preferences and plan for chosen treatment:
  - Emphasize importance of finding a therapist one feels comfortable with for psychotherapy
- Discuss common medication side effects:
  - Emphasizing temporary nature and importance of not stopping medication without calling first
  - Discuss more serious adverse effects, especially suicidal ideation; emphasize careful monitoring due to increased risk earlier in treatment
- Develop safety plan for acute crisis, deterioration of symptoms
- Consider ongoing mental health consultation
- Evaluate response at 6–8 weeks (American College of Preventive Medicine, 2011).

FOLLOW-UP MANAGEMENT (AT 6–8 WEEK VISIT)

Mild depression:

- If persistent: institute treatment as moderate cases or refer to mental health
- If improved: continue monitoring monthly for 6 months, regular follow-up for 2 years after resolution of symptoms.

Moderate or severe:

- If not improved
  - Reassess the diagnosis
  - Consider adding a medication, increasing the dosage, or changing medications if already on maximum dosage
  - Add psychotherapy if not already using, or intensifying current therapy
  - Consider referral to mental health
  - Provide further education, review safety plan, continue ongoing monitoring
  - Evaluate response again at 6–8 weeks
- If partially improved:
  - Consider adding a medication or increasing the dosage
  - Add psychotherapy if not already using, or intensifying current therapy
  - Consider referral to mental health
  - Provide further education, review safety plan, continue ongoing monitoring
  - Evaluate response again at 6–8 weeks
- If improved:
  - Continue prescribed medication for 1 year after symptom resolution
  - Continue monthly monitoring for 6 months
  - Provide regular follow-up for 2 years after resolution of symptoms.

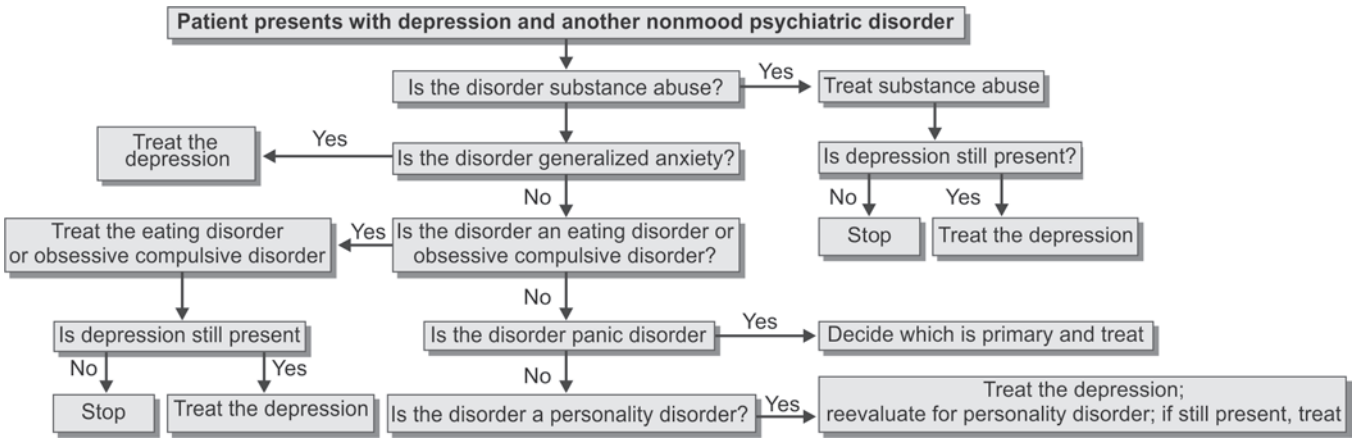
FINAL THOUGHTS

Adolescent depression challenges everyone—from the affected young person to the parents and providers, and the entire healthcare system. The fragmented care and lack of support for primary care undermines early identification and timely treatment.

- Routine screening and diagnosis:
  - Periodically screen children and youth for early signs of depression and/or anxiety. Record these results in the patient's problem list
  - Ask questions of the child (or parent where applicable) when there are red flags including unexplained somatic complaints, unexplained behavioral changes, teenage

ALGORITHM 1

Treatment protocol for management of depression

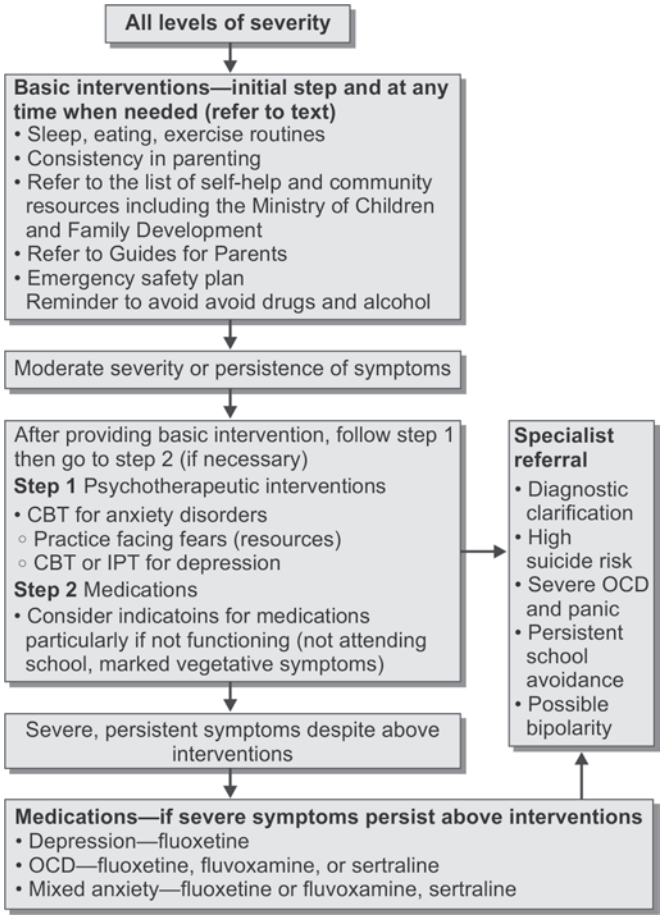


pregnancy, school absences, and family members with depression, anxiety, alcohol, or other substance abuse

- Suggested questions
  - Do you find yourself sad, irritable, or worried a lot?
  - Is the child withdrawing from or avoiding their usual activities?
  - Family involvement is invaluable for assisting with and monitoring treatments as well as providing assurance and emotional support for the child or youth. Assure the family that the questions and fact-finding is not to assign blame but to better understand the situation
  - Choose an appropriate diagnostic questionnaire available for download on the internet. If the screen indicates a possible problem then either begin or schedule time to begin a detailed inquiry about anxiety or depressive symptoms, evaluate severity, and the potential for self-harm
  - Consider that there may be more than one psychiatric disorder when screening because anxiety and depressive disorders are highly comorbid in children and adolescents. All youth, with mood or anxiety disorders should be screened for alcohol or drug use
  - Note red flags for risk of bipolar depression: family history, psychotic depression, mania with SSRIs, hypersexuality, risk-taking behavior, and prepubertal depression. Consider referral if bipolar disorder is suspected. Manage the patient while waiting for referral and provide follow-up
- Diagnosis
  - Take a medical history and do a physical examination with attention to conditions that may mimic anxiety or depressive disorders. Consider indications for diagnostic tests such as thyroid-stimulating hormone. Consider the family situation and social stressors
  - Investigations: clinical basis, identify hypothyroidism and anemia
- Attempt nonpharmacological management strategies first:
  - Nonpharmacological approaches are essential first line treatments for both anxiety and depression. If physician counseling, parental involvement, and use of books does not effect a significant improvement, it is appropriate to refer to a specialist or to the child and youth mental health team for treatment (Algorithms 1–4).

ALGORITHM 2

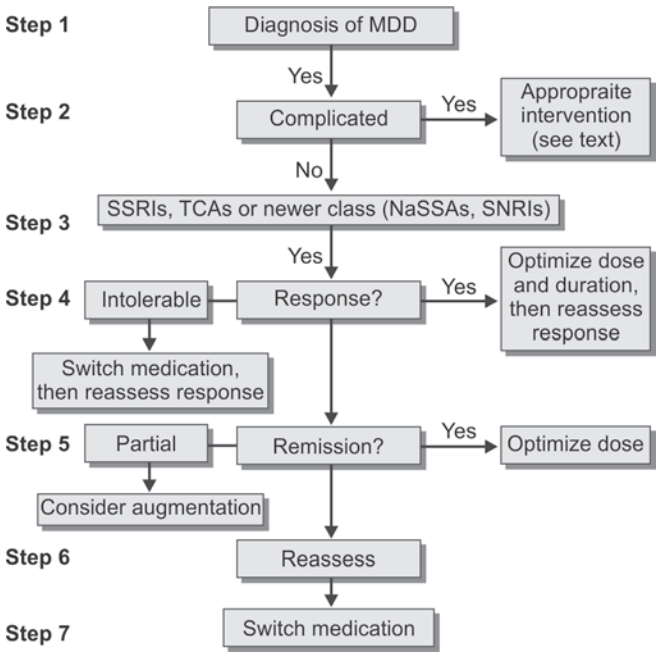
Management of children and youth with anxiety or depression



CBT, cognitive behavioral therapy; IPT, interpersonal psychotherapy; OCD, obsessive compulsive disorder.

ALGORITHM 3

Pharmacotherapy of major depressive disorder



MDD, major depressive disorder; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; NaSSAs, noradrenergic and specific serotonergic antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitors.

INDICATIONS FOR PHARMACOTHERAPY

Indications for pharmacotherapy include persistent depression and/or a comorbid anxiety disorder which have not responded to psychosocial interventions.

Depression: psychotherapy can be effective for treating depression, particularly in adolescents. If unavailable, medications may be indicated:

- The drug most often used is fluoxetine
- If bipolar vulnerability, start with a shorter-acting SSRI (e.g., sertraline)
- If comorbid anxiety, fluvoxamine or sertraline are possible alternatives.

Spontaneous remission in community diagnosed adolescent depression is 50% within 2 months. However, those not remitting in this time period have a high risk of chronicity. Refer to a specialist.

Medication Dosing and Follow-up for Anxiety and Depression

General Dosing Suggestions

Start with one-fourth or half of the adult dose and wait at least 1 week to increase dosages. For adolescents, the maximum dose can be similar to adults, while the dose is less than the adult dose for children

- Anxiety: children who are anxious are sensitive to physical sensations. Provide support, reassurance, and monitor frequently. Generalized anxiety disorder may respond at lower doses (e.g., 25–50 mg sertraline), obsessive compulsive disorder (OCD) (100–200 mg sertraline), generally start low and increase slowly. Dosing example: 10 mg daily fluoxetine for an adolescent. For an anxious 6 year old, start with 5 mg daily and use increments of 5 mg every 2 weeks if needed
- Depression: the response often requires full doses for youth and the response to medication is slower. Example: start the first week with 10 mg daily of fluoxetine and increase to 20 mg daily as soon as tolerated. Increase again up 30 mg daily if not improved after 6 weeks to a maximum of 40 mg daily. If not responding after 10–12 weeks, refer to specialist.

Adverse effects: in children, SSRIs and other new antidepressants produce a higher rate of behavioral and emotional adverse effects (such as agitation, disinhibition, irritability, and occasionally thoughts of self-harm). The largest drug-placebo difference in the number of cases of suicidal ideation and behavior is greatest for the under-24 age group. For all ages, the risk is highest during the first few months of drug therapy, therefore, monitor patients closely during this time

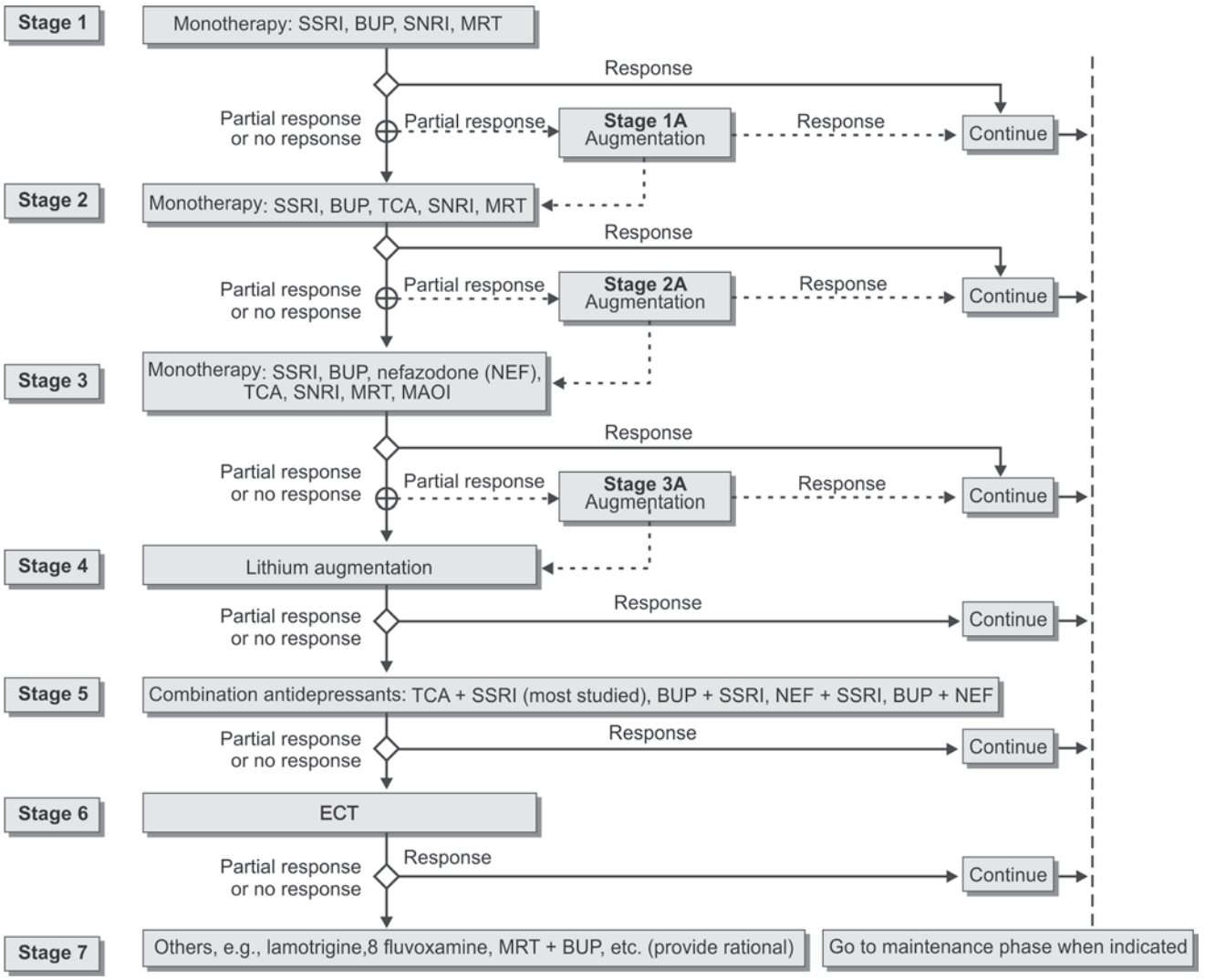
- Monitoring: request assistance of the family and/or teenager, to monitor both symptoms and functions
- Continuation: for both anxiety and depression, the usual length of treatment is 6–12 months before a trial of tapering
- Discontinuation: anxious patients are very sensitive to physical sensations during discontinuation. So, taper off particularly slowly over 1–2 months by approximately 5 mg per reduction.

Antidepressants Commonly Used in Treatment of Major Depressive Disorders (Table 1)

- Selective serotonin reuptake inhibitors (sertraline, paroxetine, etc.): these medications are somewhat less toxic in overdosage. As compared to adults, adolescents are a bit more likely to become agitated or to develop a mania while they are taking an SSRI. These medications can decrease libido in both adolescents and adult. Fluoxetine, sertraline, citalopram, and escitalopram are commonly used as an initial medication. Fluoxetine now has Food and Drug Administration (FDA) approval for the treatment of depression in children and adolescents. The other SSRI medications do not as of yet have FDA approval for depression in children. These last two have fewer interactions with other medications.
- Bupropion (Wellbutrin): this medication can be helpful for depression and attention deficit hyperactivity disorder but is less effective for comorbid anxiety. It does not seem to cause weight gain.
- Tricyclics (imipramine, desipramine, nortriptyline): these medications are still used if the SSRIs and bupropion do not work. As the tricyclics are more likely to cause rhythm changes in children, baseline and periodic electrocardiograms (ECGs) should be considered. Side effects may include dry mouth, dry eyes (problem if contact wearer) dizziness, and ECG, pulse, and rhythm changes. Clomipramine (anafranil) is quite effective in individuals with OCD.

ALGORITHM 4

Major depression (nonpsychotic)



SSRI, selective serotonin reuptake inhibitor; BUP, bupropion; SNRIs, serotonin-norepinephrine reuptake inhibitors; MRT, mirtazapine; TCAs, tricyclic antidepressants; NEF, nefazodone; MAOI, monoamine oxidase inhibitors; ECT, electroconvulsive therapy.

TABLE 1: Antidepressants commonly used in treatment of major depressive disorders

Class	Drugs
Selective serotonin reuptake inhibitors	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone
Serotonin-norepinephrine reuptake inhibitors	Desvenlafaxine, duloxetine, venlafaxine
Monoamine oxidase inhibitors	Isocarboxazid, phenelzine, selegiline, tranylcypromine
Tricyclic antidepressants	Amitriptyline, desipramine, doxepin, imipramine, nortriptyline
Miscellaneous	Bupropion, mirtazapine

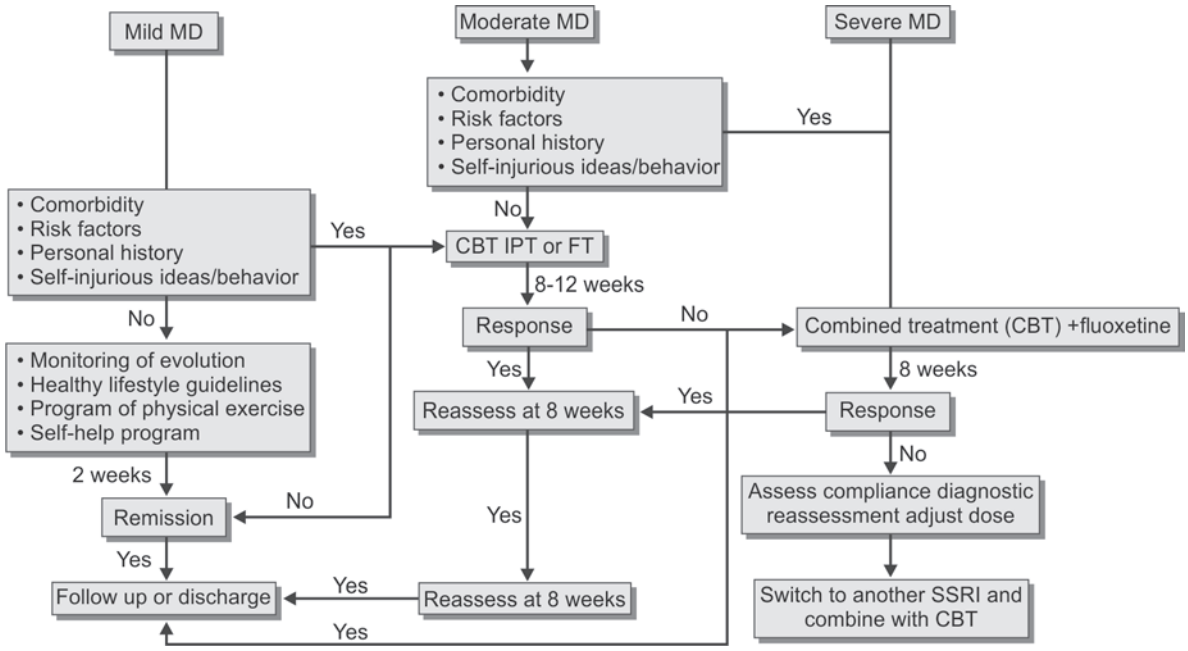
Prevalence of anxiety disorders in children aged 5–17 is 6.4%. The debilitating nature of these disorders is routinely underestimated and the need for help may not be realized until serious impairment in social and academic functioning has occurred. Untreated anxiety disorders in children and adolescents are associated with higher rates of comorbid depression and substance abuse (Algorithm 5).

SUICIDE

Death due to suicide is more common in boys than girls. Most acts of suicide are preceded by an expression of death wish either to friends or to a trustworthy adult in the previous 24 hours. May be made impulsively without much forethought or can be premeditated. Emotional development is at its peak

ALGORITHM 5

Major depressive disorder



CBT, cognitive behavior therapy; IPT, interpersonal therapy; FT, family therapy; SSRI, selective serotonin reuptake inhibitors.

during middle adolescence, the control of emotions is still incomplete due to evolving and immature prefrontal lobes.

Predisposing Factors

- Adolescents with poor coping skills and problem solving skills. Low levels of serotonin and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA)
- Chaotic childhood with problems during child rearing, domestic violence, abusive adults
- High achiever adolescent may resort to suicide when humiliated for perceived failure. Adolescents with other coexisting mental illnesses may resort to suicide as they are vulnerable to stressors much more than normal population.

Approach to an Adolescent with Suicide Behavior

Adolescents should be posed directly about the existence of suicide ideation. They may not have confided in parents, hence parental history may not be reliable. Questions should be developmentally appropriate as it helps in devising management strategies in form of cognitive behavior therapy and interpersonal therapy. All suicide ideation should be taken seriously and evaluated thoroughly and repeatedly.

What, when, where, how, and why aspects of suicidal behavior should be explored and evaluated.

What:

- Was the action
- Was the thoughts about life after death
- The adolescent expect to happen on completion of suicide
- Any alternative plans thought to accomplish the objective.

How:

- Was the plot to suicide conceived
- How were the steps planned
- Any previous attempts?

When and where:

- Was the suicidal action planned
- Where was the place chosen
- Where was the place where the suicidal note if any was planned to be placed. Significant life events are chosen for suicide.

Why:

- Psychological details are probed
- Feelings of worthlessness, helplessness, emotional pain, humiliation, emptiness, rejection, abandonment, fear of death, fear of mental breakdown, self hatred, guilt.

Adolescents with multiple attempts usually take care to execute the next in a manner which is difficult to intervene. Single attempters usually equip themselves with coping skills with time.

Suicide prevention can be primary, secondary, or tertiary:

- Primary suicide prevention aims to reduce the number of new cases of suicide in the general population
- Secondary suicide prevention aims to decrease the likelihood of a suicide attempt in high risk patients
- Tertiary suicide prevention occurs in response to completed suicides and attempts to diminish suicide contagion (clusters of suicides in a geographical area that occur predominantly among teenagers and young adults) and copy cat suicides.

Risk Factors for Suicide

- Biological risk factors for suicide include:
  - Low cerebrospinal fluid 5-HIAA levels
  - Hypothalamic-pituitary-adrenal axis dysregulation
  - Low blood cholesterol levels
  - Medical or neurological illnesses (such as multiple sclerosis, stroke, Huntington disease and epilepsy)
  - Cigarette smoking
- Psychological risk factors include:
  - Acceptability of suicide
  - A childhood history of physical or sexual abuse
  - Discouraged help-seeking behavior
  - Aggressive/impulsive traits
  - Pessimism
  - Hopelessness
  - Low self-esteem
  - Poor access to psychiatric treatment
  - Relationship problems
  - Financial troubles
  - A family or personal history of suicide
  - Major depression
  - Substance use.

Rating Scales for Suicide Behavior and Related Mental Health Conditions

The most widely used scales for rating suicidal behaviors include:

- The Scale for Suicidal Ideation has good reported reliability and validity and measures three major factors: (i) active suicidal desire, (ii) specific plans for suicide, and (iii) passive suicidal desire
- The Suicide Intent Scale measures the degree of suicide intent
- The Risk-Rescue Rating Scale is an interviewer-administered measure that assesses the lethality and intent of a suicide attempt
- The Columbia-Suicide Severity Rating Scale assesses severity of suicidal ideation and tracks suicidal events
- The Beck Hopelessness Scale is a self-report inventory designed to measure three major aspects of hopelessness: feelings about the future, loss of motivation, and expectations
- The Hamilton Depression Rating Scale is a clinician-applied scale rating dimensions of depression
- The Beck Depression Inventory is a multiple choice self-report inventory that measures the severity of depression.

The Search for Biological Markers for Suicide

Many researchers have been trying to find biological markers related to suicidal behavior that could improve secondary suicide prevention. Several biological features related to failures in neurotransmitter and neuroendocrine systems, such as the serotonergic, noradrenergic, dopaminergic, and hypothalamic-pituitary-adrenocortical (HPA) systems, have been proposed, e.g., considerable evidence accrued using various research approaches suggests a potentially causal association between suicidal behavior and the serotonin neurotransmission system.

To date, the most promising biological predictors of suicidal behavior are low cerebrospinal fluid 5-HIAA (the main serotonin metabolite) and HPA axis dysregulation as indicated by dexamethasone nonsuppression.

What are the Most Effective Secondary Suicide Prevention Strategies?

In a recent systematic review of suicide prevention strategies, Mann et al., found evidence of effectiveness in five secondary suicide prevention methods:

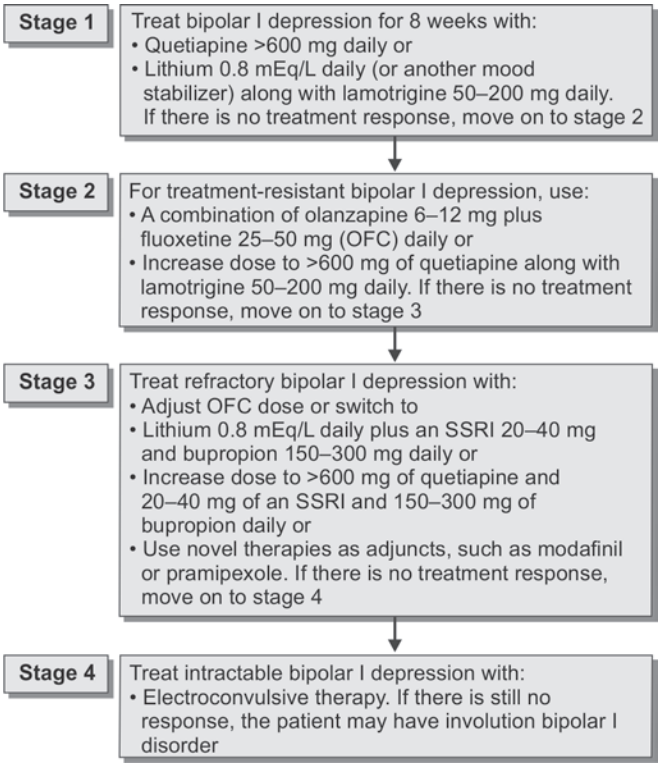
1. Pharmacological interventions
2. Psychological interventions
3. Follow-up care
4. Reduced access to lethal means
5. Responsible media reporting of suicide (Algorithms 6 and 7).

Clinical Pearls

- Counselors and clinicians should actively use specialize tools such as patient health questionnaire
- An algorithm of nonpharmacological intervention makes it easier to manage depression
- Pharmacological management, when necessary, should follow correct doses as per body weight and side effects have to be monitored
- Treatment of adolescent depression/suicidal tendency is a long-term process with regular monitoring and follow up as small social and psychological trigger factors can produce sudden relapse.

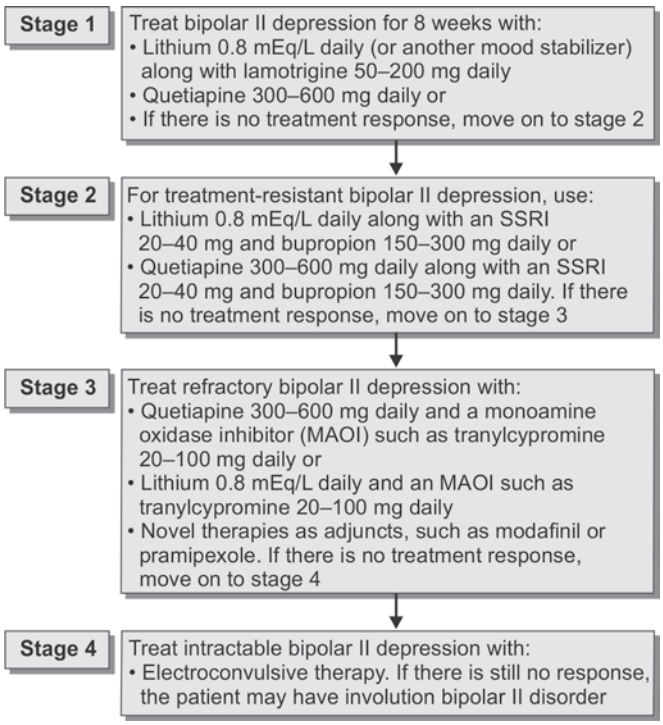
ALGORITHM 6

Treatment of bipolar I depression



ALGORITHM 7

Treatment of bipolar II depression



KEY POINTS

- ☞ Adolescent depression is a common and serious problem increasing the risk of suicide
- ☞ Early detection and treatment is key to effective management
- ☞ Behavioral changes at home, amongst peers and at school should be noticed and acted upon
- ☞ Both nonpharmacological and pharmacological methods have to be used in stepwise integrated approach involving family members and school staff
- ☞ Suicidal ideation needs to be identified early by psychological profiling and the necessary corrective actions have to be initiated.

SUGGESTED READINGS

1. Andersen UA, Andersen M, Rosholm JU, Gram LF. Contacts to the health care system prior to suicide: A comprehensive analysis using registers for general and psychiatric hospital admissions, contacts to general practitioners and practicing specialists and drug prescriptions. Acta Psychiatr Scand. 2000;102.
2. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol. 1979;47(2):343-52.
3. Jacobs DG, Baldessarini RJ, Conwell Y, Fawcett JA, Horton L, Meltzer H, et al. (2003). Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors. [online] Available from: psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide.pdf. [Accessed November, 2015].
4. Johansson L, Lindqvist P, Eriksson A. Teenage suicide cluster formation and contagion: implications for primary care. BMC Fam Pract. 2006;7:32.
5. Lönnqvist JK, Henriksson MM, Isometsä ET, Marttunen MJ, Heikkinen ME, Aro HM, et al. Mental disorders and suicide prevention. Psychiatry Clin Neurosci. 1995;49(Suppl 1):S111-6.
6. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide prevention strategies: a systematic review. JAMA. 2005;294(16):2064-74.
7. Murphy GE. The prediction of suicide: why is it so difficult? Am J Psychother. 1984;38(3):341-9.
8. Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. Am J Psychiatry. 2004;161(8):1433-41.
9. Pignone MP, Gaynes BN, Rushton JL, Burchell CM, Orleans CT, Mulrow CD, et al. Screening for depression in adults: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med. 2002;136(10):765-76.
10. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-43.
11. Sher L, Oquendo MA, Mann JJ. Risk of suicide in mood disorders. Clin Neurosci Res. 2001;1:337-44.
12. Sher L. Preventing suicide. QJM. 2004;9(10):677-80.
13. Van Heeringen K. The neurobiology of suicide and suicidality. Can J Psychiatry. 2003;48(5):292-300.
14. World Health Organization. (2003). World Health Report 2003: Shaping the Future. [online] Available from: www.who.int/whr/2003/en/whr03_en.pdf. [Accessed November, 2015].

CHAPTER 25

Teen Aggression: Steps in Management

Kiran SK Vaswani

INTRODUCTION

Aggression aimed at harming others and/or self, with many negative outcomes, like violence, delinquency, substance use, scholastic problems, is common in adolescence. It may be the first sign/manifestation of childhood psychiatric disorders or organic diseases. Therefore, it is imperative for the primary caregiver to recognize aggression and intervene early. Approximately 3–7% of school children have signs of aggression.

The objective of this chapter is to understand the following aspects of teen aggression:

- Definition, subtypes, and related term anger
- Normative development
- Risk and protective factors
- Related comorbidities
- Prevention and parent support
- Assessment and intervention: algorithm.

DEFINITION, SUBTYPES, AND RELATED TERM ANGER

Anger is defined as a person's response to a threat actual or perceived, against an individual or group (Lazarus, 1991). It may be adaptive or when uncontrolled, associated with aggression.

Box 1: Three pathways/clusters

- "Authority conflict" (avoidance/conflict): stubborn-disobedience-avoidance (truancy/running away from home)
- "Covert" (property loss): sneaky acts—stealing, vandalism progressing to fraud and serious theft
- "Overt" (physical harm): starts with annoying, bullying, then physical fighting to forced sex

Aggression is "any behavior intended to harm another person who is motivated to avoid the harm". Clusters of aggression, a disruptive behavior, are as shown in box 1.

Aggression by definition is intentional, thus an autistic teen's aggression is not primary disruptive behavior.

Proactive and Reactive/Affective Aggression

Aggression can be proactive or reactive (affective), features of these are summarized in table 1.

Disruptive Behavior Disorders

Disruptive behavior disorders (DBD) are characterized by predominance of oppositional, defiant, or antisocial behaviors, range from the milder oppositional defiant disorder (ODD) to the more serious conduct disorder (CD). Features of DRD are given in table 2.

TABLE 1: Features of proactive and reactive/affective aggression

Features	Proactive (premeditated) aggression	Reactive/affective (impulsive) aggression
Purpose	• Obtain specific rewards/goals • Establish social dominance	• Learned behavioral response to abuse; perceive threat/provocation in neutral/friendly situations
Relation to anger	• Calculated/cold-blooded • No significant display of anger	• Emotionally driven/hot-blooded • Visible display of anger
Peer relations	• Leadership skills and a sense of humor	• Peer rejection/victimization
Clinical implications and prognosis	• Externalizing behavior/subsequent criminal behavior uncommon	• Common psychotic symptoms/need lithium or neuroleptics
Intervention implications	• Systematic interventions	• Cognitive behavioral therapy and medications

TABLE 2: Diagnostic features of disruptive behavior disorders

Features	Oppositional defiant disorder	Conduct disorder
American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition	Ongoing symptoms of "negativistic, defiant, disobedient, and hostile behaviors toward authority figures"	"A repetitive and persistent pattern of behavior in which the basic rights of others or major age appropriate social rules are violated"
Onset	Mainly <8 years/early adolescence	Child onset: <10 years Adolescent onset: >10 years, rarely >16 years
Symptoms	• Trouble with authority • Breaks school rules • Angry/argumentative • Noncompliant • Blame others for their errors • Have not broken major societal rules	• Significant aggression towards others • Animal cruelty • Destruction of property/theft/setting fires • Law breaking/serious violation of rules • Substance abuse • Poor school performance • Have broken major societal rules; suspended from school or have police involvement
Duration of symptoms for diagnosis	For at least 6 months	More than three incidents within the last 12 months, and at least one in past 6 months

Intermittent Explosive Disorder

This manifests in late adolescence as discrete episodes of aggression, unrelated to stressors, remits spontaneously with no impulsivity; unexplained by personality disorders/attention deficit hyperactivity disorder (ADHD)/substance intoxication, is probably an epileptoid state with aura, postictal-like changes in sensorium, responding to anticonvulsants, β-blockers, and calcium channel inhibitors.

NORMATIVE DEVELOPMENT

Aggression, a normal and highly frequent behavior in kids/teens, facilitates competence in social assertiveness, games, and developing autonomy. It is mostly directed towards peers, and very little towards adult caregivers.

RISK AND PROTECTIVE FACTORS

Insight of these factors helps in prevention of and intervention in aggression. Risk factors are depicted in figure 1 and box 2.

Protective factors contributing to a significant reduction in antisocial behavior are listed in box 3.

PREVENTION OF AGGRESSION

Parent support and other factors that contribute to prevention of aggression are listed in box 4.

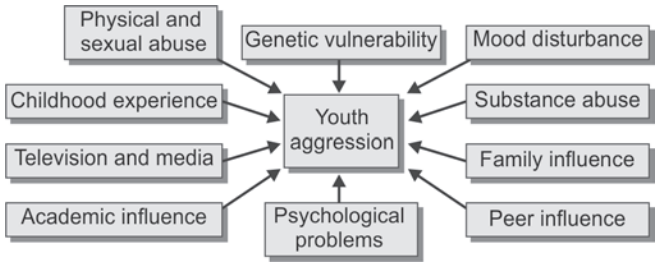


Fig. 1: Aggression risk factors

Box 2: Risk factors

- Age at onset of aggression: important risk factor for conduct disorder (CD). Children displaying aggression are at the highest risk for conduct related problems as adults
- Psychological maltreatment: neglect (infancy), humiliation, rejection, witnessing intimate partner violence
- Physically and sexually abused: likely to become seriously delinquent and violent juveniles
- Physical discipline by parents, models aggression as coping tool
- Media violence and internet addiction, extensively studied, significant role in shaping the developing brain/"wired" for aggression
- Vicious cycle exists between substance use and violence
- Associating with delinquent peers and gangs; peer group rejection and victimization; females tend to be with the gang for a refuge and belong to more troubled families
- Easy access to weapons
- Related psychiatric disorders: 65–95% of boys with CD have attention deficit hyperactivity disorder:
  - Girls have depression with CD:
    - Look for comorbid conditions, especially suicidal attempts, in girls with antisocial behavior as they are at a great risk
    - Other associations: anxiety, autism spectrum disorder, intellectual disability, language deficits, bipolar disorder
- Social cognitive risk factor: aggressive children misread interpersonal cues and interpret ambiguous/prosocial communication as hostile and react aggressively

Box 3: Protective factors: contribute to significant reduction in antisocial behavior

- A good relationship with at least one parent
- Consistent parental discipline
- A caring relationship with competent adult
- School and family connectedness
- Prosocial peers
- Normal/above: normal intelligence
- Good work habits, extracurricular activities

Box 4: Prevention and parent support

- Kids/teens with several risk factors demonstrating intense anger/loss of temper, extreme irritability/impulsiveness, or easy frustration need to be evaluated/intervened
- Studies show aggression can be decreased/prevented by:
  - Violence leads to violence, therefore, reduce exposure to violence at home/community/media
  - Prevention of child abuse. Victim identification, care and support programs
  - Reducing availability and harmful use of alcohol
  - Reducing access to lethal means: weapons/pesticides
  - Promoting gender equality, sex education, and parenting program for teens
  - Developing life skills in kids/teens
  - Changing cultural/social environment supporting violence
  - Promoting Alternative Thinking Strategies (PATHS): 3-steps to calm down:
    - Stop
    - Take a deep breath
    - Identify problem and your feelings

Clinical Pearls

- Teens with childhood onset of aggression are more likely to manifest delinquent activity during adolescence, persisting into adulthood compared to those with adolescent onset
- Aggression in a child at any age needs to be evaluated/intervened and not dismissed as "child will grow out of it"
- Physically/sexually abused children and adolescents are more likely to become seriously delinquent and violent juveniles
- Child neglect in infancy is associated with aggressive behavior in childhood
- Media and aggression: children watching violent shows are "more likely to strike out at playmates, argue, and disobey authority and less willing to wait for things" Gerbner
- Look for comorbid conditions, especially suicide ideation and attempts in girls with antisocial behavior
- Inquire and counsel for possible abuse
- Teens with symptoms of both attention deficit hyperactivity and conduct disorders have poor outcomes.

ASSESSMENT

Evaluate:

- Development related: short-lived, without significant/persistent dysfunction
- Context of action: better prognosis when impulsive/on peers' encouragement than when planned and individually executed
- Behavior details
- Comorbid conditions
- Eliminate other diagnoses
- Protective and risk factors
- Perception of the issue and motivation for change. Box 5 briefly enumerates the process of assessment.

Box 5: Assessment

Parent interview

- Child's temperament as an infant and young child
- Development history and assessment, including language
- Details of disturbing behavior-onset, psychosocial stressors (death/separation/crisis/loss of pet) at the onset
- Frequency, intensity, duration of an episode, triggers/trends, degree of disruption
- Parenting styles, expectations, strategies for dealing with stress
- Media exposure
- Aggressive neighborhood

Adolescent interview

- Opportunity to observe:
  - Evidence of anxiety, hyperactivity
  - Motivation for change
- HEEADDSS assessment:
  - Home: family dynamics, abuse, and neglect
  - Education: peer activities, acceptance, bullying
  - Activities: hobbies, media use, leisure, sleep
  - Drugs: substance abuse
  - Depression/suicide
  - Sexual health: sexuality, sexual activity/abuse
  - Safety: possession of arms, vehicle driving

Teacher interview

- Behavior details
- Academic performance

Peer interview

- Behavior details
- Academic performance
- Bullying, participation in peer activities

Standardized Rating Scales: completed by teens, parents, teachers

- Help in assessing: depression, anxiety, aggression, withdrawal, inattention, hyperactivity, delinquent behavior, suicide ideation
- Based on others' opinions
- Used in combination with other data
- The Youth Self Report, Child Behavior Checklist, Direct and Indirect Aggression Scale: commonly used

Eliminate other diagnoses

- Mood disorders: major depression, bipolar disorder
- Anxiety disorders: post-traumatic stress disorder, generalized anxiety disorder, panic attack
- Psychotic disorders: with active delusions or hallucinations
- Substance use: active phase or withdrawal
- Developmental disorders: autism, mental retardation
- Temporal lobe epilepsy, endocrinal disorders, intracranial space occupying lesions, megaloblastic anemia

INTERVENTION

- Effective strategies: group intervention—time and cost-effective
- Take necessary precautions to keep "self" safe
- Targeting teens: cognitive behavioral therapy to change social cognitive distortions involves practising alternative ways of dealing with conflicts

- Limitations: lack of motivation, immature cognition, and language deficits
- Problem-solving skills training by role-playing, practising, and homework assignments
- Glick's aggression replacement therapy:
  - Learning social skills through structured learning training has 4 steps:
    1. Shows behavior (saying thank you/sorry/asking for permission)
    2. Try the skill by role-playing
    3. Practise
    4. Use in actual situations
  - Anger control training: identify triggers, cues, self-talk, use reducers (deep-breathing), and self-evaluation
  - Moral education: justice, personal rights/responsibilities
- Parent involvement (parent management training): parents trained to observe, teach prosocial behavior by role-playing, practising, and feedback
- Adolescent transition program: parenting skills, improved family relationships and communication, limit-setting, and problem-solving
- Family therapy to improve communication, reduce blaming

Tips for parents (and teachers) to deal with an aggressive adolescent are listed in table 3.

Teens and parents inclusive interventions (most effective):

- Schools: prosocial peers
- Life skills programs
- Utilize mental health professionals to train teachers, counsel teens and parents involve in school and community activities

Media literacy and deconstruction exercises:

- Develop critical viewing skills to make kids/teens less susceptible to negative messages of media
- Monitor television viewing habits
- Role-model: limit time and content
- Discuss media contents and deconstruct:
  - Does it resemble any person/situation in real life?
  - Was there a problem/conflict and how was it solved? Can we adopt these methods? Given a choice what would have been your strategy?
  - What are victim's feelings? Was it possible to avoid hurting/harming them? How?

Risk factors and comorbidities: identify and treat appropriately:

- Medication: as an adjunct to behavioral therapy
- Mainly for comorbid conditions: depression, anxiety, selective serotonin reuptake inhibitors, fluoxetine
- No specific antiaggressive agents, mood stabilizers, antiepileptic drugs—valproate, or atypical antipsychotics used
- Risperidone in severe aggression affecting function
- Selective serotonin reuptake inhibitors useful in irritable depressed/anxious.

Clinical Pearls

- Behavioral interventions are the mainstay of treatment
- Effective strategies include all stakeholders in management: the teen, parents, school, peers, and the community
- Medication has a limited role in management of aggression.

Prompt referral to the expert:

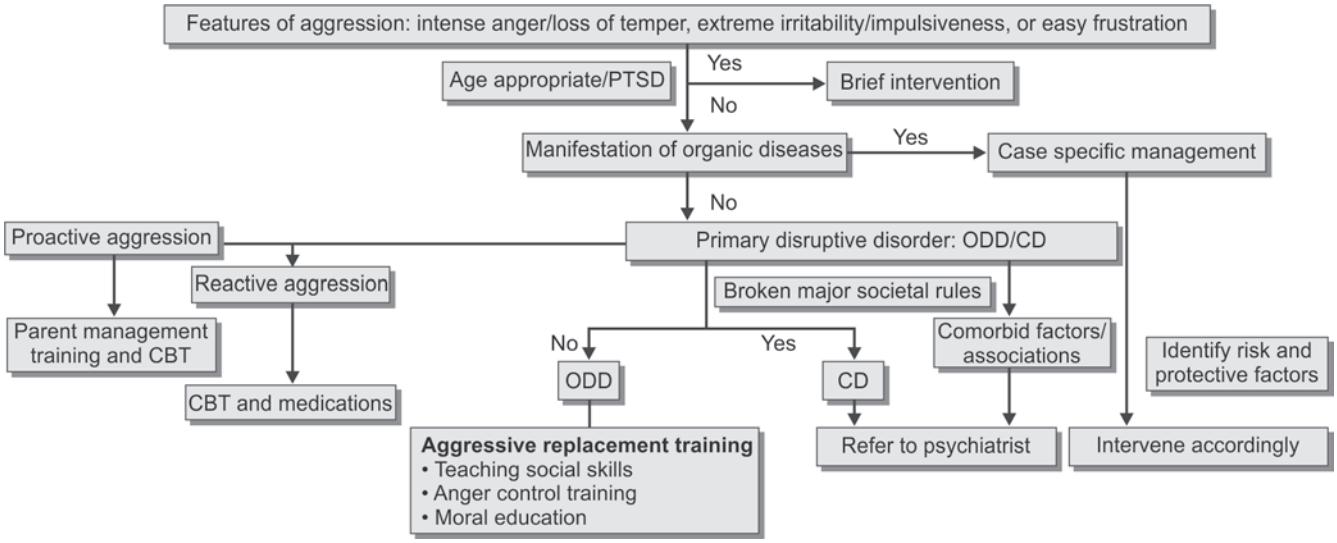
- Escalating behavior, from vandalism to harming
- Multiple domains of involvement: mood, substance, psychotic, suicide ideation/attempts.

TABLE 3: Tips for dealing with an aggressive adolescent for parents and teachers (gatekeepers)

No child is always bad	Attend/praise positive behaviors
Respect	Let the adolescent know that you care and respect him and do not like the inappropriate behaviors and (not the individual)
Do not ignore	Inappropriate aggression
Be positive	Remain calm and model positive problem-solving
Behavior contracts	Target behaviors: stated as positive behaviors dos and not don'ts, e.g., if he often argues, target behavior: discuss things calmly
Effective commands	One at a time, avoid question commands/vague/chained: multiple requests/much explanation
House rules	Clearly stated
Communication	Increase ongoing communication and cohesion
Problem-solving	Model effective problem solving: identify problem, generate alternative responses, evaluate these, and plan implementing
Relaxation	Quick, effective techniques (deep breathing/counting to 10)
Coping statements	Develop a list
Perspective talking	Understanding others' thinking/feelings
Negotiating	Less likely to use defiance/aggression to meet needs
Autonomy	Value and encourage positive ideas/independent-thinking/decision-making
Monitoring	Caring/not violating privacy

ALGORITHM 1

Steps in management of teens aggression



ODD, oppositional defiant disorder; CD, conduct disorder; CBT, cognitive behavioral therapy; PTSD, post-traumatic stress disorder.

KEY POINTS

- ☞ Behavioral and mental health concerns are common in pediatrician's office practice, and aggression is both a challenging and significant concern
- ☞ Aggression may represent a normal developmental stage or indicate a serious mental health disorder, and has grave implications for both the individual and his family and also community at large
- ☞ As clinicians, we need to identify those with multiple risk factors, and suggest interventions before the behavior becomes chronic, severe, and frequent
- ☞ Identify comorbidities and deal with them
- ☞ Consider medical causes of aggression
- ☞ Effective strategies of management involve teens, parents, and schools.

SUGGESTED READINGS

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR). Washington, DC, USA: American Psychiatric Association; 2000. pp. 645-50.
2. National Association of School Psychologists. [online] Available from: http://www.nasponline.org/publications/booksproducts/nas-cbiii-05-1001-009-r02.pdf
3. National Association of School Psychologists. [online] Available from: http://www.nasponline.org/resources/principals/nasp_aggression.pdf.
4. Oppositional and aggressive behaviors. [online] Available from: http://www.brightfutures.org/mentalhealth/pdf/bridges/oppositional.pdf.
5. Rappaport N, Thomas C. Recent research findings on aggressive and violent behavior in youth: implications for clinical assessment and intervention. J Adolesc Health. 2004;35(4):260-77.
6. Sadock BJ, Sadock VA. Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/clinical Psychiatry, 9th edition. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 2003.
7. Sexson SB. Child and Adolescent Psychiatry: Blackwell's Neurology and Psychiatry Access Series, Second Edition. Wiley. 2005
8. Sharma MK, Marimuthu P. Prevalence and psychosocial factors of aggression among youth. Indian J Psychol Med. 2014;36(1):48-53.
9. Working with aggressive adolescents. (1998). [online] Available from: http://www.practicenotes.org/vol3_no2/working_with_adolescents.htm. [Accessed March, 2016].
10. World Health Organization (WHO). (2010). Violence prevention the evidence: Series of briefings on violence prevention. [online] Available from www.who.int/violence_injury_prevention/violence/4th_milestones_meeting/evidence_briefings_all.pdf. [Accessed November, 2015].
11. Yadav A. MEDIA VIOLENCE and Aggression among Adolescents: Media Literacy as an Intervention. [online] Available from ciet.nic.in/MediaClub/pdf/Media_Violence_Media_Literacy.pdf. [Accessed November, 2015].
12. Zahrt DM, Melzer-Lange MD. Aggressive behavior in children and adolescents. Pediatr Rev. 2011;32(8):325-32.

CHAPTER 26

Immunization in Childhood

Monjori Mitra

INTRODUCTION

Along with the routine vaccines in national immunization program, Indian Academy of Pediatrics recommends routine vaccination to prevent other vaccine-preventable diseases that occur in infants, children, and adolescents.

There has been a constant surveillance of the various vaccine-preventable diseases and the outcome has prompted the various advisory bodies to reschedule the vaccination program based on the reports.

The schedule recommended is based on the best seroprotective outcome of the vaccines which are being continuously studied in various environmental settings. The vaccination providers should try to influence the community or the individual to follow the same to get the best protective efficacy for individual and community.

Optimal response to a vaccine depends on multiple factors, including the type of vaccine, age of the recipient, and immune status of the recipient. Recommendations for the age at which vaccines are administered are influenced by age-specific risks for disease, age-specific risks for complications, age-specific responses to vaccination, and potential interference with the immune response by passively transferred maternal antibodies. Vaccines are recommended for members of the youngest age group at risk for experiencing the disease for which efficacy and safety have been demonstrated.

Certain products, including inactivated vaccines, toxoids, recombinant subunit vaccines, polysaccharide conjugate vaccines, and live vaccines, require two doses or more to elicit an adequate antibody response. Tetanus and diphtheria toxoids require booster doses to maintain protective antibody concentrations. Unconjugated polysaccharide vaccines do not induce T-cell memory, and additional doses (although they elicit the same or a lower antibody concentration) might increase the level of protection. Conjugation with a protein carrier improves the effectiveness of polysaccharide vaccines by inducing T-lymphocyte-dependent immunologic function. Many vaccines that stimulate both cell-mediated immunity and neutralizing antibodies (e.g., live, attenuated virus vaccines) usually can induce prolonged immunity, even if antibody titers decline over time. Subsequent exposure to such viruses usually results in a rapid anamnestic antibody response without viremia.

Approximately, 90–95% of recipients of a single dose of certain live vaccines administered by injection at the recommended age (i.e., measles, rubella, and yellow fever vaccines) develop protective antibodies, generally within 14 days of the dose. For varicella and mumps vaccines, 80–85% of vaccines are protected after a single dose. However, because a limited proportion (5–15%) of measles, mumps, and rubella (MMR) or varicella vaccines fails to respond to first dose, a second dose is recommended to provide another opportunity to develop immunity. Of those who do not respond to the first dose of MMR or varicella vaccine, 97–99% responds to a second dose.

COMBINATION VACCINES AND DRUG CONTROLLER GENERAL OF INDIA LICENSURE

Only combination vaccines licensed by Drug Controller General of India (DCGI) should be used. Vaccination providers should not combine separate vaccines into the same syringe to administer together unless mixing is indicated for the patient's age and is explicitly specified on the DCGI-approved product label inserts. Only two combination vaccines [diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b (DTaP-IPV/Hib) vaccine] contain separate antigen components for which DCGI approves mixing by the user. The safety, immunogenicity, and effectiveness of unlicensed combinations are unknown and should not be used.

INTERCHANGEABILITY OF FORMULATIONS

Regulatory body generally licenses a combination vaccine based on studies demonstrating that the product's immunogenicity (or efficacy) and safety are comparable or equivalent

to monovalent or combination products licensed previously. The combination vaccine may be used interchangeably with monovalent formulations and other combination products with similar component antigens produced by the same manufacturer to continue the vaccination series. For example, DTaP, DTaP/Hib, and future DTaP vaccines that contain similar acellular pertussis antigens from the same manufacturer may be used interchangeably, if licensed and indicated for the patient's age.

Ideally, the doses of vaccine in a series should be from the same manufacturer; however, if this is not possible or if the manufacturer of doses given previously is unknown, providers should administer the vaccines that are available.

VACCINATION ALGORITHM

Bacillus Calmette-Guérin Vaccine

- This should be given at birth before discharge from the hospital or at first contact
- Catch-up may be given up to 5 years.

Hepatitis B Vaccine

- Minimum age of administration is at birth. Administer monovalent hepatitis B vaccine to all newborns before hospital discharge. Hepatitis B vaccine may also be given in any of the following schedules:
  - At birth, 1, and 6 months
  - At birth, 6, and 14 weeks
  - At 6, 10, and 14 weeks
  - At birth, 6, 10, and 14 weeks, etc.
- Monovalent hepatitis B vaccine should be used for doses administered before age of 6 weeks
- Administration of a total of four doses of hepatitis B vaccine is permissible when a combination vaccine containing hepatitis B is administered after the birth dose
- Infants who did not receive a birth dose should receive three doses of a hepatitis B containing vaccine starting as soon as feasible
- The ideal minimum interval between first and second dose is 4 weeks, and between second and third dose is 8 weeks
- Ideally, the final (third or fourth) dose in the hepatitis B vaccine series should be administered not earlier than the age of 24 weeks and at least 16 weeks after the first dose.

Catch-up Vaccination

- Administer the three-dose series to those not previously vaccinated
- In catch-up vaccination, use 0, 1, and 6 months schedule.

Poliovirus Vaccines: Oral Polio Vaccine/ Inactivated Polio Vaccine

- Birth dose: oral polio vaccine (OPV) before discharge from hospital
  - Inactivated polio vaccine (IPV): 6, 10, and 14 weeks. Oral polio vaccine in place of IPV. If IPV is unaffordable or unavailable
- Oral polio vaccine: at 6 months with hepatitis B and at 9 months with measles
  - Additional doses of OPV on all national immunization days and subnational immunization days
- Booster dose: 18 months with first booster
  - Inactivated polio vaccine: two instead of three doses can also be used if primary series started at 8 weeks
  - Inactivated polio vaccine catch-up schedule: two doses at 2 months apart followed by a booster after 6 months.

Catch-up Vaccination

- Inactivated polio vaccine catch-up schedule: two doses at 2 months apart followed by a booster after 6 months of previous dose.

Diphtheria, Tetanus Toxoids, and Pertussis Vaccine

Routine Vaccination

- Minimum age: 6 weeks
- The first booster (fourth dose) may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose
- Diphtheria, tetanus, and acellular pertussis (DTaP) vaccine/combinations should preferably be avoided for the primary series
- Diphtheria, tetanus, and acellular pertussis may be preferred to Diphtheria, tetanus, and whole-cell pertussis (DTwP) in children with history of severe adverse effects after previous dose/s of DTwP or children with neurologic disorders
- First and second boosters may also be of DTwP. However, considering a higher reactogenicity, DTaP can be considered for the boosters
- If any "acellular pertussis" containing vaccine is used, it must at least have three or more components in the product
- No need of repeating/giving additional doses of whole-cell pertussis vaccine to a child who has earlier completed their primary schedule with acellular pertussis vaccine-containing products.

Catch-up Vaccination

- Catch-up schedule: the second childhood booster is not required if the last dose has been given beyond the age of 4 years
- Catch-up below 7 years: DTwP/DTaP at 0, 1, and 6 months
- Catch-up above 7 years: Tdap, Td, and Td at 0, 1, and 6 months, respectively.

Haemophilus influenzae Type B Conjugate Vaccine

Minimum age: 6 weeks as combination with DTwP/DTaP. Primary series includes Hib conjugate vaccine at ages 6, 10, and 14 weeks with a booster at age 12 through 18 months.

Catch-up

- In 6–12 months: two doses, 1 month apart and one booster
- In 12–15 months: one primary and one booster
- Above 15 months: single dose.

If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12–18 months at least 8 weeks after the second dose.

Pneumococcal Vaccines

Routine Vaccination

- Minimum age: 6 weeks
- Both PCV10 and PCV13 are licensed for children from 6 weeks to 5 years of age (although the exact labeling details may differ by country). Additionally, PCV13 is licensed for the prevention of pneumococcal diseases in adults >50 years of age
- Primary schedule (for both PCV10 and PCV13): three primary doses at 6, 10, and 14 weeks with a booster at age 12–15 months.

Catch-up Vaccination

- Administer one dose of PCV13 or PCV10 to all healthy children aged 24–59 months who are not completely vaccinated for their age
- For PCV13, catch-up in 6–12 months—two doses 4 weeks apart and one booster; 12–23 months—two doses 8 weeks apart; 24 months and above—single dose
- For PCV10, catch-up in 6–12 months—two doses 4 weeks apart and one booster; 12 months to 5 years—two doses 8 weeks apart
- Vaccination of persons with high risk conditions:
    - Pneumococcal vaccines and pneumococcal polysaccharide vaccine (PPSV) both are used in certain high risk group of children.
    - For children aged 24–71 months with certain underlying medical conditions, administer one dose of PCV13 if three doses of PCV were received previously, or administer two doses of PCV13 at least 8 weeks apart if fewer than three doses of PCV were received previously
    - A single dose of PCV13 may be administered to previously unvaccinated children aged 6–18 years who have anatomic or functional asplenia (including sickle cell disease), HIV infection or an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak
    - Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions.

Pneumococcal Polysaccharide Vaccine (PPSV23)

- Minimum age: 2 years
- Not recommended for routine use in healthy individuals. Recommended only for the vaccination of persons with certain high-risk conditions
- Administer PPSV at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions like anatomic or functional asplenia (including sickle cell disease), HIV infection, cochlear implant, or cerebrospinal fluid leak
- An additional dose of PPSV should be administered after 5 years to children with anatomic/functional asplenia or an immunocompromising condition
- Pneumococcal polysaccharide vaccine should never be used alone for prevention of pneumococcal diseases amongst high risk individuals
- Children with following medical conditions for which PPSV23 and PCV13 are indicated in the age group 24–71 months:
    - Immunocompetent children with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leaks; or cochlear implant
    - Children with anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction)
    - Children with immunocompromising conditions: HIV infection, chronic renal failure and nephrotic syndrome, diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation, congenital immunodeficiency.

Rotavirus Vaccines

- Minimum age: 6 weeks for both *Rotavirus* (RV)-1 (Rotarix) and RV-5 (RotaTeq)
- Only two doses of RV1 are recommended at present and three doses for RV5
- The maximum age for the first dose in the series is 14 weeks, 6 days; and 8 months, 0 days for the final dose in the series
- Vaccination should not be initiated for infants aged 15 weeks, 0 days, or older and should not cross 32 weeks.

Catch-up Vaccination

- The maximum age for the first dose in the series is 14 weeks, 6 days
- Vaccination should not be initiated for infants aged 15 weeks, 0 days or older
- The maximum age for the final dose in the series is 8 months, 0 days.

Measles, Mumps, and Rubella Vaccine

Routine Vaccination

- Minimum age: 9 months or 270 completed days.
- Administer the first dose of MMR vaccine at age 9–12 months, and the second dose at age 15–18 months.
- The second dose must follow in second year of life. However, it can be given at anytime 4–8 weeks after the first dose
- No need to give stand alone measles vaccine

Catch-up Vaccination

- Ensure that all school aged children and adolescents have had two doses of MMR vaccine; the minimum interval between the two doses is 4 weeks
- One dose if previously vaccinated with one dose
- Stand alone measles/measles containing vaccine can be administered to infants aged 6–8 months during outbreaks. However, this dose should not be counted.

Varicella Vaccine

- Minimum age: 12 months
- The risk of breakthrough varicella is lower if given 15 months onwards
- The second dose may be administered before the age of 4 years, provided at least 3 months have elapsed since the first dose
- For children aged 1–12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid
- Children greater than 13 years should receive two doses, 4–8 weeks apart.

Catch-up Vaccination

- Ensure that all persons aged 7–18 years without 'evidence of immunity' have two doses of the vaccine
- For children aged 12 months to 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid
- For persons aged 13 years and older, the minimum interval between doses is 4 weeks
- For persons without evidence of immunity, administer two doses if not previously vaccinated or the second dose if only one dose has been administered
- Evidence of immunity to varicella includes any of the following:
  - Documentation of age appropriate vaccination with a varicella vaccine
  - Laboratory evidence of immunity or laboratory confirmation of disease
  - Diagnosis or verification of a history of varicella disease by a healthcare provider
  - Diagnosis or verification of a history of herpes zoster by a health-care provider
- Postexposure prophylaxis: vaccine is 90% effective in preventing or modifying the disease if given within 3 days of exposure and 70% effective in preventing if given within 5 days and in both the situation, modification occurs 100%.

Hepatitis A Vaccine

Routine Vaccination

- Minimum age: 12 months
- Killed hepatitis A vaccine: start the two dose hepatitis A vaccine series for children aged 12–23 months; separate the two doses by 6–18 months
- Live attenuated H2-strain Hepatitis A vaccine: single dose starting at 12 months and through 23 months of age.

Catch-up Vaccination

- Either of the two vaccines can be used in 'catch-up' schedule beyond 2 years of age
- Administer two doses for killed vaccine at least 6 months apart to unvaccinated persons
- Only single dose of live attenuated H2-strain vaccine
- For catch-up vaccination, prevaccination screening for hepatitis A antibody is recommended in children older than 10 years as at this age the estimated seropositive rates exceed 50%.

Typhoid Vaccine

Routine Vaccination

- Both Vi-PS conjugate and Vi-PS (polysaccharide) vaccines are available
- Minimum ages:
  - Vi-PS (Typbar-TCV®): 6 months;
  - Vi-PS (polysaccharide) vaccines: 2 years
- Vaccination schedule:
- Typhoid conjugate vaccines (Vi-PS): single dose at 9–12 through 23 months and a booster during second year of life
- Vi-PS (polysaccharide) vaccines: single dose at 2 years; revaccination every 3 years
- Currently, two typhoid conjugate vaccines, Typbar-TCV® and PedaTyph® available in Indian market
- An interval of at least 4 weeks with the MMR vaccine should be maintained while administering Typbar-TCV® vaccine
- Primary dose of conjugate vaccine should follow a booster at 2 years of age
- Either Typbar-TCV® or Vi-polysaccharide (Vi-PS) can be employed as booster
- Typhoid revaccination every 3 years, if Vi-polysaccharide vaccine is used
- No evidence of hyporesponsiveness on repeated revaccination of Vi-polysaccharide vaccine so far
- Need of revaccination following a booster of Typbar-TCV® not yet determined.

Catch-up Vaccination

- Recommended throughout the adolescent period, i.e., 18 years.

Human Papilloma Virus Vaccine

Routine Vaccination

- Minimum age: 9 years
- Human papilloma virus (HPV)-4 [Gardasil] and HPV2 vaccines [Cervarix] are licensed and available
- Only two doses of either of the two HPV vaccines (HPV4 and HPV2) for adolescent/preadolescent girls aged 9–14 years
- For girls 15 years and older, and immunocompromised individuals three doses are recommended
- For two-dose schedule, the minimum interval between doses should be 6 months

- Either HPV4 (0, 2, and 6 months) or HPV2 (0, 1, and 6 months) is recommended in a three-dose series for females aged 15 years and older
- Human papilloma virus 4 can also be given in a three-dose series for males aged 11 or 12 years, but not yet licensed for use in males in India
- The vaccine series can be started beginning at age 9 years
- For three-dose schedule, administer the second dose 1–2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).

Catch-up Vaccination

- Administer the vaccine series to females (either HPV2 or HPV4) at age 13–45 years if not previously vaccinated
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

Influenza Vaccine

- Minimum age: 6 months for trivalent inactivated influenza vaccine
- Recommended only for the vaccination of persons with certain high-risk conditions
  - First time vaccination: 6 months to below 9 years—two doses 1 month apart; 9 years and above—annual revaccination with single dose
  - Dosage [trivalent influenza vaccine (TIV)]: aged 6–35 months 0.25 mL; 3 years and above 0.5 mL
  - For children aged 6 months through 8 years: administer two doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time
  - All the currently available TIVs in the country contain the swine flu or A (H1N1) antigen; no need to vaccinate separately
- For children aged 6 months to below 9 years: for the 2012 season, administer two doses (separated by at least 4 weeks) to those who did not receive at least one dose of the 2010–11 vaccine. Those who received at least one dose of the 2012–13 vaccine require one dose for the 2013–14 season
- Best time to vaccinate: as soon as the new vaccine is released and available in the market and just before the onset of rainy season.

Meningococcal Vaccine

- Meningococcal conjugated and polysaccharide vaccines are available
- Minimum age: 2 years for both the vaccines
  - Recommended only for certain high risk group of children, during outbreaks, and international travelers, including students going for study abroad and travelers to Hajj and sub-Sahara Africa
  - Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection and their increased immunogenicity, particularly in children <2 years of age
  - As of today, quadrivalent conjugate and polysaccharide vaccines are recommended only for children 2 years and above. Monovalent group A conjugate vaccine, PsA–TT can be used in children above 1 year of age. Revaccination only once after 3 years in those at continued high risk for polysaccharide vaccine, conjugate vaccine as of now no booster required.

Cholera Vaccine

- Minimum age: 1 year; killed whole cell *Vibrio cholerae* vaccine (Shanchol)
- Not recommended for routine use in healthy individuals; recommended only for the vaccination of persons residing in highly endemic areas and traveling to areas where risk of transmission is very high
- Two doses 2 weeks apart for greater than 1 year.

Japanese Encephalitis Vaccine

Routine Vaccination

- Recommended only for individuals living in endemic areas
- The vaccine should be offered to the children residing in rural areas only and those planning to visit endemic areas (depending upon the duration of stay)
- Three types of new generation Japanese encephalitis (JE) vaccines are licensed in India: one, live attenuated, cell culture derived SA 14-14-2, and two inactivated JE vaccines, namely vero cell culture-derived SA 14-14-2 JE vaccine (JEEV®) and vero cell culture-derived, 821564XY, JE vaccine (JENVAC®)
- Live attenuated, cell culture derived SA 14-14-2:
  - Minimum age: 8 months
  - Two dose schedule, first dose at 9 months along with measles vaccine and second at 16–18 months along with DTP booster
  - Not available in private market for office use
- Inactivated cell culture derived SA 14-14-2 (JEEV®):
  - Minimum age: 1 year (United States Food and Drug Administration: 2 months)
  - Primary immunization schedule: two doses of 0.25 mL each administered intramuscularly on days 0 and 28 for children aged more than or equal to 1 year to less than or equal to 3 years
  - Two doses of 0.5 mL for children aged more than 3 years and adults aged 18 years and above
  - Need of boosters still undetermined
- Inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC®)
  - Minimum age: 1 year
  - Primary immunization schedule: two doses of 0.5 mL each administered intramuscularly at 4 weeks interval
  - Need of boosters still undetermined.

Catch-up Vaccination

- All susceptible children up to 15 years should be administered during disease outbreak/ahead of anticipated outbreak in campaigns.

Rabies Vaccine

- Practically all children need vaccination against rabies
- Following two situations included in high risk category of children for rabies vaccination and should be offered preexposure prophylaxis:
  - Children having pets in home
  - Children perceived with higher threat of being bitten by dogs such as hostellers, risk of stray dog menace while going outdoor
- Only modern tissue culture vaccines and intramuscular routes are recommended for both postexposure and preexposure prophylaxis in office practice
- Postexposure prophylaxis (PEP) is recommended following a significant contact with dogs, cats, cows, buffaloes, sheep, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, squirrel, bears, and others. Domestic rodent (rat) bites do not require postexposure prophylaxis in India
- Postexposure prophylaxis:
  - Modern tissue culture vaccines are recommended for all category II and III bites
  - Dose: 1.0 mL intramuscular in anterolateral thigh or deltoid (never in gluteal region) for human diploid cell vaccine, purified chick embryo cell vaccine, purified duck embryo vaccine; 0.5 mL for purified vero cell vaccine. Intradermal administration is not recommended in individual practice
  - Schedule: 0, 3, 7, 14, and 30 with day '0' being the day of commencement of vaccination. A sixth dose on day 90 is optional and may be offered to patients with severe debility or those who are immunosuppressed
  - Rabies immunoglobin (RIG) along with rabies vaccines are recommended in all category III bites
  - Equine RIG (dose 40 U/kg) can be used if human rabies immunoglobin is not available
- Preexposure prophylaxis:
  - Three doses are given intramuscularly in deltoid/anterolateral thigh on days 0, 7, and 28 (day 21 may be used if time is limited but day 28 preferred)
  - For reexposure at any point of time after completed (and documented) pre- or postexposure prophylaxis, two doses are given on days 0 and 3
  - Rabies immunoglobin is not required during reexposure therapy.

INDIAN ACADEMY OF PEDIATRICS RECOMMENDED VACCINES FOR HIGH RISK CHILDREN (VACCINES UNDER SPECIAL CIRCUMSTANCES)

Indian Academy of Pediatrics recommended vaccines for high risk children (vaccines under special circumstances) are as follows:

- Influenza vaccine
- Meningococcal vaccine
- Japanese encephalitis vaccine
- Cholera vaccine
- Rabies vaccine
- Yellow fever vaccine
- Pneumococcalpolysaccharide vaccine (PPSV23).

High risk category of children:

- Congenital or acquired immunodeficiency (including human immunodeficiency virus infection)
- Chronic cardiac, pulmonary (including asthma if treated with prolonged high dose oral corticosteroids), hematologic, renal (including nephrotic syndrome), liver disease, and diabetes mellitus
- Children on long-term steroids, salicylates, immunosuppressive, or radiation therapy
- Diabetes mellitus, cerebrospinal fluid leak, cochlear implant, malignancies
- Children with functional/anatomic asplenia/hyposplenia
- During disease outbreaks
- Laboratory personnel and healthcare workers
- Travelers.

Clinical Pearls

- Constant surveillance is maintained of the various vaccine preventable diseases
- Vaccine schedule is formulated as per the epidemiology of the disease, need of that particular vaccine, and feasibility
- Optimal response to a vaccine depends on multiple factors, including the type of vaccine, age of the recipient, and immune status of the recipient.

KEY POINTS

- ☞ Certain vaccines are given free of cost to all children in India under National Immunization Program
- ☞ Indian Academy of Pediatrics has formulated immunization schedule for guiding the members about the available vaccines
- ☞ All the children should be immunized as per the guidelines at specified time and age.

SUGGESTED READINGS

1. Plotkin SA, Orenstein WA, Offit PA. Vaccine, 5th ed. Philadelphia: WB Saunders; 2008.
2. Vijay Yewale, Panna Choudhury, Naveen Thacker (Eds). IAP Guide Book on Immunization. IAP Committee on Immunization 2009-2011. Mumbai: Indian Academy of Pediatrics; 2011.
3. IAP Immunization Timetable 2014-Figure with range and Footnotes. Available from: http://acvip.org/professional/columns/pdf/IAP%20Immunization%20Timetable%202014-Figure%20with%20range%20&%20Footnotes.docx.

CHAPTER 27

Missed Immunization

Ritabrata Kundu

INTRODUCTION

Vaccine regimen for children whose vaccine has been missed or delayed should preferably be individualized, but certain general principles should be followed. As vaccines produce immunological memory, any delay between recommended doses does not require reinitiation of the entire vaccine series. Administrations of vaccine at intervals shorter than recommended minimal interval produce poor immunological response and should be avoided.

Two or more live injectable vaccines, administered at shorter intervals, inhibits immunological response to the second or later dose. Whereas oral live virus vaccines do not interfere with injectable live vaccines administered at any time interval. Hence, two or more live injectable vaccines can either be given simultaneously or 4 weeks minimal interval is needed between doses. Inactivated vaccines and live vaccines can be administered simultaneously or at any interval between the doses.

If live vaccines are inadvertently administered at an interval of less than 4 weeks, revaccination with the second vaccine should be done.

Simultaneous administration of several vaccines may be needed at the same sitting, if the chances of the child's return to the vaccine facility are minimal. If more than one injection has to be given in the same limb, thigh is preferred for its large muscle mass, but 1–2 inches gap between two injection sites should be maintained to prevent overlapping of local reaction. Tables 1, 2, and 3 shows different vaccine schedules in three age groups, namely between 6 months and 1 year, at 3 years and at 5 years respectively..

Child with unknown or undocumented immunization states should be considered as unimmunized and should be vaccinated accordingly.

TABLE 1: Vaccination in a child presenting at the age between 6 months and 1 year

Vaccine	Interval between doses
Hepatitis B	• First dose on presentation • Second dose after 4 weeks • Third dose 6 months after first dose
DTaP/DTwP	• First dose on presentation • Second dose after 4 weeks • Third dose after 8 weeks • Fourth dose at 15–18 months • Fifth dose at 4–6 years • There should be gap of at least 6 months between third and fourth dose and same between fourth and fifth dose
Hib	• First dose on presentation • Second dose after 4 weeks • Third dose after 8 weeks • Fourth dose at 12–15 months • If the first dose is administered at 7–11 months then second dose 4 weeks later, and final dose 12–15 months of age
IPV	• First dose on presentation • Second dose after 4 weeks • Third dose after 8 weeks • Fourth dose at 12–15 months
PCV	• First dose on presentation • Second dose after 4 weeks • Third dose after 8 weeks • Forth dose at 12–15 months • If the first dose is administered at 7–11 months, then second dose after 8 weeks and third dose at 12–15 months
Measles	• At 9 months or before 1 year
Rest of the vaccines, like varicella and hepatitis A at specified age	

DTaP, diphtheria, tetanus, and pertussis; DTwP, diphtheria, tetanus toxoids and whole-cell pertussis; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio vaccine; PCV, pneumococcal conjugate vaccine.

TABLE 2: Vaccination in a child presenting at the age of 3 years

Vaccine	Interval between dose
Hepatitis B	• First dose on presentation • Second dose after 1 month • Third dose after 6 months from first dose
DTaP/DTwP	• First dose on presentation • Second dose after 4 weeks from first dose • Third dose 6 months after second dose
Hib	Single dose at presentation
IPV	• First dose on presentation • Second dose after 8 weeks • Third dose after 6 months from first dose
PCV	• Single dose at presentation
MMR	• First dose at presentation • Second dose between 4–6 years of age
Hepatitis A	• First dose at presentation • Second dose 6 months after first dose
Varicella	• First dose at presentation • Second dose 3 months after first dose

DTaP, diphtheria, tetanus, and pertussis; DTwP, diphtheria, tetanus toxoids and whole-cell pertussis; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio vaccine; PCV, Pneumococcal conjugate vaccine; MMR, measles, mumps, and rubella.

TABLE 3: Vaccination in a child presenting at the age of 5 years

Vaccine	Interval between dose
Hepatitis B	• Same as in 3 years
DTaP	• Same as in 3 years
MMR	• First dose at presentation • Second dose 8 weeks after the first dose
Hepatitis A	• Same as in 3 years
Varicella	• Same as in 3 years

DTaP, diphtheria, tetanus, and pertussis; MMR, measles, mumps, and rubella.

Clinical Pearls

- Two or more live injectable vaccine, administered at shorter intervals, inhibits immunological response to the later dose
- Live injectable vaccines are given either simultaneously or at 4 weeks interval
- Simultaneous administration of several vaccines may be given at the same sitting.

KEY POINTS

- ☞ Certain general principles should be followed for children who has missed vaccine regimen
- ☞ Child with unknown or undocumented immunization state should be considered as unimmunized.

SUGGESTED READINGS

1. Plotkin SA, Orenstein WA, Offit PA. Vaccine, 5th edition. Philadelphia: WB Saunders; 2008.
2. Vijay Yewale, Panna Choudhury, Naveen Thacker (Eds). IAP Guide Book on Immunization. IAP Committee on Immunization 2009-2011. Mumbai: Indian Academy of Pediatrics; 2011.

CHAPTER 28

Animal Bites

Jaydeep Choudhury

INTRODUCTION

Rabies is a fatal encephalitis. It is a zoonotic disease and transmission to humans occurs by bite of an infected animal. In India, the transmitting animal is dog in more than 95% cases. Though rabies is fatal, once symptoms of the disease develop, it is almost 100% preventable if prophylactic measures are instituted soon after the exposure.

PROBLEMS OF RABIES INFECTION IN CHILDREN

In India and other developing countries, 50–60% of all rabies deaths occur in children (<15 years of age). There are several reasons as to why children are more susceptible:

- Children play in the streets and are more prone for dog bites. Because of their playful nature, they also tend to tease dogs and in consequence, dogs attack them
- Because of their short stature, bites on heads, neck, and upper parts of the body are more common and bites tend to be severe. This results in greater risk for infection with relatively shorter incubation period. Because of their short stature, even bites on lower parts of the body may result in shorter incubation period
- Many times, because of the fear of painful injections that may be given, they even tend to hide the fact that they were bitten
- As children have soft skin, even minor scratches and trivial bites may result in category III exposures.

POSTEXPOSURE PROPHYLAXIS

In rabies endemic country like India, every animal bite is potentially suspected as a rabid animal bite; the treatment should be started immediately. Rabies has long incubation period. Prophylactic postexposure treatment should be started at the earliest to ensure that the individual will be immunized before the rabies virus reaches the nervous system. The classification of animal bite for postexposure prophylaxis (PEP) has been based on these World Health Organization recommendations (Table 1).

Vaccination status of the biting animal: history of rabies vaccination in an animal is not always a guarantee that the biting animal is not rabid. Animal vaccine failures may occur because of improper administration or poor quality of the vaccine, poor health status of the animal, and the fact that one vaccine dose does not always provide long-lasting protection against infection in dogs.

Observation of biting animal: the treatment should always be started immediately after animal bite. The treatment may be modified if animal involved (dog or cat) remains healthy throughout an observation period of 10 days by converting

TABLE 1: Type of contact, exposure, and recommended postexposure prophylaxis

Category	Type of contact	Type of exposure	Recommended postexposure prophylaxis
I	• Touching or feeding of animals • Licks on intact skin	None	None, if reliable case history is available
II	• Nibbling of uncovered skin • Minor scratches or abrasions without bleeding	Minor	Wound management + antirabies vaccine
III	• Single or multiple transdermal bites or scratches, licks on broken skin • Contamination of mucous membrane with saliva (i.e., licks)	Severe	Wound management + rabies immunoglobulin + antirabies vaccine

PEP to preexposure vaccination by skipping the vaccine dose on day 14 and administering it on day 28 while using Essen schedule. The observation period is valid for dogs and cats only. The natural history of rabies in mammals other than dogs or cats is not fully understood and therefore the 10-day observation period is not applicable.

Approach to Postexposure Prophylaxis

The PEP consists of three parameters and should be done simultaneously as per the category of the bites:

1. Management of animal bite wound(s)
2. Passive immunization: rabies immunoglobulins (RIGs)
3. Active immunization: antirabies vaccines (ARVs).

Management of Animal Bite Wound

Wound toilet: since the rabies virus enters the human body through a bite or scratch, it is imperative to remove as much saliva as possible. Since the rabies virus can persist and even multiply at the site of bite for a long time, wound toilet must be performed even if the patient reports late (Table 2).

Prompt and gentle thorough washing with soap or detergent and flushing the wound with running water for 10 minutes can do this.

The application of irritants is unnecessary and damaging. In case irritants have been applied on the wound, enough gentle washing with soap or detergent to remove the extraneous material, especially oil, should be done followed by flushing with copious amount of water for 10 minutes immediately.

Application of antiseptic: after thorough washing and drying the wound, any one of the available chemical agents should be applied, viz.: povidone iodine (solution), alcohol, chloroxylenol, chlorhexidine gluconate, and cetrimide solution in appropriate recommended dilution.

Local infiltration of RIGs: in category III bites, RIG should be infiltrated in the depth and around the wound to inactivate the locally present virus as described below.

Suturing of wound: it should be avoided as far as possible. If surgical intervention is unavoidable, minimum loose sutures should be applied after adequate local treatment along with proper infiltration of RIGs.

Tetanus toxoid injection (anti-tetanus prophylaxis): this should be given to those children who had not received a booster dose. A properly immunized child can only take one dose of tetanus toxoid if there is a lapse of a period of 5 years from the last dose of tetanus toxoid.

To prevent sepsis in the wound, a suitable course of an antibiotic may be recommended.

Rabies Immunoglobulin

The RIG provides passive immunity to tide over the initial phase of the infection.

Two types of RIGs are available:

1. Equine rabies immunoglobulin (ERIG): it is of heterologous origin raised by hyperimmunization of horses. The currently manufactured ERIGs are highly purified and enzyme refined, with these preparations, the occurrence of adverse reaction has been significantly reduced.
2. Human rabies immunoglobulins (HRIGs): as it is homologous, HRIG is free from the side effects encountered in a serum of heterologous origin, and because of their longer half-life, are given in half the dose of equine antirabies serum.

Dose of rabies immunoglobulins:

- The dose of ERIG is 40 IU/kg body weight of patient and is given after testing for sensitivity, up to a maximum of 3,000 IU. The ERIG produced in India contains 300 IU/mL
- The dose of the HRIG is 20 IU/kg body weight (maximum 1,500 IU). HRIG does not require any prior sensitivity testing. HRIG preparation is available in concentration of 150 IU/mL.

Administration of immunoglobulins: as much of the calculated dose of RIG as is anatomically feasible should be infiltrated into and around the wounds. Remaining, if any, after all wounds have been infiltrated, should be administered by deep intramuscular (IM) injection at an injection site distant from the vaccine injection site. The total recommended dose of immunoglobulin must not be exceeded as it may suppress the antibody production by the vaccine.

If immunoglobulin was not administered when vaccination was begun, it can be administered up to the seventh day after the administration of the first dose of vaccine.

In circumstances where no immunoglobulins are available, greater emphasis should be given to proper wound toileting followed by Essen schedule of cell-culture vaccine (CCV) with double dose on day 0 at two different sites intramuscularly (0 day: 2 doses on left and right deltoid, following the single

TABLE 2: Do's and don'ts of wound management

Step of wound management	Purpose
Do's	
Physical wash under running tap water for at least 10 minutes	Mechanical removal of virus from the wound
Chemical washing the wound with soap and water, dry, and apply disinfectant	Inactivation of the virus
Biological infiltration of immunoglobulins in the depth and around the wound in category III exposures	Neutralization of the virus
Don'ts	
Touch the wound with bare hand	
Apply irritants like soil, chilies, oil, herbs, chalk, betel leaves, etc.	

dose on each day, i.e., day 3, 7, 14, and 28). It is emphasized that doubling the first dose of CCV is not a replacement to RIG. A full course of vaccine should follow thorough wound cleansing and passive immunization.

Antirabies Vaccines

Active immunization is achieved by administration of safe and potent CCVs or purified duck embryo vaccines (PDEV). The dosage schedule of cell culture rabies vaccine (CCV/CCRV) is same irrespective of the body weight or age of the children.

- Storage and transportation: it is recommended that these vaccines should be kept and transported at a temperature range of 2–8°C. Freezing does not damage the lyophilized vaccine but there are chances of breakage of ampoule containing the diluent. Liquid vaccines should never be frozen
- Reconstitution and storage: the lyophilized vaccine should be reconstituted with the diluent provided with the vaccine immediately prior to use. In case of unforeseen delay it should be used within 6–8 hours of reconstitution.

Intramuscular regimen: the currently available vaccines and regimens in India for IM administration are described below.

- Antirabies vaccines:
  - Cell-culture vaccines:
    - Human diploid cell vaccine: produced locally in private sector
    - Purified chick embryo cell vaccine: produced locally in private sector
    - Purified vero-cell rabies vaccine: imported and produced locally in public and private sectors
  - Purified duck embryo vaccine:
    - Produced locally in private sector.

Note: All CCRVs and purified duck embryo vaccine used for PEP should have potency (antigen content) greater than 2.5 IU/dose.

- Regimen:
  - Essen schedule (5-dose IM regimen): the course for PEP should consist of IM administration of 5 injections on day 0, 3, 7, 14, and 28. Day 0 indicates date of first injection
  - Site of inoculation: the anterolateral thigh region is ideal for the inoculation of these vaccines in infants and younger children, whereas the older children can take in deltoid regions. Gluteal region is not recommended because the fat present in this region retards the absorption of antigen and hence impairs the generation of optimal immune response.

Intradermal (ID) regimens: it consists of administration of a fraction of IM dose of CCVs on multiple sites in the layers of dermis of skin. The use of ID route leads to considerable savings in terms of total amount of vaccine needed for full pre- or postexposure vaccination, thereby reducing the cost of active immunization. In ID route, small amount (0.1 mL) of rabies vaccines/antigen is deposited in the layers of the skin at two or more sites:

- Intradermal vaccine regimen:
  - Updated Thai Red Cross Schedule (2-2-2-0-2): this involves injection of 0.1 mL of reconstituted vaccine per ID site and on two such ID sites per visit (one on each deltoid area, an inch above the insertion of deltoid muscle) on day 0, 3, 7, and 28. The day 0 is the day of first-dose administration of intradermal rabies vaccines (IDVR) (ID inoculation of ARV) and may not be the day of rabies exposure/animal bite
  - Antirabies treatment centers which meet the following criteria may use ID administration:
    - Have adequately trained staff to give IDRV
    - Can maintain cold chain for vaccine storage
    - Ensure adequate supply of suitable syringes and needles for ID administration
    - Are adequately well versed in management of open vial and safe storage practices.

Postexposure Therapy for Previously Vaccinated Children

Children who have previously received full PEP or preexposure vaccination (either by IM or ID routes) with a potent CCV should now be given only two booster doses: IM (0.5 mL/1 mL)/ ID (0.1 mL at 1 site) on day 0 and 3 irrespective of the duration of previous vaccination. Proper wound toilet should be done. Treatment with RIG is not necessary.

Preexposure Vaccination of Children

As rabies is a 100% fatal disease and children constitute a special risk for getting the infection, it may be advisable to vaccinate children after they attain the age of 3 years and start playing in the streets and may come in contact with street or pet dogs.

Schedule of Preexposure Vaccination

- Intramuscular: 3 doses of any CCVs (1 mL or 0.5 mL depending on the brand) administered on the anterolateral thigh on day 0, 7, and 28
- Intradermal: the dose is same for all vaccine brands and 0.1 mL is administered ID over the deltoid on day 0, 7, and 28.

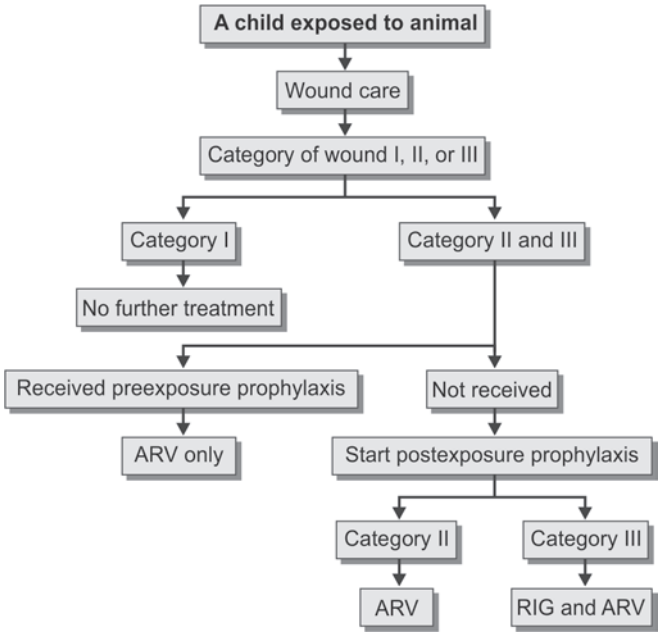
The management of children exposed to animal bites is shown in algorithm 1.

Clinical Pearls

- The transmitting animal of rabies is dog in more than 95% cases
- Rabies is fatal once symptoms of the disease develop, but it is almost 100% preventable if prophylactic measures are instituted soon after the exposure
- Intradermal rabies vaccination is given in state run rabies clinics, where many people come for rabies vaccine daily
- Rabies immunoglobulins is not needed for person who have received full course of rabies vaccine.

ALGORITHM 1

Algorithm for management of children exposed to animal bites



ARV, antirabies vaccines; PEP, postexposure prophylaxis; RIG, rabies immunoglobulins.

KEY POINTS

- ☞ In rabies endemic country like India, every animal bite is potentially suspected as a rabid animal bite the treatment should be started immediately
- ☞ Children have soft skin, therefore, even minor scratches and trivial bites may result in category III exposures
- ☞ Prompt and gentle thorough washing with soap or detergent and flushing the wound with running water for 10 minutes
- ☞ Children above 3 years of age may be routinely given preexposure prophylaxis of antirabies vaccines.

SUGGESTED READINGS

1. Sudarshan MK. (2003). Assessing burden of rabies in India: WHO sponsored National Multi-centric Rabies Survey. [online] Available from: rabies.org.in/rabies-journal/rabies-06/SpecialArticle1.htm. [Accessed November, 2015].
2. Sudarshan MK. Rabies. In: Parthasarathy A, Kundu R, Agrawal R, et al. (Eds). Textbook of Pediatric Infectious Diseases, 1st edition. New Delhi, India: Jaypee Brothers Medical Publishers; 2013.
3. World Health Organization. WHO Expert Consultation on Rabies: First Report. Technical Report Series 931. Geneva, Switzerland: World Health Organization; 2005.
4. World Health Organization. WHO Recommendations on Rabies Post-exposure Treatment and the Correct Technique of Intra-dermal Immunization against Rabies. Geneva, Switzerland: World Health Organization; 1997.

CHAPTER 29

Adverse Event Following Immunization

Amar J Chitkara

INTRODUCTION

Childhood morbidity and mortality has witnessed tremendous decrease following widespread immunization in the last 30–40 years across the globe. Many new vaccines are being developed and introduced in both the public and private sectors. Though the vaccines are of documented safety and efficacy, yet infrequently have adverse events. These adverse events can be a strong deterrent to the acceptability of vaccines; hence it is imperative to have a comprehensive surveillance system to address these concerns, especially with the introduction of many new vaccines/products and that too in a country with 27 million births per year and an extensive expanded program of immunization with constraints of medical care access. The adverse event following immunization (AEFI) is defined as "a medical incident that takes place after immunization, causes concern, and is believed to be caused by the immunization".

WHY REPORT ADVERSE EVENT FOLLOWING IMMUNIZATION?

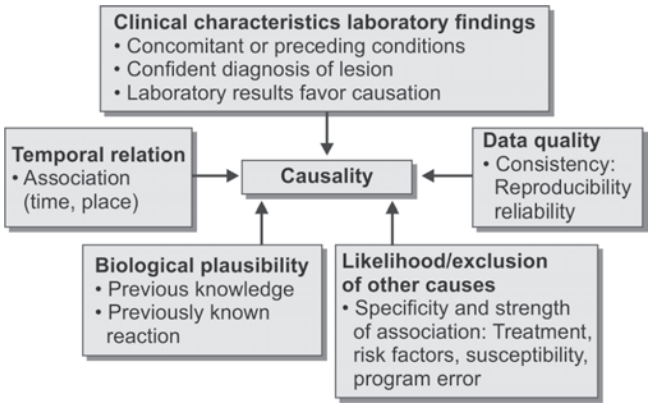
Vaccines are always administered to healthy infants and children to provide protection against dreadful diseases, hence any alteration in health with a temporal association with the vaccine be it fever, erythema, local pain and swelling, or a major event leading to disability, hospitalization, or death, erodes the confidence of the caregivers in the program and any nonacceptance can have serious outcomes as regards morbidity and mortality by vaccine preventable deaths (VPDs). Ironically, with widespread vaccination, the disease burden decreases and even mild AEFI become noticeable.

NATIONAL ADVERSE EVENT FOLLOWING IMMUNIZATION PROGRAM

Though started along with Universal Immunization Program in 1985, the real thrust started only in 2005 in collaboration with the World Health Organization (WHO)/National Polio Surveillance Project, India. Operational guidelines were developed and disseminated widely across the country in the public sector by organizing multiple workshops. The program was further strengthened in 2010 with the highest AEFI reports during the year. The initiative by the Indian Academy of Pediatrics (IAP) to collaborate with the national program has been a welcome step. The detailed operational guidelines and standard operating procedures are available in the public domain as well as print. The cases are then taken up for causality assessment as per the standard WHO protocol (Algorithm 1).

ALGORITHM 1

World Health Organization: Causality assessment of serious adverse event following immunizations



WHAT TO REPORT

Serious AEFI, such as death, disability, and hospitalization, need to be reported immediately while minor AEFI, such as fever, local reactions, etc., are reported through monthly reports in the public health. The reporting hierarchy and the timelines are given in algorithm 2. From the programmatic

TABLE 1: Types of adverse event following immunizations

Types of adverse event	Examples
Vaccine reaction	High grade fever following diphtheria, pertussis, and tetanus toxoids vaccination, anaphylaxis
Program error	Bacterial abscess due to unsterile injection/wrong diluent
Coincidental	Pneumonia after oral polio vaccine
Injection reaction	Fainting spell after immunization
Unknown	–

purpose, the AEFIs are classified into five broad categories of AEFI: (i) programmatic error, (ii) vaccine reaction, (iii) injection reactions, (iv) coincidental, and (v) unknown (Table 1).

REPORTING FROM PRIVATE SECTOR

It has been estimated that about 9% of the national population gets vaccinated at private facilities and there exists a considerable heterogeneity varying from 10 to 30%, especially being high in urban and metros across the country. The AEFI reporting from private sector has been exceptionally low because of a fear of reporting and harassment following the event. It should also be noted that since all new vaccines evolve from the private sector, the AEFI from this sector has a very high potential for assessing the safety of these vaccines. Since 2011, IAP has taken an initiative to collaborate with national AEFI program to encourage reporting. The infectious disease surveillance, a web and SMS-based surveillance of VPDs has a built in portal of reporting AEFI that follows the standard operating procedures. The information automatically reaches the concerned district immunization officer (DIO), state immunization officer, and Ministry of Health and Family Welfare (MoHFW) for appropriate action. Also, the fear and anxiety of IAP members in reporting has been allayed to a great extent by official communication and talks with MoHFW in this regard. The doctors can also report to their district immunization officers, medical officer, of nearest primary health center directly. The event is then investigated by DIO and the local AEFI committee; however, the reporting physician is expected to cooperate. The keyword remains creating awareness about utility of AEFI reporting and allaying fears associated with reporting. An increased collaboration with the various AEFI committees and nominating the practicing physicians to these committees can further augment national AEFI program.

Clinical Pearl

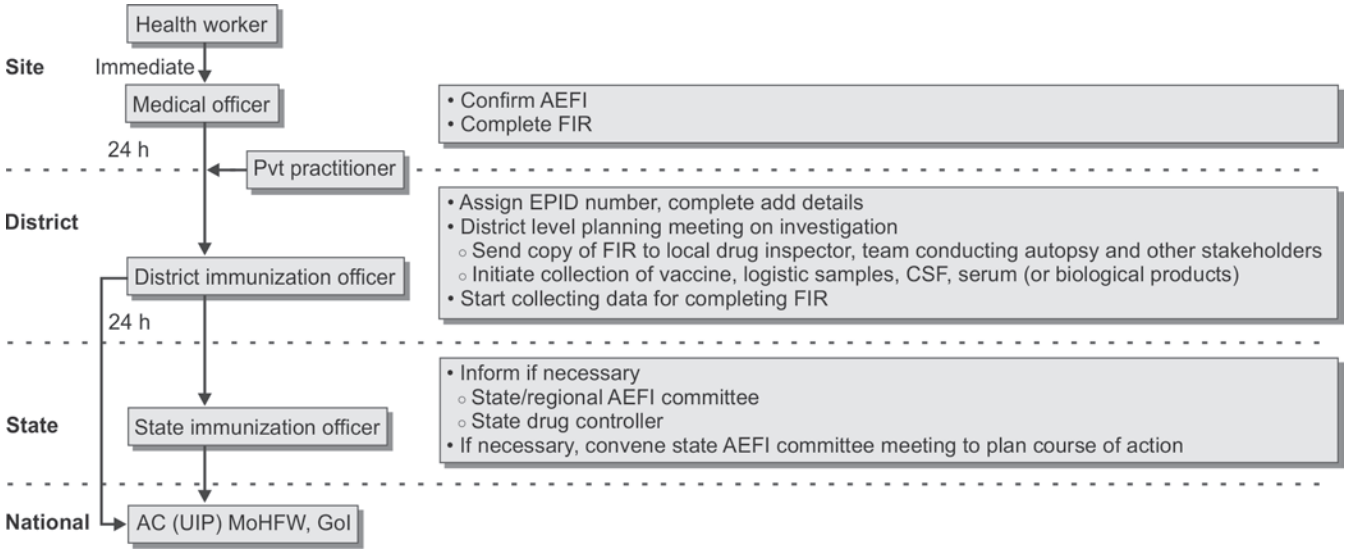
- Report adverse event following immunization and feel safe.

THE WAY FORWARD

- Collaboration with all professional bodies who vaccinate their patient's across all ages to report AEFI
- Create awareness amongst medical fraternity about the strengths of AEFI reporting to evaluate safety aspects of vaccines used and available currently. This can be achieved by a concerted effort through the continuing medical educations, conferences, and print publications of various professional organizations
- National, state, and district AEFI committees to have representatives from private sector to instill confidence amongst reporting physicians

ALGORITHM 2

Reporting framework and timelines



AEFI, adverse event following immunizations; Pvt, private; CSF, cerebrospinal fluid; AC, assistant commissioner; UIP, Universal Immunization Program; MoHFW, Ministry of Health and Family Welfare; GoI, Government of India.

- Creating user friendly reporting network, especially an E-network like IDSURV.org and promoting public private partnership towards achieving this
- Inculcate confidence amongst practicing doctors in reporting AEFI by strong assurance from the MoHFW and state health departments regarding no harassment following these reports.

SUGGESTED READINGS

1. World Health Organization (WHO), United Nations Children's Fund (UNICEF), World Bank. State of World Vaccines and Immunization. 3rd ed. Geneva, Switzerland: World Health Organization; 2009.
2. Centers for Disease Control and Prevention (CDC). Global routine vaccine coverage, 2010. MMWR Morb Mortal Wkly Rep. 2011;60(44):1520-2.
3. Black RE, Counsens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375(9730):1969-87.
4. World Health Organization. Surveillance of Adverse Events following Immunization: Field Guide for Managers of Immunization Programs. Geneva, Switzerland: World Health Organization; 1997.
5. World Health Organization. Aide Memoir on AEFI investigation. Geneva, Switzerland: World Health Organization; 2005.
6. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The vaccine adverse event reporting system (VAERS). Vaccine. 1994;12(6):542-50.
7. Ministry of Health and Family Welfare (MoHFW), Government of India (GoI). Adverse Events Following Immunization: Surveillance and Response Operational Guidelines. 2006.
8. Ministry of Health and Family Welfare (MoHFW), Government of India (GoI). Adverse Events Following Immunization: surveillance and response operational guidelines. 2010.
9. Ministry of Health and Family Welfare, Government of India (GoI). Adverse Events Following Immunization: surveillance and response Standard operating procedures. 2010.
10. Ministry of Health and Family Welfare (MoHFW), Government of India (GoI). Multi Year Strategic Plan (MYP) for UIP of India 2005-10. 2010.

SECTION 4: OFFICE EMERGENCIES

CHAPTER 30

Approach to Respiratory Distress in Children

Narendra R Nanivadekar

INTRODUCTION

Respiratory distress is one of the most common complaints presenting to the pediatric emergency department. It requires a rapid yet systematic assessment to facilitate diagnosis and quick efficient management, because many conditions causing respiratory distress have the potential to lead to respiratory failure. Thus, a systematic approach can help us to recognize respiratory distress sufficiently early, even before it progresses to respiratory failure, and initiate appropriate supportive and specific management which can dramatically improve the outcome.

APPROACH

This section discusses the diagnostic approach to respiratory distress. Management of respiratory distress is dealt with in another section subsequently.

Initial Impression

The first step is a quick audiovisual assessment done within seconds of establishing contact with the child. The aim is to identify the need for cardiopulmonary resuscitation (CPR), and prioritize interventions before proceeding further with a detailed systematic assessment (Table 1).

This is followed by detailed evaluation which consists of primary, and secondary assessments and diagnostic tests. This helps us to identify the type and severity of the problem.

TABLE 1: Initial impression

	Initial impression
Consciousness	Level of consciousness (e.g., unresponsive, irritable, alert)
Breathing	Increased work of breathing, absent/decreased respiratory effort, or abnormal sounds heard without auscultation
Color	Abnormal skin color such as cyanosis, mottling, pallor

Primary Assessment

Primary assessment is a hands-on evaluation of airway, breathing, circulation, disability, and exposure, which, includes vital signs and pulse oximetry.

Airway

Airway patency can be checked by looking for the movement of the chest and abdomen and listening for the air movement and breath sounds (Table 2).

A child with a foreign body airway obstruction may require an advanced airway technique like laryngoscopy or bronchoscopy. Increased inspiratory effort with retractions, abnormal inspiratory sounds (snoring or high-pitched stridor) suggests that the child has upper airway obstruction (UAO). Episodes where no airway or breath sounds are present despite respiratory effort may suggest complete airway obstruction.

Breathing

Evaluation of breathing is helpful to diagnose majority of causes of respiratory distress. Evaluation includes:

- Respiratory rate
- Effort
- Chest expansion and air movement

TABLE 2: Assessment of the airway

Observation	Inference (airway status)	Implication
Normal chest movement and silent breathing	Clear	Open and unobstructed
Stridor, gurgling, snoring +/– suprasternal retractions	Partially obstructed/ maintainable	Maintained by simple measures like position, suction, etc.
No chest movement or breath sounds	Complete obstruction/not maintainable	Needs advanced measures like intubation

- Lung and airway sounds
- O_2 saturation by pulse oximetry.

Respiratory rate should be evaluated before the hands-on evaluation as anxiety and agitation will make it difficult to assess.

Children with respiratory distress are typically tachypneic. Though the normal respiratory rate varies with age, for practical purposes, at any age respiratory rate greater than 60 indicates abnormality. Though nonspecific, it is the first sign of respiratory distress. Quiet tachypnea (with normal respiratory effort) may be due to nonpulmonary causes like fever, anemia, pain, sepsis, congestive cardiac failure, or mild metabolic acidosis. Bradypnea may be due to either neuromuscular weakness primarily or after persistent tachypnea leading to fatigue secondarily. Either way it is an ominous sign. Occasionally, it may be due to central causes. Any respiratory rate below 10 per minute requires further evaluation.

Clinical Pearl

- Bradycardia when associated with other signs of decreased perfusion, most commonly indicates hypoxia, and is an ominous sign demanding urgent action.

Respiratory effort: usually, a child with respiratory distress will have increased effort. Increased effort will be seen as nasal flaring, use of other accessory muscles, retractions, head bobbing or see-saw respirations. Additionally, we may encounter prolonged inspiration or expiration, open mouth breathing, or gasping. Grunting indicates that the child has severe respiratory distress.

Nasal flaring will be seen commonly in infants and younger children. Subcostal, substernal, or intercostal retractions indicate mild distress whereas supraclavicular, suprasternal, or sternal retractions suggest severe distress. The type of retractions may also vary with the site of disease—predominant suprasternal retractions are seen in UAO, intercostal retractions in parenchymal lung disease, and subcostal retractions in lower airway obstruction (LAO) (Table 3).

Head bobbing is a sign of respiratory failure and warrants an early intervention. Similarly see-saw respiration is characteristic of neuromuscular weakness in infants and children and also indicates that the patient is getting fatigued fast and needs urgent intervention.

TABLE 3: Abnormal sounds and their explanation

Stridor	An inspiratory, coarse, high-pitched sound	Upper airway obstruction (extrathoracic)
Grunting	Expiratory short and low-pitched sound	Smaller airway collapse, alveolar collapse, or both
Wheezing	Musical sound heard chiefly during expiration.	Lower airway obstruction, chiefly smaller airways (intrathoracic)
Crackles	Sharp, crackling sounds	Wet in a lung tissue disease like pneumonia or pulmonary edema or dry as in atelectasis or interstitial lung disease
Gurgling	Coarser sounds	Secretions, vomitus, or blood

Chest wall expansion: decreased or asymmetric chest wall expansion can be due to inadequate effort, airway obstruction, atelectasis, pneumothorax, hemothorax, pleural effusion, mucus plug, or foreign, body aspiration. By and large the diseased side would be moving less.

Air movement: while normal inspiratory sounds will be soft quiet noises with observed inspiratory effort, expiration may be short and quiet, at times inaudible. Presence of abnormal sounds along with respiratory distress often gives clue to the diagnosis.

Pulse oximeter can be considered as another vital sign which may indicate hypoxia long before cyanosis or bradycardia is evident. Preferably it should be done continuously during stabilization of the patient.

Circulation

Circulation assessment consists of evaluation of heart rate and rhythm, pulses (both central and peripheral), capillary refill time, skin color and temperature, and blood pressure. This needs to be done to complete the overall evaluation of the patient and to categorize whether the child also has a circulatory disorder which may be secondary to the respiratory insufficiency or may be coexisting.

Disability

The aim is to assess the neurological perfusion/function, either by the alert, voice, pain, unresponsive (AVPU scale) or the Glasgow Coma Scale.

Exposure

This will give an idea about the presence of bruises, petechiae, and the body temperature of the child.

Secondary Assessment

This is to be done after primary assessment is completed and appropriate interventions have been instituted to stabilize the child. It comprises of a focused history and focused physical examination. The focused history can be best remembered by the mnemonic SAMPLE: Signs and symptoms, Allergies, Medications, Past medical history, Last meal, Events. This can be followed with a focused physical examination. This should include careful assessment of the primary area of concern of the illness or injury.

Diagnostic Tests

These are performed to confirm the diagnosis or to determine the severity of illness. They are chiefly laboratory evaluation like complete blood count, arterial blood gas, biochemistry, and radiology like X-ray, computed tomography scan, etc.

At any point of time, if a life-threatening situation is encountered, one must initiate CPR (Table 4).

In view of the potential life-threatening situation, a detailed history taking may be done only after the child is stabilized (Table 5).

TABLE 4: Signs of life-threatening illness in a child with respiratory distress

Airway	Complete or severe airway obstruction
Breathing	Apnea/bradypnea, markedly increased work of breathing
Circulation	Absence of detectable pulse, poor perfusion, hypotension, bradycardia
Disability	Unresponsiveness
Exposure	Significant hypothermia or bleeding, petechiae or purpura consistent with septic shock

TABLE 5: Additional diagnostic evaluation that may help in respiratory distress

History	Time frame	Acute, recurrent, or chronic nature of progression
	Associated symptoms	Cough, fever, rash, chest pain
	Preceding events	Choking, foreign body inhalation, trauma, exposure to chemical or environmental irritants
	Family history	Exposure to infections, tuberculosis, atopy
Diagnostic workup	Direct laryngoscopy	If upper airway obstruction is detected/suspected
	X-rays	Chest, lateral neck, and decubitus
	Arterial blood gas	Hypoxia (PaO_2 <60 mmHg) Hypercarbia ($PaCO_2$ >40 mmHg) and SaO_2 monitoring
		Acidosis (pH <7.3), alkalosis (pH >7.5)
	Sepsis workup	Blood counts and culture studies

PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, saturated oxygen of arterial blood.

GENERAL APPROACH TO A CHILD IN RESPIRATORY DISTRESS

Children, who present with breathlessness to the emergency department, are likely to be suffering from respiratory, cardiac, or metabolic conditions. The history is extremely useful in deciding the probable etiology of breathlessness. A careful evaluation of what the chief complaint/s is/are, as well as the onset, duration, and progress of the same, provide valuable clues. Specific findings on physical examination can further suggest the probable diagnosis.

The most common causes of breathlessness are "respiratory". If one identifies the problem to be primarily respiratory, after the assessment one should be able to decide the physiological type of the problem and the severity of the respiratory problem in the patient, which may help us in initiating a specific treatment.

Based on the severity, respiratory problems can be classified into respiratory distress and respiratory failure (Table 6).

TABLE 6: Categorization by type and severity

	Type	Severity
Respiratory distress	• Upper airway obstruction • Lower airway obstruction • Lung tissue disease • Disordered control of breathing	• Respiratory distress • Respiratory failure

Respiratory Distress

Respiratory distress is a clinical state characterized by abnormal respiratory rate or effort. It is commonly characterized by tachypnea and increased respiratory effort (increased work of breathing). Thus, it is a physiological state in which the child is trying to maintain adequate gas exchange despite a respiratory pathology, by increasing the rate and effort. However, in the absence of effective intervention, a point may be reached at which adequate gas exchange can no longer be maintained in spite of the increased rate and effort. When this happens, the child is said to have progressed into the state of respiratory failure.

During this progression, at times, the respiratory rate and effort may actually fall secondary to respiratory fatigue; thus, at times, severe respiratory distress is clinically evident in the form of hypoventilation, and is an indication of respiratory failure.

Respiratory Failure

Respiratory failure is defined as inadequate oxygenation, ventilation, or both. Since respiratory distress and respiratory failure represent a continuum, respiratory failure can be identified clinically by recognizing definite clinical signs of hypoxemia or hypercarbia, in addition to the signs of respiratory distress (Table 7).

Though neurological illnesses can lead to "breathlessness", they are unlikely to present with breathlessness as the only/chief complaint. Whether the neurological illness is acute (head injury, encephalitis, or meningitis) or subacute/chronic (Guillain-Barré syndrome, or spinal muscular atrophy) there will usually be a prominent history of the initiating/primary events which will suggest the possible cause of hypo/hyperventilation. It is important to note that alteration of sensorium in a child with hypo/hyperventilation does not necessarily mean a primary neurological illness; it

TABLE 7: Clinical signs of respiratory distress and failure

Respiratory distress	Respiratory failure
• Tachypnea • Tachycardia • Increased respiratory effort • Abnormal airway sounds • Pale cool skin • Changes in mental status	• (Early) Marked tachypnea/tachycardia • (Late) Bradypnea, apnea/bradycardia • Increased/decreased/no respiratory effort • Cyanosis agitation, incessant crying, fighting the oxygen mask or combativeness, diaphoresis • Stupor/coma

could be the end result of any progressive cardiorespiratory pathology as well. Similarly, though see-saw respiration is classically seen in neuromuscular weakness, it could be seen as a preterminal event in any severe respiratory pathology. Therefore, as mentioned above, the history is crucial.

If the clinical signs suggest that the type of respiratory problem is "lung tissue disease", the more common causes are pneumonia, acute respiratory distress syndrome (ARDS), and cardiac causes. The detection of cardiac failure, shock, or cyanosis may suggest a cardiac cause of breathlessness (Table 8).

Clinical Pearl

- In general, management of respiratory distress does not require an immediate chest radiograph; most conditions are apparent clinically and waiting for radiography to initiate treatment can waste precious time.

Approach to a child with breathing difficulty is represented in algorithm 1.

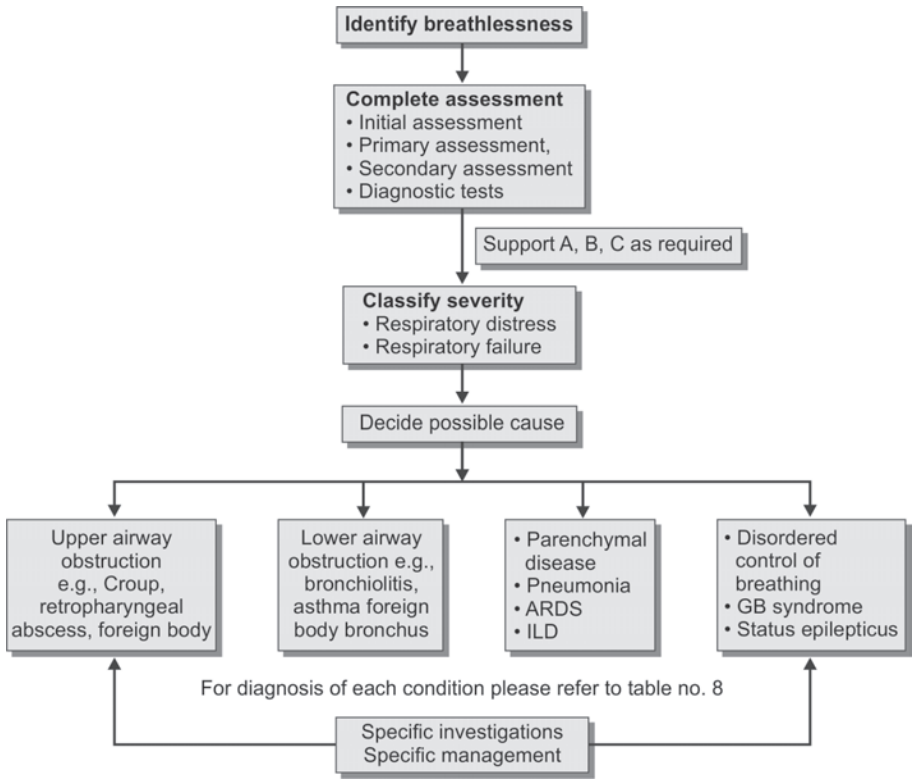
TABLE 8: Diagnostic clues to the cause of breathlessness

"Type" of problem	Specific features	Common causes and their additional clues
Upperairway obstruction	• Stridor, a change in voice, e.g., hoarseness, the presence of a barking cough, drooling, suprasternal retractions	• Supraglottic—Epiglottitis, retropharyngeal abscess • Glottic—Acute laryngotracheobronchitis • Infraglottic—Bacterial tracheitis
Lowerairway obstruction	• Wheezing, a particularly increased expiratory effort, subcostal retractions	• Asthma—Acute onset, episodic/intermittent breathlessness; fever +/–, prominent cough. Bronchiolitis—infant, prodrome, seasonality, fever +/–
Lung tissue disease	• Grunting, crackles, diminished breath sounds	• Pneumonia—high fever, chest pain +/– • Pulmonary edema, ARDS (both usually secondary to other causes)
Disordered control of breathing	• History of primary illness, significant alteration of sensorium, variable respiratory rate (tachypnea alternating with bradypnea), and poor respiratory effort (shallow breathing, see-saw breathing)	• Neurological illnesses

RP, retropharyngeal; ARDS, acute respiratory distress syndrome.

ALGORITHM 1

Approach to a child with breathing difficulty



ARDS, acute respiratory distress syndrome; ILD, interstitial lung disease; GBS, Guillain-Barré syndrome.

KEY POINTS

- ☞ Initial assessment: appearance, work of breathing, circulation
- ☞ Manage/restore airway, breathing, circulation
- ☞ Provide high flow oxygen
- ☞ Immediate management of specific clinical condition
- ☞ Detailed clinical assessment to localize illness to respiratory system (upper airway obstruction, lower airway obstruction, and parenchymal illness), cardiovascular system or neurological illness
- ☞ X-ray chest is not mandatory in the initial stage in majority of the cases
- ☞ Specific investigations and treatment should be based on the likely cause identified on clinical evaluation
- ☞ Start cardiopulmonary resuscitation at any point a life-threatening event is encountered

SUGGESTED READINGS

1. Hazinski MF, Gonzals L, O'Neill L (Eds). BLS for Healthcare Providers. American Heart Association; 2006.
2. Manual For GEM Course. Indian Academy of Paediatrics.
3. Mathew JL, Singhi SC. Approach to a child with breathing difficulty. Indian J Pediatr. 2011;78:118-26.
4. Mathew JL. Examination of respiratory system. In: Gupta P (Ed). Clinical Methods in Paediatrics. New Delhi; 2009. pp. 183-218.
5. Meyburg J, Bernhard M, Hoffmann GF, Motsch J. Principles of emergency medical care. Dtsch Arztebl Int. 2009;106:739-47.
6. PALS Providers Manual, American Heart Association; 2011.
7. Rajesh VT, Singhi S, Kataria S. Tachypnoea is a good predictor of hypoxia in acutely ill infants under 2 months. Arch Dis Child. 2000;82:46-9.
8. Schuh S, Lalani A, Allen U, Manson D, Babyn P, Stephens D, et al. Evaluation of the utility of radiography in acute bronchiolitis. J Paediatr. 2007:150;429-33.
9. Singhi S, Mathew JL. Acute respiratory distress. In: Singh M (Ed). Medical Emergencies in Children, 4th edition. New Delhi: Sagar Publications; 2007. pp. 352-72.

CHAPTER 31

Recognition of Child in Shock

Kiran SK Vaswani

INTRODUCTION

Shock is a common cause of morbidity and mortality in children. Early recognition of shock and prompt intervention remains the cornerstone of intact survival. The objective of this chapter is:

- Early recognition of shock, by evaluating clinical signs of systemic perfusion and compensation
- To ascertain the type of shock: hypovolemic, distributive, cardiogenic, or obstructive.
- To assess the severity of shock, whether compensated or hypotensive

DEFINITION

Shock is a critical condition that results from inadequate tissue delivery of oxygen and nutrients to meet tissue metabolic demand, often, but not always characterized by inadequate peripheral and end-organ perfusion.

Lactic acid and waste products accumulate in the tissues as a result of anaerobic metabolism when oxygen delivery is compromised and a vicious cycle sets in as illustrated in the figure 1 below.

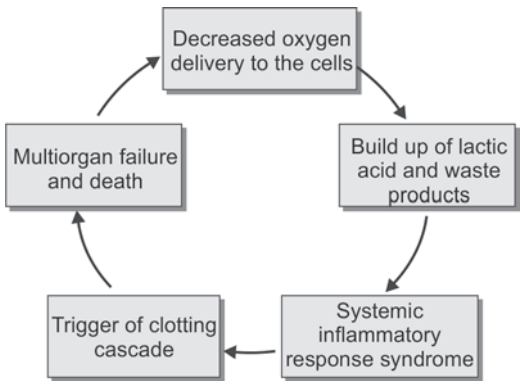


Fig. 1: Shock cycle

RECOGNITION OF SHOCK

For prompt and proper management of ill children, it is important to recognize:

- Shock is present
- Type of shock
- Severity of shock.

Recognizing Shock

Simple clinical evaluation of airway, breathing, circulation, disability, exposure (ABCDE) of a patient gives sufficient clues to recognition of shock and also type and severity of shock.

- Respiratory rate, effort, and sounds: tachypnea, a breathing rate that is more rapid than normal for age with or without signs of increased work of breathing, decreased air entry, asymmetrical chest rise, and crackles (crepitations), need to be looked for, along with pulse oximetry
- Heart rate and pulse quality: tachycardia is a resting heart rate that is faster than the normal range for a child's age. Tachycardia is body's first response and the main compensatory mechanism especially in infants.

Clinical Pearl

- Tachycardia should not be ignored though it does not always indicate shock.

Evaluation of pulses, both central and peripheral, gives vital information regarding perfusion (Table 1). Vasoconstriction

TABLE 1: Easily palpable central and peripheral pulses

Central pulses	Peripheral pulses
• Femoral • Brachial (in infants) • Carotid (in older children) • Axillary	• Radial • Dorsalis pedis • Posterior tibial

results in weak peripheral pulses while a low systemic vascular resistance (SVR) and increased blood flow to the skin in distributive shock results in bounding pulses.

Bradycardia, weak central pulses are relatively late features and sinister signs implying exhaustion of physiological compensatory mechanisms.

- Systolic blood pressure and pulse pressure: systolic blood pressure measured appropriately helps in assessing the severity of shock. It is important to realize that a normal or low systolic pressure is not a criterion to recognize shock. An observed decrease in systolic blood pressure of 10 mm Hg from baseline should prompt to evaluate further and identify shock
- Pulse-pressure: vasoconstriction manifests as narrow pulse pressure, less than 25% of systolic pressure in cold shock and a low SVR as wide-pulse pressure
- End-organ perfusion
  - Brain: level of consciousness is assessed on AVPU scale
    - A- Alert
    - V- Responsive to voice
    - P- Responsive to pain
    - U- Unresponsive

  Pupillary size and response to light, muscle tone, and seizures give vital clues to cerebral and brain-stem perfusion and function.
  - Skin: skin perfusion is assessed by examining three parameters—***c***olor, ***r***efill time, and ***t***emperature of skin (CRT)
    - Color: look for changes in skin color, pallor, cyanosis and, mottling (an irregular and patchy discoloration of skin)
    - Refill time: capillary refill time (CRT) is the time it takes for blood to return to tissue blanched by pressure. It increases in a neutral thermal environment, as skin perfusion decreases. Normal CRT is less than 2 seconds. It may be very rapid, flash, as in warm shock

Clinical Pearl

- Though a sluggish (color, refill time, and temperature of skin) may be a feature of shock, a normal or rapid CRT does not rule out shock. A rising fever or a cold environment will result in a prolonged CRT.

    - Temperature: skin temperature should be normal and consistent over the trunk and extremities. With decreased skin perfusion, skin becomes cool, hands and feet getting affected first. A temperature difference between "toe and tummy" indicates decreased perfusion. As the condition worsens, even trunk temperature drops. Temperature of skin also helps in monitoring improvement, as perfusion improves the line of demarcation moves distally
  - Kidneys: urine output is a simple and essential parameter to assess kidney perfusion. Children with shock have decreased urine output, less than 1 mL/kg/hr. An increase in the output reflects improved kidney perfusion. It is important to remember that initial urine output is not a reliable indicator of present status.
- Exposure: exposing one area at a time, avoiding discomfort and hypothermia, look for core temperature, fever and, evidence of trauma, burns, petechiae, purpura, rashes of "allergy", acute surgical emergencies like acute abdomen, torsion of testis (including one in an undescended testis), and poisoning.

A focused medical history, easy to recall by the mnemonic SAMPLE (Signs and symptoms, Allergies, Medicines given, Past medical history, Last meal, Events leading to the present illness) gives valuable information regarding the cause or other comorbid conditions to help tailor intervention strategy. For example, history of diarrhea, trauma, known allergies to food or medicines, premature birth, recent travel, a known case of congenital heart disease or arrhythmias, seizures, neuromuscular disease, diabetes, renal disease, or last menstrual period in an adolescent girl, can help identify the type of shock or need to modify drugs or dosages.

Certain laboratory tests can be crucial in recognition and management of shock. These include rapid bedside glucose, arterial blood gas, venous blood gas, hemoglobin concentration, arterial lactate, central venous or invasive arterial pressure monitoring, chest X-ray, electrocardiogram, echocardiogram, and abdominal ultrasound.

TYPES

Shock can be categorized into four basic types:

1 Hypovolemic
2 Distributive
3 Cardiogenic
4 Obstructive.

Shock can result from a variety of clinical causes, like decreased blood volume resulting from blood or fluid loss, cardiac-pump dysfunction, maldistribution of blood as in sepsis or anaphylaxis, and/or physical obstruction to blood flow.

Clinical Pearls

- Hypovolemic shock is characterized by "quiet tachypnea"
- Increased respiratory effort distinguishes cardiogenic from hypovolemic shock
- Children with cardiogenic shock may demonstrate retractions, grunting, and use of accessory muscles.
- Treatment of obstructive shock is cause-specific; however, the most critical task is prompt recognition
- Without early recognition and immediate treatment, obstructive shock rapidly progresses to cardiopulmonary failure and cardiac arrest.

SEVERITY

Compensated and Hypotensive Shock

Compensated shock is characterized by maintenance of systolic blood pressure within the normal range with signs of

inadequate tissue perfusion. The compensatory mechanisms try to maintain blood flow to the heart and brain, when oxygen delivery is limited.

Hypotensive shock represents failure or exhaustion of physiological responses to maintain systolic blood pressure and perfusion, that is, hypotension with poor perfusion. It is a late finding in most types of shocks and may signal impending cardiac arrest but can occur early in septic shock as a result of vasodilation by mediators.

Hypotension is defined by systolic blood pressure and age (Table 2).

TABLE 2: Definition of hypotension by systolic blood pressure and age

Age	Blood pressure
Term neonates	<60 mmHg
Infants (1–12 months)	<70 mmHg
Children 1–10 years of age	<70 mmHg + (child's age in years × 2) mmHg
Children >10 years	<90 mmHg

TABLE 3: Clinical features characteristic of type of shock

Clinical signs	Hypovolemic shock	Distributive shock	Cardiogenic shock	Obstructive shock
Patency	Airway open and maintainable/not maintainable			
Respiratory rate	Increased			
Respiratory effort	Normal to increased		Labored	
Breath sounds	Normal	Normal/crackles	Crackles, grunting	
Heart rate	Increased			
Peripheral pulse quality	Weak	Bounding or weak	Weak	
Systolic blood pressure	Compensated → Hypotensive			
Pulse pressure	Narrow	Variable	Narrow	
Skin color	Pale	Pale/flushed	Pale	
Capillary refill	Delayed	Variable	Delayed	
Peripheral temperature	Cool	Warm or cool	Cool	
Sensorium	• Irritable early • Lethargic late			
Urine output	Decreased			

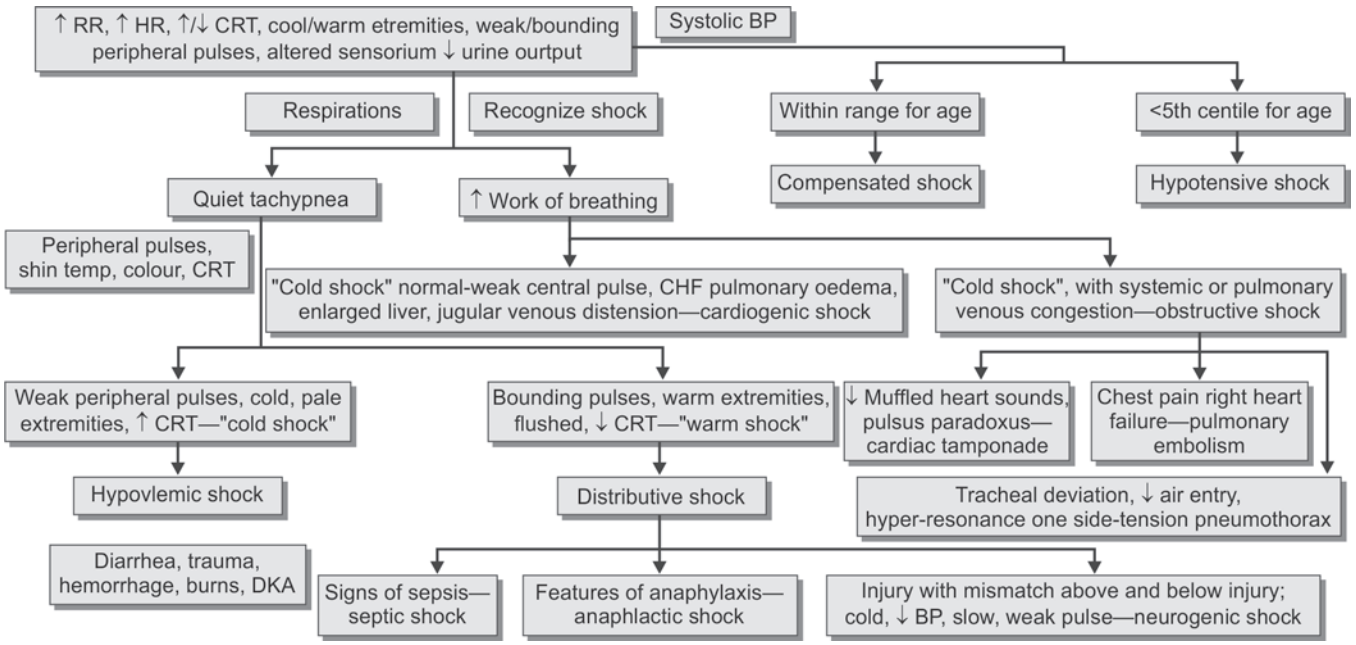
TABLE 4: Comprehensive table showing clinical examples, characteristic features and compensatory mechanisms in the course of different types of shock

Type of shock	Clinical examples	Characteristic features and compensatory mechanisms		
Hypovolemic shock	• Diarrhea, vomiting, large burns, hemorrhage, osmotic diuresis—DKA, third space losses	• Absolute deficiency of intravascular volume—↓preload leading to ↓ stroke volume and cardiac output • Tachycardia, ↑SVR, ↑cardiac contractility		• Most common cause of shock in children. • "Cold shock"
Distributive shock • Septic shock • Anaphylactic shock • Neurogenic shock	• Severe infections—caused by organisms or endotoxins	• Inappropriate distribution of blood volume	• Early in the course: • ↓SVR and ↑blood flow to the skin results in warm extremities and bounding peripheral pulses, wide pulse pressure—"warm shock" • Late phase: • Hypovolemia and/or myocardial dysfunction result in ↓COP • SVR can then ↑, resulting in • ↓blood flow to skin, cold extremities and weak pulses, narrow pulse pressure—"cold shock" • Septic shock most common distributive shock	
	• Anaphylaxis	• Pulmonary vasoconstriction		
	• High cervical spine injury	• Loss of vascular tone • Inability to ↑ HR in response to ↓BP		
Cardiogenic shock	• Congenital heart disease, myocarditis, arrhythmias, sepsis, poisoning/drug toxicity	• Myocardial dysfunction	• Marked tachycardia, ↑SVR, ↓COP	• ↑LV afterload • ↓renal flow with fluid retention • ↑respiratory effort
Obstructive shock	• Cardiac tamponade, tension pneumothorax, massive pulmonary emboli	• Cardiac output is impaired by physical obstruction to blood flow	• Signs of systemic or pulmonary venous congestion not consistent with hypovolemic shock and ↑respiratory effort	

DKA, diabetic ketoacidosis; SVR, systemic vascular resistance; HR, heart rate; BP, blood pressure; COP, colloid osmotic pressure; LV, left ventricular.

ALGORITHM 1

Recognition of shock



Though different types of shock are shown in this algorithm, it is impotant to realize that a given child may not present with any of these in isolation. One type of shock may progress to another type as condition progresses, as has been illustrated in tables 3 and 4.

RR, respiratory rate; HR, heart rate; CRT, capillary refill time; BP, blood pressure; DKA, diabetic ketoacidosis; CHF, congestive heat failure

It is important to realize that these threshold values were established in normal, resting children; and children with injury or serious illness would have increased blood pressure. So a low-normal range is abnormal in a seriously ill child.

At times, with poor perfusion and feeble distal pulse and cool extremities, blood pressure recording may not be feasible. Change in the level of consciousness, progressive tachypnea, and tachycardia indicate worsening status. Bradycardia and weak central pulses in a child with signs of shock are signs of impending cardiac arrest.

It is crucial to recognize the shock in the compensated stage and manage promptly. Though shock progression is unpredictable, it may take hours to deteriorate from compensated to hypotensive shock but only minutes for hypotensive shock to end up in cardiopulmonary failure and cardiac arrest.

Clinical Pearl

- Shock can be categorized but not diagnosed by blood pressure.

Shock can be categorised but not identified or defined by blood pressure.

KEY POINTS

- ☞ The presence of shock and the type of shock can be recognized by simple, systematic clinical examination
- ☞ Shock can exist and should be diagnosed even in the presence of normal blood pressure; the presence of hypotension only helps to categorize the severity of shock
- ☞ It is crucial to recognize shock before hypotension develops, so that prompt treatment can be instituted
- ☞ Majority of patients presenting to us in shock have, fortunately, "normal" blood pressure, giving us a window period to revive them
- ☞ Tachycardia should not be ignored; though it does not always indicate shock
- ☞ In acute illnesses, cold extremities demand prompt action.

SUGGESTED READINGS

1. Goldenhour Emergency Management (GEM) Course Manual. Indian Academy of Pediatrics. 2013.
2. Indian Pediatrics. Principles of Pediatric and Neonatal Emergencies, 3rd edition. New Delhi: Jaypee Brothers Medical Publishers; 2011.
3. PALS Provider Manual. American Academy of Paediatrics and American Heart Association. 2011.

CHAPTER 32

Croup

Bhavesh M Mithiya

INTRODUCTION

Croup is a common, primarily pediatric viral respiratory tract illness. As its alternative names (laryngotracheitis/laryngotracheobronchitis) indicate, croup generally affects the larynx and trachea with the maximal narrowing occurring in the upper, extrathoracic trachea, although this illness may also extend to the bronchi.

It is the most common etiology for hoarseness, cough, and onset of acute stridor in febrile children. As with all viral infections, the severity ranges widely, with the vast majority recovering without consequences or sequelae; however, it can be life threatening.

EPIDEMIOLOGY

It is most common in monsoon and early winter but may occur at any time of year. It is commonly seen in age group of 1–3 years, with peak during 2nd year of life. Boys are more affected than girls (2:1). Around 15% of children experience at least one episode, and 5% of children experience more than one episode.

ETIOLOGY

Parainfluenza viruses are the most common amongst all viruses, responsible for as many as 80% of croup cases, though it can be caused by many other viruses.

CLINICAL FEATURES

Croup begins with nonspecific respiratory symptoms, like rhinorrhea, sore throat, cough, and generally low grade fever (38–39°C); however in next 1–2 days, the characteristic signs of hoarseness, barking cough, and inspiratory stridor develop, often suddenly, along with a variable degree of respiratory distress. "Absence of drooling of saliva" clinically confirms presence of edema below the glottic area (which differentiates croup from supraglottic causes like epiglottis/retropharyngeal abscess) (Figs 1 to 3).

Stridor is common and this abnormal sound alarms parents enough to visit healthcare facility.

Stridor is an audible harsh, high-pitched sound produced by turbulent airflow through a partially obstructed upper airway (at the level of supraglottis, glottis, subglottis, and/or trachea).

During inspiration, airways that are easily collapsible (e.g., supraglottic region) are suctioned closed because of negative intraluminal pressure and are forced open during expiration.

Stridor can be heard in inspiration, expiration, or it can be biphasic (inspiratory and expiratory).

Inspiratory stridor suggests a laryngeal obstruction, whereas expiratory stridor suggests tracheobronchial obstruction. Biphasic stridor indicates either a subglottic or glottic anomaly.

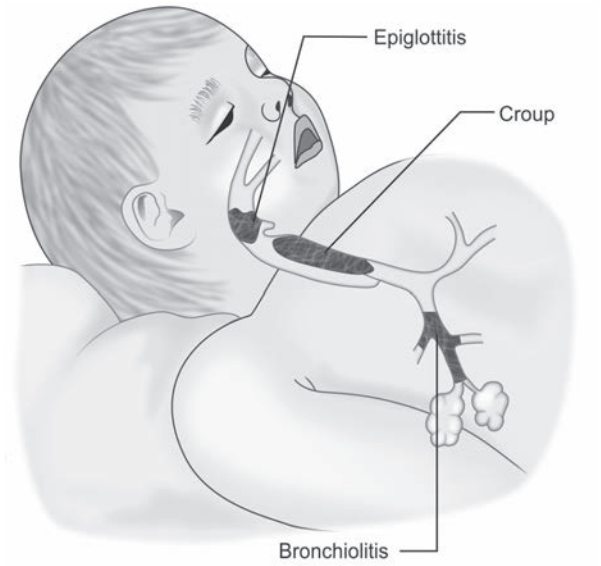


Fig. 1: Location of airway obstruction in epiglottitis, croup, and bronchilolitis

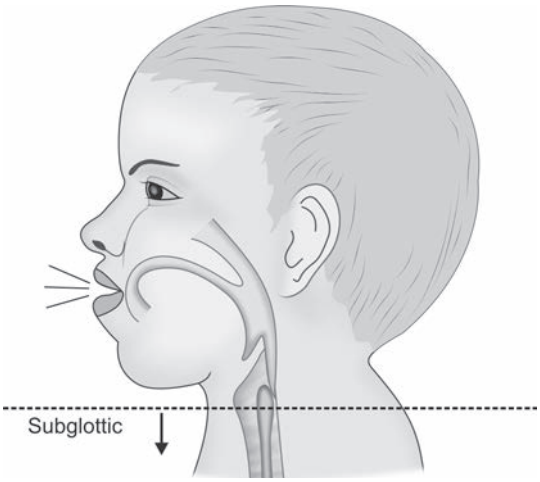


Fig. 2: Croup: inflammatory edema below the glottic area (subglottic edema)

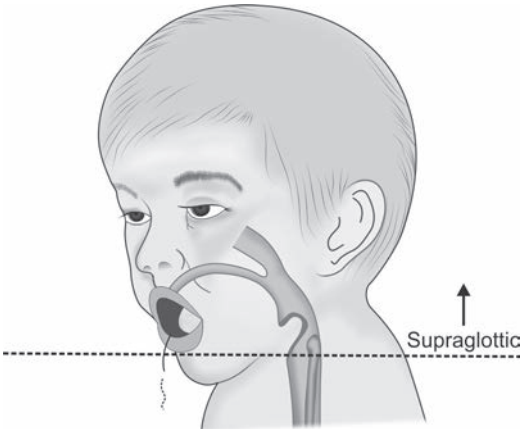


Fig. 3: Epiglottitis: inflammatory edema above the glottic area (supraglottic edema)

An acute onset of marked inspiratory stridor is one of the hallmarks of croup. The child with croup typically does not appear toxic.

Clinical Pearls

Upper airway obstruction
- Interferes mainly with inspiration
- Inspiratory stridor
- Severe retractions
- Croupy/brassy cough

Lower airway obstruction
- Interferes mainly with expiration
- Expiratory wheeze
- Mild retractions + prolonged expiration
- Repetitive cough.

SEVERITY OF CROUP

While most have only "barking" cough and hoarse cry, few have stridor on activity/agitation, and very few have audible stridor at rest with respiratory distress. Paradoxically, a severely affected child may have "quiet" stridor secondary to a greater degree of airway obstruction.

Various croup scores have been developed to assess the degree of respiratory compromise, but for practical purposes, it can be divided into mild, moderate, and severe disease.

A clinically useful croup severity assessment table has been developed by the Alberta Clinical Practice Guideline Working Group (Table 1).

DIFFERENTIAL DIAGNOSIS

Though certain conditions like congenital structural malformations can present with stridor, they are not acute. When a child presents with acute stridor, one needs to differentiate retropharyngeal (RP) abscess/epiglottitis from acute laryngotracheobronchitis (ALTB) by the presence of drooling of saliva in the former. Recurrent stridor is usually allergic and may occasionally be due to gastroesophageal reflux (GER).

INVESTIGATIONS

Croup is essentially a clinical diagnosis, based on presenting history/physical examination, and investigations rarely contribute. The complete blood count (CBC) is nonspecific.

Identifying the specific viral etiology is typically not necessary and also not available to most.

Arterial blood gas (ABG) measurements are unnecessary (unless respiratory fatigue), in fact it may worsen the airway obstruction due to excessive crying.

Typically X-ray is not needed to confirm the diagnosis of croup, and if at all, it is done to exclude other causes mimicking croup such as a radio-opaque foreign body, or an RP abscess.

If done, X-ray (AP) of the soft tissues of the neck classically reveals a steeple sign (also known as a pencil-point sign),

TABLE 1: Croup severity assessment

Mild severity	Occasional barking cough, no audible stridor at rest, and either no or mild suprasternal and/or intercostal retractions
Moderate severity	Frequent barking cough, easily audible stridor at rest, and suprasternal and sternal wall retractions at rest, with no or minimal agitation
Severe severity	Frequent barking cough, prominent inspiratory (and occasionally expiratory) stridor, marked sternal wall retractions, significant agitation and distress
Impending respiratory failure	Barking cough (often not prominent), audible stridor at rest, sternal wall retractions may not be marked, lethargy or decreased consciousness, and often dusky appearance without supplemental oxygen support

which signifies subglottic narrowing, whereas the lateral neck view may reveal a distended hypopharynx (ballooning) during inspiration (see the images below) (Figs 4 and 5). However, these findings may not be seen in upto 50% cases.

A steeple sign may also be observed in patients without croup, such as epiglottitis, thermal injury, angioedema, or bacterial tracheitis.

Laryngoscopy and/or bronchoscopy are indicated only in unusual circumstances (e.g., the course of illness is not typical or recurrent croup to rule out an underlying anatomic or congenital disorder).

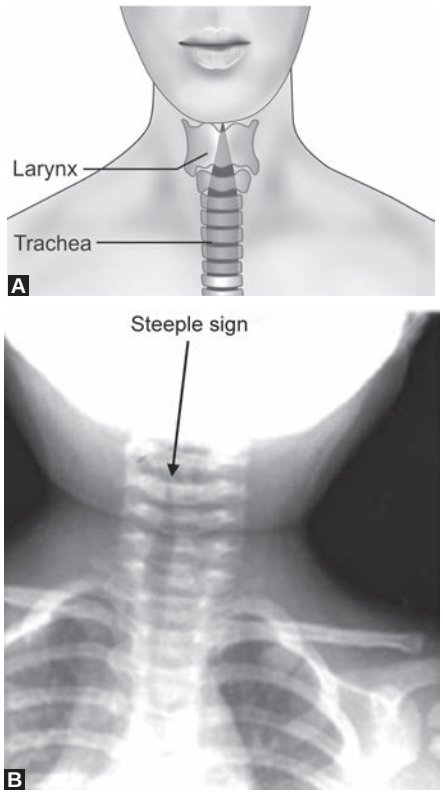


Fig. 4: A steeple sign (also known as a pencil-point sign), which signifies subglottic narrowing

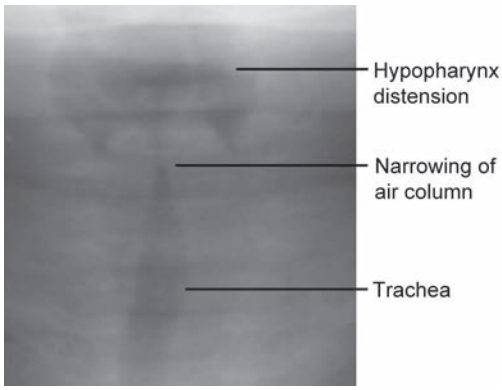


Fig. 5: A distended hypopharynx (ballooning) during inspiration

TREATMENT

The current cornerstones of treatment are corticosteroids and nebulized epinephrine.

- Nebulized epinephrine (adrenaline):
  - It is used for children with moderate-to-severe respiratory distress. Effectiveness of standard epinephrine 1:1,000 (which is available in India) is the same as racemic epinephrine, when given in dose of 0.5 mL/kg (maximum 5 mL)
  - Epinephrine stimulates α- and β2-receptors causing constrictions of precapillary arterioles thereby decreasing capillary hydrostatic pressure which leads to fluid resorption from the interstitium, thus decreasing airway edema
  - Its effectiveness is immediate with evidence of therapeutic benefit within the first 30 minutes and then, lasts from 1.5 hours to 2 hours; hence after nebulized epinephrine, patient should be observed for at least 3 hours to monitor for a rebound worsening. Patients can be discharged home if they demonstrate good color, adequate air entry, baseline consciousness, and no stridor at rest and have received a dose of corticosteroids
- Corticosteroids: they act through anti-inflammatory action, whereby decreasing mucosal edema and also decreasing the need for nebulized epinephrine. It may be warranted even in those children who present with mild symptoms. In moderate to severe disease, it improves croup scores within 12–24 hours and decrease hospitalization rates. All different routes of administration (oral/IM/nebulized) are shown to be efficacious
  - Dexamethasone: a single dose of dexamethasone has been shown to be effective in reducing the overall severity of croup, if used within the first 4–24 hours of onset. Most trials have used dexamethasone IM or oral (with equal efficacy) at 0.6 mg/kg/dose (with a maximum daily dose of 10 mg). It is 6.67 times potent than prednisone and has a long half-life of 36–56 hours. Also, patients treated with single dose of prednisolone (1 mg/kg) were found to require more follow-up visits than with dexamethasone (0.15 mg/kg)
    - Even though dexamethasone dosed at 0.15 mg/kg is as effective as 0.3 mg/kg or 0.6 mg/kg, still dose of 0.6 mg/kg is advocated as it is more effective for patients diagnosed with severe croup and remains optimal for safety and benefit
  - Inhaled budesonide:
    - It has been shown in several studies to be equivalent to oral dexamethasone. Dose is 2–4 mg. Using inhaled corticosteroids (budesonide) along with systemic steroid does not provide additional benefit
    - Usage of steroids has no significant adverse effects; however, it should be carefully evaluated for children with diabetes/immunocompromised state, recently diagnosed with varicella or tuberculosis. Urgent care of croup depends on the degree of severity

- Cool-mist therapy: Randomized studies with moderate-to-severe croup revealed no difference in outcome
- Antibiotics are not needed, as etiology is viral infection
- Heliox:Currently, the evidence is not sufficient to establish the beneficial effect of heliox in pediatric croup management (Table 2).

COMPLICATIONS

Complications in croup are rare. In most series, less than 5% of children needed hospitalization and less than 2% of those who were hospitalized were intubated. Death occurred in approximately 0.5% of intubated patients.

A secondary bacterial infection may rarely result in pneumonia or bacterial tracheitis, a life-threatening infection. This manifests as, mild-to-moderate illness for 2–7 days, followed by severe symptoms with toxic appearance and does not respond well to nebulized epinephrine.

Pulmonary edema, pneumothorax, lymphadenitis, and otitis media have also been reported in croup. Poor ability to maintain adequate oral intake plus increased insensible fluid losses can lead to dehydration.

PROGNOSIS

The prognosis for croup is excellent, and recovery is usually complete. The majority of patients are managed successfully as outpatients, without the need for hospitalization.

SPASMODIC CROUP

Spasmodic croup (laryngismus stridulus) may be a non-infectious variant of the disorder, with a clinical presentation similar to that of the acute disease but with less coryza. In spasmodic croup, subglottic edema occurs without the inflammation typical in viral disease.

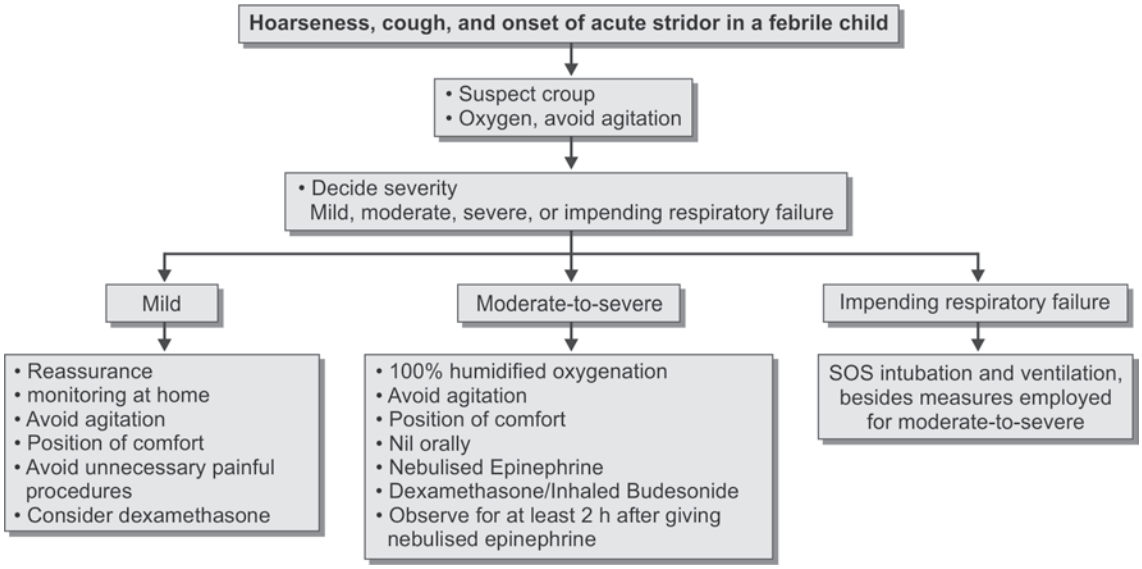
TABLE 2: Management of croup (as per severity)

Mild	Moderate-to-severe	Impeding respiratory failure
• Reassurance, education regarding course of disease and monitoring at home • Avoid agitation • Position of comfort in parent's lap • Avoid unnecessary painful procedures • Consider dexamethasone	• 100% humidified oxygenation • Avoid agitation • Position of comfort • Nill orally • Nebulized epinephrine • Dexamethasone/inhaled budesonide • Observe for at least 2 hours after giving nebulised epinephrine (to see no recurrence of stridor)	• 100% humidified oxygenation • Avoid agitation • Nebulized epinephrine • Dexamethasone IM/IV • Ventilation support, if needed, initially with a bag and mask • Endotracheal intubation* (with tube 0.5–1 mm smaller than predicted) if respiratory fatigue/worsening hypercarbia • Prepare for surgical airway if needed

*Endotracheal intubation with upper airway obstruction is a high risk procedure and should be performed by a team with airway expertise.

ALGORITHM 1

Algorithm for croup



To decide severity, refer Table 1.

Spasmodic croup (recurrent croup) typically presents at night with the sudden onset of "croupy" cough and stridor. The child may have had mild upper respiratory complaints prior to this, but more often has behaved and appeared completely well prior to the onset of symptoms.

Allergic factors may cause recurrent croup, due to the patient becoming sensitized to viral antigens. Another diagnostic consideration is GER. Studies of children presenting with recurrent croup have reported relief of their respiratory symptoms when treated for reflux.

KEY POINTS

- ☞ It is a viral (parainfluenza) infection with subglottic airway obstruction, in age 1–3 years
- ☞ Presents with upper respiratory infection days, then hoarse voice, barking cough, inspiratory stridor, distress
- ☞ Absence of drooling and nontoxic patient helps to differentiate it from supraglottic pathology
- ☞ Diagnosis is almost always clinical and no role of laboratory/radiological investigations
- ☞ Assessment of severity is clinical, which decides treatment
- ☞ Nebulized epinephrine and steroids are the cornerstone treatment of croup
- ☞ Recovery is seen within 12–24 hours of steroid and prognosis is excellent.

SUGGESTED READINGS

1. [Guideline] Alberta Medical Association. Guideline for the diagnosis and management of croup. Alberta Clinical Practice Guidelines 2005 Update.
2. American Academy of Pediatrics. Parainfluenza viral infections. In: Pickering LK (Ed). Red Book: 2003 Report of the Committee on Infectious Diseases, 26th edition. Elk Grove Village, IL: American Academy of Pediatrics; 2003. pp. 479-81.
3. Beckmann KR, Brueggemann WM. Heliox treatment of severe croup. Am J Emerg Med. 2000;18(6):735-6.
4. Benson BE, Baredes S, Schwartz RA. (2015). Stridor. [online] Available from http://emedicine.medscape.com/article/995267-overview. [Accessed December, 2015].
5. Bernstein T, Brilli R, Jacobs B. Is bacterial tracheitis changing? A 14-month experience in a pediatric intensive care unit. Clin Infect Dis. 1998;27(3):458-62.
6. Bjornson C, Russell KF, Vandermeer B, Durec T, Klassen TP, Johnson DW. Nebulized epinephrine for croup in children. Cochrane Database Syst Rev. 2011;(2):CD006619.
7. Bjornson CL, Klassen TP, Williamson J, Brant R, Mitton C, Plint A, et al. A randomized trial of a single dose of oral dexamethasone for mild croup. N Engl J Med. 2004;351(13):1306-13.
8. Cetinkaya F, Tufekci BS, Kutluk G. A comparison of nebulized budesonide, and intramuscular, and oral dexamethasone for treatment of croup. Int J Pediatr Otorhinolaryngol. 2004;68(4):453-6.
9. Chub-Uppakarn S, Sangsupawanich P. A randomized comparison of dexamethasone 0.15 mg/kg versus 0.6 mg/kg for the treatment of moderate to severe croup. Int J Pediatr Otorhinolaryngol. 2007;71(3):473-7.
10. Chun R, Preciado DA, Zalzal GH, Shah RK. Utility of bronchoscopy for recurrent croup. Ann Otol Rhinol Laryngol. 2009;118(7):495-9.
11. Donnelly BW, McMillan JA, Weiner LB. Bacterial tracheitis: report of eight new cases and review. Rev Infect Dis. 1990;12(5):729-35.
12. Edwards KM, Dundon MC, Altemeier WA. Bacterial tracheitis as a complication of viral croup. Pediatr Infect Dis. 1983;2(5):390-1.
13. Fifoot AA, Ting JY. Comparison between single-dose oral prednisolone and oral dexamethasone in the treatment of croup: a randomized, double-blinded clinical trial. Emerg Med Australas. 2007;19(1):51-8.
14. Geelhoed GC. Budesonide offers no advantage when added to oral dexamethasone in the treatment of croup. Pediatr Emerg Care. 2005;21(6):359-62.
15. Guidelines for the diagnosis and management of croup. 2008 update. Alberta Medical Association; 2011.
16. Hoa M, Kingsley EL, Coticchia JM. Correlating the clinical course of recurrent croup with endoscopic findings: a retrospective observational study. Ann Otol Rhinol Laryngol. 2008;117(6):464-9.
17. Huang CC, Shih SL. Images in clinical medicine. Steeple sign of croup. N Engl J Med. 2012;367(1):66.
18. Jones R, Santos JI, Overall JC. Bacterial tracheitis. JAMA. 1979;242(8):721-6.
19. Kairys SW, Olmstead EM, O'Connor GT. Steroid treatment of laryngotracheitis: a meta-analysis of the evidence from randomized trials. Pediatrics. 1989;83(5):683-93.
20. Kirks DR. The respiratory system. Practical Pediatric Imaging: Diagnostic Radiology of Infants and Children, 3rd edition. Philadelphia, Pa: Lippincott-Raven; 1998. pp. 651-3.
21. McGee DL, Wald DA, Hinchliffe S. Helium-oxygen therapy in the emergency department. J Emerg Med. 1997;15(3):291-6.
22. Russell K, Wiebe N, Saenz A, Ausejo SM, Johnson D, Hartling L, et al. Glucocorticoids for croup. Cochrane Database Syst Rev. 2004;(1):CD001955.
23. Russell KF, Liang Y, O'Gorman K, Johnson DW, Klassen TP. Glucocorticoids for croup. Cochrane Database Syst Rev. 2011;(1):CD001955.
24. Scolnik D, Coates AL, Stephens D, Da Silva Z, Lavine E, Schuh S. Controlled delivery of high vs low humidity vs mist therapy for croup in emergency departments: a randomized controlled trial. JAMA. 2006;295(11):1274-80.
25. Sparrow A, Geelhoed G. Prednisolone versus dexamethasone in croup: a randomised equivalence trial. Arch Dis Child. 2006;91(7):580-3.
26. Sung JY, Lee HJ, Eun BW, Kim SH, Lee SY, Lee JY, et al. Role of human coronavirus NL63 in hospitalized children with croup. Pediatr Infect Dis J. 2010;29(9):822-6.
27. Terregino CA, Nairn SJ, Chansky ME, Kass JE. The effect of heliox on croup: a pilot study. Acad Emerg Med. 1998;5(11):1130-3.
28. Vorwerk C, Coats T. Heliox for croup in children. Cochrane Database Syst Rev. 2010;(2):CD006822.
29. Vorwerk C, Coats TJ. Use of helium-oxygen mixtures in the treatment of croup: a systematic review. Emerg Med J. 2008;25(9):547-50.
30. Wald EL. Croup: common syndromes and therapy. Pediatr Ann. 2010;39(1):15-21.
31. Weber JE, Chudnofsky CR, Younger JG, Larkin GL, Boczar M, Wilkerson MD, et al. A randomized comparison of helium-oxygen mixture (Heliox) and racemic epinephrine for the treatment of moderate to severe croup. Pediatrics. 2001;107(6):E96.
32. Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med. 2004;350(5):443-50.
33. Zoorob R, Sidani M, Murray J. Croup: an overview. Am Fam Physician. 2011;83(9):1067-73.

CHAPTER 33

Approach to a Child with Acute Febrile Encephalopathy

Surpreet BS Nagi

INTRODUCTION

A child presenting with fever and altered sensorium is a common pediatric emergency. Acute febrile encephalopathy (AFE) is a clinical term used to describe an altered mental state that either accompanies or follows a short febrile illness and is characterized by a diffuse and nonspecific brain insult manifested by a combination of coma, seizures, and/or decerebration.

Encephalopathy is a diffuse disease affecting the brain that alters its structure or function and may be caused due to diverse etiology like infective, metabolic, toxic, ischemic, nutritional causes or trauma. In febrile illnesses, encephalopathy may result from pathogenic mechanisms affecting the nervous system directly or systemic complications like hypoglycemia, hypovolemia, hyperpyrexia, hypoxia, anemia, hepatic or renal failure, toxins, vasculitis, and bleeding.

Central nervous system (CNS) infections are the most common cause of AFE in children. Various causes such as viral encephalitis, cerebral malaria, bacterial meningitis, Reye's syndrome, and inflammatory encephalopathies including acute disseminated encephalomyelitis (ADEM), etc. have been implicated in the etiology; and the proportionate contribution of each varies according to the geographical area. In tropical countries like India, cerebral malaria, Japanese encephalitis (JE), herpes simplex encephalitis (HSE), and bacterial meningitis are the common causes of AFE, while tuberculous meningitis (TBM) usually presents with a subacute or chronic history. Even after a detailed diagnostic workup, one may not be able to arrive at a definitive diagnosis in many cases. Nevertheless, a detailed examination and workup is warranted, because many conditions like cerebral malaria and HSE are treatable.

SOME DEFINITIONS

Encephalopathy

Encephalopathy describes a clinical syndrome of altered mental status, manifesting as reduced consciousness or altered behavior, without any inflammation of the brain.

Acute Febrile Encephalopathy

Acute febrile encephalopathy is a clinical diagnosis and is described as a syndrome of altered sensorium associated with fever of less than 1 week duration, and altered consciousness of more than 12-hours duration, with or without seizures in a previously normal child.

Encephalitis

Encephalitis means inflammation of the brain. It is strictly a pathological diagnosis; but surrogate clinical/imaging markers may provide evidence of inflammation.

Acute Encephalitis Syndrome

Clinically, a case of acute encephalitis syndrome (AES) is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence, or abnormal behavior greater than that seen with usual febrile illness.

PATHOPHYSIOLOGY

The pathophysiology of AFE usually is multifactorial and varies according to the etiology. Encephalopathy generally results from cytotoxic injury or disruption of neurotransmission. However, the final pathway is common, which is interruption of the polysynaptic pathways and altered excitatory-inhibitory amino acid balance, leading to cerebral edema. All forms of acute toxic metabolic encephalopathy interfere with the function of the ascending reticular activating system and/or its projections to the cerebral cortex, thus leading to impairment of arousal and/or awareness, and/or seizures. Despite a wide array of pathophysiologic mechanisms, the clinical manifestations tend to be very similar because of the common final mechanism.

ETIOLOGY

The etiology of AFE varies from infectious etiologies to noninfectious metabolic disorders (Table 1). The following are some of the common causes of AFE:

- Infections:
  - Meningoencephalitis: due to viruses like herpes simplex virus (HSV) 1 and 2, human herpes virus 6, Epstein-Barr virus (EBV), varicella zoster virus, cytomegalovirus, adenovirus, influenza, enterovirus, poliovirus, measles, mumps, rubella, rabies, dengue virus, chikungunya, arboviruses (JE, West Nile virus), and retrovirus [human immunodeficiency virus (HIV)]
  - Bacterial infections like pyogenic meningitis, and other organisms like *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Listeria*, *Borrelia burgdorferi* (Lyme disease), *Leptospira*, *Brucella*, and *Salmonella typhi*
  - Rickettsial infections, fungal infections due to cryptococcosis, histoplasmosis, coccidioidomycosis, and candidiasis
  - Cerebral malaria due to *Plasmodium*, and infection with other parasites like *Toxoplasma gondii* and *Schistosoma*
  - Brain abscess, subdural, or epidural empyema
  - Sepsis with disseminated intravascular coagulation or thrombotic thrombocytopenic purpura
- Noninfective causes:
  - Overproduction of heat: Neuroleptic malignant syndrome, malignant hyperthermia, non-convulsive status epilepticus (NCSE), and thyrotoxic encephalopathy
  - Impaired heat dissipation: Heat stroke, anticholinergic toxicity
  - Structural lesions: Hypothalamic lesion, brainstem lesions, and intraventricular and subarachnoid hemorrhage
- Miscellaneous:
  - Plant toxins like *Cassia occidentalis*
  - Reye's syndrome
  - Infectious or postinfectious ADEM.

TABLE 1: Etiology of acute febrile encephalopathy

Diagnosis	Number of cases (%)
Suspected viral etiology	57 (37.3)
Pyogenic meningitis	51 (33.8)
Tubercular meningitis	12 (7.9)
Cerebral malaria	08 (5.2)
Dyselectrolytemia	06 (4)
Hepatic encephalopathy	03 (2)
DKA	03 (2)
ADEM	02 (1.3)
Septicemia	02 (1.3)
Reye's syndrome	03 (2)
Shigellosis	01 (0.67)
Enteric fever	01 (0.67)
Prolonged coma after seizure	01 (0.67)
IC bleed due to aplastic anemia	01 (0.67)
Total	151 (100)

DKA, diabetic ketoacidosis; ADEM, acute disseminated encephalomyelitis; IC, intracranial.

EVALUATION

Patients presenting with an AFE can be broadly divided into three categories (Table 2).

A detailed history and physical examination is essential to categorize the patient into one of these groups. At the outset, it is important to differentiate infective from non-infective causes, because infection mandates prompt antimicrobial therapy. There are no distinguishing clinical or radiological features to differentiate the various causes of viral encephalitis. The clinical and the radiological findings in encephalitis should be interpreted in the geographical and other epidemiological background.

APPROACH TO ACUTE FEBRILE ENCEPHALOPATHY (ALGORITHM 1)

Step 1: Initiate Resuscitation and Assess Neurological Status

As in any emergency, one needs to quickly evaluate the airway, breathing, and circulation (ABC's). It is during this assessment that alteration of sensorium is first recognized (or confirmed). Initial neurological examination includes only a survey of vital signs, including respiratory patterns, Glasgow Coma Scale (GCS) score, pupillary response, and extraocular muscle examination. The common goal in the treatment of a patient with encephalopathy is to prevent secondary injury by maintaining oxygen delivery and supply of nutrients to the brain. Thus, the ABC's of basic life support supersede all other interventions.

If the initial assessment suggests that the child is unstable, then the management priorities should be directed to ensuring

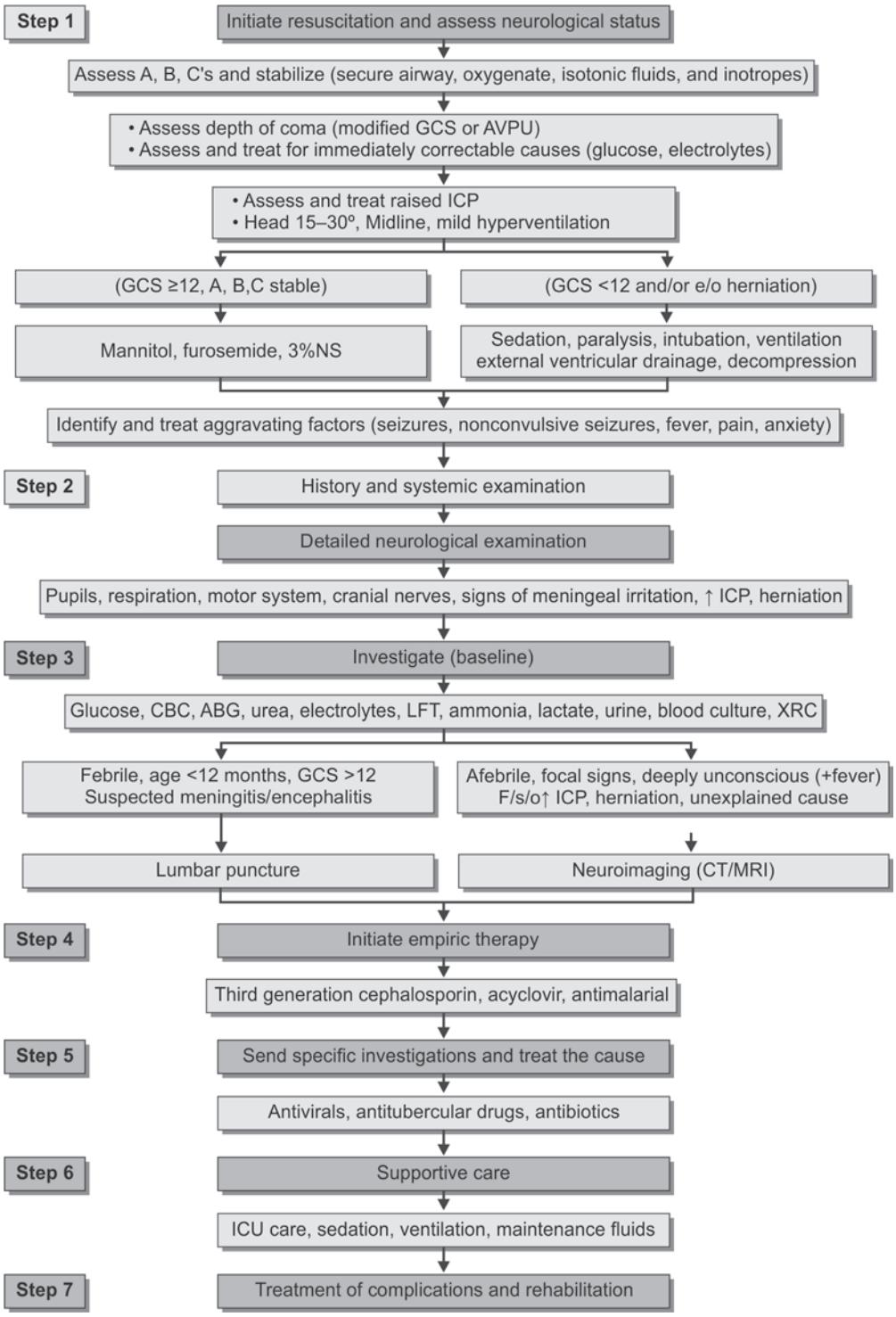
TABLE 2: Categories of patients presenting with an acute febrile encephalopathy

Category	Common causes
Primary CNS infections	Meningitis, encephalitis (HSV, JE), TBM, and brain abscess
Systemic infections	Shigella, typhoid, malaria, dengue, and rickettsial infections
Noninfectious causes	ADEM, Reye's syndrome, and mitochondrial and other IEMs, drugs and toxins, SOLs

CNS, central nervous system; HSV, herpes simplex virus; JE, Japanese encephalitis; ADEM, acute disseminated encephalomyelitis; IEMs, inborn errors of metabolism; SOLs, space occupying lesions; TBM, tuberculous meningitis.

ALGORITHM 1

Approach to a child with acute febrile encephalopathy



ABC's, airway, breathing, and circulation; GCS, Glasgow Coma Scale; ICP, intracranial pressure; NS, normal saline; CBC, complete blood count; ABG, arterial blood gas; LFT, liver function test; CT, computed tomography; MRI, magnetic resonance imaging; ICU, intensive care unit; AVPU, alert, voice, pain, and unresponsive scale; XRC, X-ray chest.

adequacy of airway, breathing, and circulatory function, irrespective of the etiology. Depending on the degree of instability, this initial management may actually precede the assessment of the degree of impairment of consciousness; though usually, both are carried out nearly simultaneously.

The depth of coma can be assessed by the GCS or the AVPU scale (Wherein A-Alert, V-Response to Voice, P-Response to Pain and U-Unresponsive). A modified GCS should be used for infants and young children. In case of any confusion about the assessment, it is preferable to err on the side of recording a lower score initially, since it is easier to withdraw treatment in a child who is improving, rather than to resuscitate a child who is deteriorating.

Assessment of the airway and need for intubation is of paramount importance as the children with impaired consciousness are at a high risk for aspiration (Box 1). These children have loss of tone of the oropharyngeal muscles causing the tongue to fall back and obstruct the airway, and pooling of secretions (leading to aspiration). Measures should be taken to secure the airway. If the child shows signs of airway obstruction, repositioning of the head with the chin lift maneuver may alleviate the obstruction. If cervical spine injury is suspected, a jaw thrust maneuver is preferable and the neck immobilized while securing the airway. An oral airway may be inserted if required and secretions cleared using a large-bore-suction cannula.

Once the airway patency has been established, the adequacy of breathing should be evaluated. Auscultation of the lung fields should assess for air entry, symmetry of breath sounds, and presence of adventitious breath sounds such as crackles or wheezes. Pulse oximetry can be used to evaluate oxygenation. Oxygen should be administered to all seriously-ill children via non-rebreathing face mask. Adequacy of ventilation should be assessed by examination and arterial blood gases. If the airway is patent but the child's respiratory effort is deemed inadequate, positive pressure ventilation should be initiated. The airway interventions should be instituted as nontraumatically as possible, as they may cause spikes in intracranial pressure (ICP). Rapid-sequence intubation is preferred. Moderate hyperventilation (target $PaCO_2$ 30–35 mmHg) to produce arterial constriction and lower ICP should only be initiated for patients with signs of increased ICP. Extreme hyperventilation has been associated with brain ischemia; the risks of aggressive hyperventilation ($PaCO_2$ <30 mmHg) are only justified in patients with transtentorial herniation.

Attempt should be made to maintain the cerebral perfusion pressure (CPP), which is the major factor that affects cerebral blood flow and hence, adequate oxygenation. Cerebral perfusion pressure depends on the mean arterial pressure (MAP) and the ICP (CPP = MAP – ICP). Cerebral perfusion pressure can reduce as a result of reduced MAP or raised ICP or a combination of these two. Therefore, adequate MAP should be maintained. If the ICP rises, the blood pressure (BP) rises as a compensatory phenomenon in order to try and maintain the cerebral perfusion. However, there is a limit to such compensation, beyond which the cerebral perfusion may suffer. Cerebral ischemia is the single-most important determinant that decides the outcome of such patients.

Once the airway and breathing have been addressed, circulation must be evaluated. This involves assessment of the cardiac output. Symptoms of shock include tachycardia, cool extremities, delayed capillary refill time, mottled or pale skin, and effortless tachypnea. Hypotension is a late finding in shock. Vascular access is necessary for volume resuscitation in patients with impaired circulation. While establishing an intravenous access, samples should be drawn for various investigations. If there is evidence of circulatory failure, fluid bolus (20 mL/kg of normal saline; maximum 60 mL/kg) should be administered. If there is evidence of septic shock, larger volumes (60–80 mL/kg) may be needed to correct the shock. Once an intervention is performed, the clinician must reassess the patient. Raised ICP is not a contraindication for fluid administration for the correction of shock. Effective circulation through intravenous isotonic fluid administration and inotropes, if necessary, is essential to deliver oxygen and metabolic substrates to the brain and remove toxic metabolites. Hypotonic fluids like 5% or 10% dextrose can lead to cerebral edema in children with raised ICP and should not be administered. Aim should be to maintain the BP at around the 95th percentile in order to maintain CPP in the face of an elevated ICP.

Raised ICP is a common cause of death in children with AFE. It is important to recognize and promptly manage signs of raised ICP (Box 2). A common mistake in the emergency departments is to mistake decerebrate posturing for seizures, and inappropriately treat with antiepileptic drugs. Almost all cases of non-traumatic coma have an element of raised ICP. Signs of raised ICP should be picked up early. A careful examination of the fundus is mandatory in all children with

Box 1: Recommendations for intubation

- GCS <12, or deteriorating GCS scores
- Impaired airway reflexes
- Abnormal respiratory pattern (Respiratory depression)
- Neurogenic hyperventilation
- Signs of raised intracranial pressure
- Evidence of herniation
- Asymmetric or dilated pupils
- Oxygen saturation <92% despite high flow oxygen
- Fluid refractory shock

GCS, Glasgow Coma Scale.

Box 2: Signs of raised intracranial pressure

- Worsening Glasgow Coma Scale despite correction of airway, breathing, and circulation
- Persistence of abnormal posturing
- Abnormal breathing patterns
- Abnormal pupillary response
- Doll's eye reflex
- Cushing's triad (late sign)
- Papilledema

altered sensorium. Acute elevation of ICP will not cause papilledema in the acute stages. Hence, its absence must not be taken as a reassuring sign. Neither, will a computed tomography (CT) pick up raised ICP in the acute stage.

If there are features of raised ICP, measures to decrease ICP should be rapidly instituted. Early interventions to reduce ICP include treating fever, maintaining the head in the midline with an elevation of 15–30° above the horizontal and moderate hyperventilation (target $PaCO_2$ 30–35 mmHg). Mannitol should be given in a dose of 0.25–0.5 g/kg intravenously over 15 minutes, and repeated every 4–6 hourly; only if required. It should not be administered round the clock and is unlikely to be effective after 48–72 hours. Furosemide is often used in conjunction with mannitol. Hypertonic saline (3%) may be preferred in hypotensive or hypoperfused patients for reducing the ICP while maintaining the MAP and CPP. A neurosurgical consultation should be asked for.

Clinical Pearls

- Airway, breathing and circulation of basic life support supersede all other interventions
- Initial management may actually precede the assessment of the degree of impairment of consciousness in an unstable child
- Preferable to record a lower glasgow coma scale score initially
- Airway interventions should be instituted as nontraumatically as possible
- Maintain cerebral perfusion pressure
- Reassess after every intervention
- Almost all cases of nontraumatic coma have an element of raised intracranial pressure
- Normal fundus or normal neuroimaging does not rule out a raised intracranial pressure.

Treatment of associated conditions is of paramount importance. Normothermia should be maintained. The use of therapeutic hypothermia (32–34°C) may be appropriate for children with out-of-hospital arrest and persistent coma or those with ventricular fibrillation or pulseless ventricular tachycardia. Acid-base and electrolyte abnormalities should be corrected.

If hypoglycemia is present, intravenous glucose bolus should be administered. In a neonate, 2 mL/kg of 10% IV dextrose bolus; and in an older child 5 mL/kg of 10% IV dextrose bolus should be given. Thereafter, the sugar levels should be monitored and the glucose infusion rates modified accordingly. Hyperglycemia resulting from stress is a more common finding in these conditions. Hypoglycemia damages the brain immediately and needs urgent correction. Hyperglycemia, on the other hand, is associated with a higher morbidity and mortality if not treated; and hence tight glycemic control should be the aim.

If the child is having seizures, or there is history of a seizure preceding the encephalopathy, anticonvulsants (intravenous benzodiazepine followed by phenytoin loading 20 mg/kg or fosphenytoin) should be administered. The standard protocol for the management of status epilepticus may be followed in case of refractory seizures. Subtle seizures (NCSE) should be identified and treated appropriately, as unrecognized seizure activity increases the ICP and could precipitate herniation. Non convulsive status epilepticus manifests, as an abnormal and fluctuating impairment of consciousness, diminished responsiveness; and may be picked up on an electroencephalogram (EEG), and often showing a delayed response (4–5 days in some patients) to anticonvulsant medications.

Agitation may increase ICP, interfere with respiratory support, and increase the risk of injury. Efforts should be taken to provide pain relief and sedation during painful procedures. Significant sedation, however, may obscure the neurologic examination, may contribute to hypotension and hypoventilation, and should be administered only when the benefits of relieving agitation outweigh the need for close neurologic monitoring by examination.

KEY POINTS

Initial steps in resuscitation

- ☞ Assess airway, breathing and circulation and stabilize
- ☞ Assess level of consciousness (modified Glasgow Coma Scale or Alert, Voice, Pain Unresponsive Scale)
- ☞ Secure airway, oxygenation, and ventilation, rapid sequence intubation preferred, maintain cerebral perfusion pressure
- ☞ Secure vascular access, isotonic fluids, inotropes
- ☞ Assess and treat for immediately correctable causes (glucose, electrolytes, acid-base abnormalities)
- ☞ Assess and treat raised intracranial pressure: Head 15–30°, midline, mild hyperventilation, mannitol, furosemide, 3% normal saline
- ☞ In case of signs of herniation—sedation, paralysis, intubation, ventilation
- ☞ Identify and treat aggravating factors—seizures, nonconvulsive status epilepticus, fever, pain, anxiety
- ☞ Continuous monitoring of heart rate, respiratory rate, blood pressure, temperature, oxygen saturations, electrocardiogram, Glasgow Coma Scale.

Step 2: Take History and Perform Focused Examination

History (Table 3)

The patient's history may hold the most important and sometimes the only clue to a correct diagnosis. A careful history should be taken with special emphasis on the onset and duration of encephalopathy and the type and degree of fever. The child, who has been apparently well prior to the onset of encephalopathy and has an acute onset of illness, may have suffered from poisonings, drug overdose, metabolic disorders or child abuse, as the probable causes. Central nervous system infections, on the other hand, would present with complaints evolving over a few days associated with a history of fever or recent illness. Disorders in which encephalopathy may be

TABLE 3: Important clues in the history of acute febrile encephalopathy

History	Probable etiology
Geographic area or residence of the child	Endemic for JE, malaria
Recent travel	Malaria, dengue, typhus, arbovirus
Similar illness in the family or locality	Epidemic of AES, HSV, JE
Prodromal symptoms like a URI, flu-like illness or diarrhea	H1N1, enterovirus, polio
Congenital heart disease, chronic ear infections, sinusitis, orbital cellulitis, or dental infection	Brain abscess
Dog bite	Rabies
Insect or mosquito bite	Rickettsial infection, malaria, dengue, JE
Contamination with dirty water	Leptospirosis
Contact with tuberculosis	TBM
Recent immunizations	ADEM
Treatment history prior to the presentation	Partially-treated bacterial meningitis
Exposure to drugs or toxins at home	Poisoning, nonaccidental trauma
Past history of similar episodes	IEM

JE, Japanese encephalitis; AES, acute encephalitis syndrome; HSV, herpes simplex virus; URI, upper respiratory infection; TBM, tuberculous meningitis; ADEM, acute disseminated encephalomyelitis; IEM, inborn error of metabolism.

preceded by a febrile illness include ADEM, Reye's syndrome, mitochondrial and other inborn errors of metabolism.

The associated symptoms may indicate the focus of infection. Symptoms such as headache, nausea and vomiting, irritability, seizures, focal deficits, rash, and joint pain should be enquired into in depth. Other concurrent systemic illnesses, e.g., jaundice (hepatic failure), pneumonia (hypoxic encephalopathy), diarrhea (dyselectrolytemia), and dysentery (shigella encephalopathy) need to be elicited in the history. Nonaccidental trauma should always be considered in a lethargic infant.

Other history which may offer some aid in the diagnosis:

- History of trauma, recent illness, or surgery (splenectomy, neurosurgery)
- Family history of seizure disorders or previous child deaths
- Comorbid conditions like congenital heart disease, diabetes, chronic liver, or renal diseases
- Premorbid developmental or neurological status of the child
- Immunosuppressive states (HIV), chemotherapy, and prolonged steroids.

Examination

General examination (Table 4)

The general examination may provide helpful etiological clues. Vital signs are often overlooked but are valuable in assessing ill children. The degree of fever, the presence of tachycardia out-of-proportion to the fever, and the presence of tachypnea and hypotension, when present, are ominous signs.

TABLE 4: Important clues in general examination in acute febrile encephalopathy

Clinical finding	Probable etiology
Pallor	Cerebral malaria, typhoid, intracranial bleed
Icterus	Leptospirosis, cerebral malaria
Generalized lymph-adenopathy	EBV, leptospirosis, HIV
Skin rashes	Meningococcemia, arboviruses, varicella, rickettsia, dengue, measles, enterovirus
Petechiae	Meningococcemia, dengue, viral hemorrhagic fevers
Erythema nodosum	Tuberculosis, histoplasmosis
Parotid swelling and orchitis	Mumps
Mucous membrane lesions and shallow ulcers	Herpes simplex virus
Abnormal odor of breath	Diabetic ketoacidosis, hepatic coma
Myalgia, arthralgia	Leptospirosis, dengue
Hypotension, shock	Dengue, leptospirosis, cerebral malaria
Organomegaly	EBV, dengue, leptospirosis, HIV

EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

The presence of fever suggests an infective process (sepsis, pneumonia, meningitis, encephalitis, or brain abscess); but may also indicate heat stroke or abnormality of hypothalamic temperature regulatory mechanisms. Tachycardia may be a result of fever, hypovolemic or septic shock, heart failure, or arrhythmias. Bradycardia may result from raised ICP or a result of myocardial injury (myocarditis, hypoxia, sepsis, or toxins). Tachypnea with respiratory distress indicates lung pathology (pneumonia, pneumothorax, empyema, or asthma). Quiet tachypnea is indicative of acidosis which may be present in diabetic ketoacidosis (DKA), uremia, or some poisonings. Hypotension may be seen in sepsis, cardiac dysfunction, toxic ingestion, or adrenal insufficiency, and may lead to poor cerebral perfusion, resulting in diffuse or watershed hypoxic-ischemic injury. Hypertension may be the cause of altered sensorium in hypertensive encephalopathy or may be a compensatory mechanism to maintain cerebral perfusion in children with increased ICP or stroke.

A thorough systemic examination should be performed to look for a source of sepsis. Systemic examination must be performed to look for hepatosplenomegaly (infections or liver disease), pulmonary involvement such as pneumonia, pleural effusions, and empyema, skin and bone lesions and cardiac involvement such as myocarditis or a pre-existing congenital or rheumatic heart disease (which may predispose to endocarditis and subsequently intracranial abscess).

Detailed neurological examination

The neurological examination is targeted to document the level and localization of brain dysfunction. It may also provide information about the potential causes. This includes assessment of the level of consciousness, patterns of respiration, and signs of meningeal irritation, fundus and pupillary examination, signs of cranial nerve involvement, presence of focal deficits, signs of raised ICP, brainstem signs and autonomic signs.

The level of consciousness must be recorded in the form of an objective scale, such as the GCS or the AVPU score. While the GCS allows efficient, standardized communication of a child's state, a more detailed description of the child's clinical findings is often more useful for relaying detailed information and detecting changes over time.

Respiratory pattern abnormalities signify either a metabolic derangement or a neurological insult (Table 5).

Pupils

Pupillary size, shape, symmetry, and response to light provide valuable clues to brainstem and third nerve dysfunction. The presence or absence of the pupillary reaction to light is one of the most important differentiating features to distinguish between structural and metabolic disorders as metabolic disturbances affect the pupillary pathways late. Usually in metabolic disorders leading to altered level of consciousness, pupils remain reactive in the initial stages. But in structural disorders with increased ICP, signs of herniation syndrome will appear. Topical administration of mydriatics must be avoided, but if done, should be documented to avoid confusion in interpretation. Abnormalities of eye position and movement may provide some clues. Conjugate lateral deviation of the eyes is a sign either of an ipsilateral hemisphere lesion, a contralateral hemisphere seizure focus, or damage involving the contralateral pontine horizontal gaze center (parapontine reticular formation). Lateral gaze palsy may signal central herniation with compression of bilateral sixth nerves. Tonic upward gaze has been associated with bilateral hemispheric damage.

The presence of oculocephalic (doll's eye), oculovestibular, corneal, cough, and gag reflexes must be looked for to check for brainstem function. Brainstem dysfunction is an important feature in some causes of viral encephalitis such as enterovirus 71, mumps, and rabies and in all causes when the ICP has risen progressively.

Fundus examination must be performed to look for papilledema and retinal hemorrhages. Retinal hemorrhages are an important clue for cerebral malaria in endemic setting, being present in nearly a quarter of the patients.

Clinical Pearl

- Unilateral pupillary dilatation in the comatose patient should be considered as evidence of oculomotor nerve compression from ipsilateral uncal herniation, unless proved otherwise.

Motor examination (Table 6)

Assessment of muscle strength, tone, and tendon reflexes should be done for normality and symmetry. The trunk, limb position, spontaneous movements, and response to stimulation must be observed to look for any focal deficits (suggestive of postictal Todd's palsy or structural abnormality), and posturing (decerebrate or decorticate).

Special attention should be given to posturing because it often signals a brainstem herniation syndrome.

- Decorticate posturing: Flexion of upper limbs and extension of the lower limbs. It suggests involvement of the cerebral cortex and preservation of brainstem function
- Decerebrate posturing: Rigid extension of both arms and legs indicative of cortical and brainstem dysfunction
- Opisthotonus: Neck is hyperextended and the teeth are clenched; the arms are adducted and hyperextended; and the legs are extended with feet plantar flexed. It indicates severe brainstem dysfunction
- The flaccid patient with no response to painful stimuli indicates deep brainstem dysfunction
- Monoplegia or hemiplegia, except when in postictal phase, suggests a structural disturbance of the contralateral hemisphere (herniation across falx).

TABLE 5: Types of abnormal respiratory patterns

Pattern	Lesion	Presentation	Conditions
Cheyne-Stokes respiration	Deep hemispheric or diencephalic dysfunction	Hyperpnea alternates with apnea	Strokes, traumatic brain injuries, brain tumors, carbon dioxide poisoning, metabolic encephalopathy, high altitude sickness, normal side effect of IV morphine administration
Central neurogenic hyperventilation	Midbrain dysfunction	Sustained, deep, regular, and rapid respiration	Strokes, traumatic brain injuries. Increasing irregularity of this respiratory pattern generally is a sign that the patient will enter into coma
Apneustic	Damage to the pons or upper medulla	Inspiratory pauses, lasting 2–3 seconds, alternating with end-expiratory pauses	Strokes, trauma, pontine infarction, anoxic encephalopathy, and ketamine (temporary)
Ataxic	Damage to the medulla oblongata	Completely irregular breathing pattern with irregular pauses and unpredictable periods of apnea	Trauma, stroke, opioid use This respiratory pattern indicates a very poor prognosis

TABLE 6: Important clues in neurological examination in acute febrile encephalopathy

CNS signs	Probable etiology
Abnormal behavior or psychosis	HSV, NCSE
Meningeal signs	Meningitis, TBM, encephalitis, ADEM
Ataxia	ADEM, varicella, enterovirus
Asymmetric signs and symptoms	TBM, encephalitis, ADEM
Papilledema	SOL, hydrocephalus in TBM
Opisthotonus	JE, autoimmune encephalitis
Cranial nerve palsies	TBM, encephalitis, JE, vasculitis
Bowel and bladder dysfunction	ADEM
Visual loss	Optic neuritis, ADEM, HT encephalopathy
Rapidly changing CNS signs	JE
Acute flaccid paralysis	Enterovirus, poliomyelitis, ADEM
Seizures	JE, cerebral malaria, TBM, meningitis
Dystonia or extrapyramidal movements	JE, TBM
Myoclonic jerks	Enterovirus

CNS, central nervous system; HSV, herpes simplex virus; NCSE, nonconvulsive status epilepticus; TBM, tuberculous meningitis; ADEM, acute disseminated encephalomyelitis; SOL, space occupying lesion; JE, Japanese encephalitis; HT, hypertensive.

Presence of signs of meningeal irritation (neck rigidity, Kernig's sign, and Brudzinski's sign) must be looked for. Kernig's sign involves flexion of the hip to 90° with subsequent pain on extension of the leg; Brudzinski's sign involves involuntary flexion of the knees and hips after passive flexion of the neck while supine. In younger children, Kernig's and Brudzinski's signs are not consistently present; especially with an open fontanel. Signs of meningeal irritation may be present in meningitis, encephalitis, and subarachnoid hemorrhage. Neck rigidity is present in meningitis, tonsillar herniation, or craniocervical trauma.

The commonly seen focal signs are hemiparesis, ataxia, aphasia, pyramidal signs, and involuntary movements (myoclonus, dystonia, tremors). Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerve should be looked for.

Signs of increased intracranial tension in children range from headache, vomiting to herniation. It is best to suspect raised ICP and start treating it, on clinical grounds alone. Raised ICP, when untreated, can also lead to herniation of the brain, which causes direct mechanical damage as well as ischemia and hemorrhage secondary to vascular distortion. Brain tissue deforms intracranially and moves from higher to lower pressure when there is asymmetric, unilateral, or generalized increased ICP. This gives rise to the various herniation syndromes. These syndromes, in this order (from higher to lower pressures), signify a progression in severity. Changes from one syndrome to the next, signifies progressive worsening.

TABLE 7: Clinical recognition of herniation syndromes

Type of herniation	Clinical manifestations
Uncal	• Unilateral ptosis • Unilateral fixed dilated pupil • Minimal deviation of eyes on oculocephalic/oculovestibular testing hemiparesis
Diencephalic	• Small or midpoint pupils reactive to light • Full deviation of eyes on oculocephalic/oculovestibular testing • Flexor response to pain and/or decorticate posturing • Cheyne-Stokes respiration • Hypertonia and/or hyperreflexia with extensor plantars
Midbrain	• Midpoint pupils, fixed to light
Upper pontine	• Minimal deviation of eyes on oculocephalic/oculovestibular testing • Extensor response to pain and/or decerebrate posturing • Hyperventilation
Lower pontine	• Midpoint pupils, fixed to light • No response on oculocephalic/oculovestibular testing • No response to pain or flexion of legs only • Flaccidity with extensor plantars • Shallow or ataxic respiration
Medullary	• Pupils dilated, fixed to light • Slow, irregular, or gasping respiration • Respiratory arrest with inadequate cardiac output

The various herniation syndromes can be recognized clinically. The importance lies in recognition and prompt treatment, before the damage becomes irreversible. Treatment of herniation involves removal of the etiologic mass and surgical decompression in the form of external ventricular drainage and hemicraniectomy may be indicated (Table 7).

Step 3: Send Basic Investigations

Basic Investigations

Basic workup like complete blood count with platelet count, peripheral smear, blood culture, blood glucose, liver and renal profile, coagulation parameters, and electrolytes should be obtained in all patients presenting with an AFE. An arterial blood gas, chest X-ray, serum ammonia, and serum lactate should be sent if required.

All patients with febrile encephalopathy should undergo blood cultures. Relative lymphocytosis in the peripheral blood is common in viral encephalitis. Leukopenia and thrombocytopenia are noted in viral hemorrhagic fevers and rickettsial infections. Typhoid fever and cerebral malaria may be associated with severe anemia and thrombocytopenia.

Hypoglycemia and electrolyte imbalance are usually associated with CNS infection and they may contribute to altered sensorium. Serum creatinine and blood urea are helpful to assess the renal function and serum bilirubin, transaminases and prothrombin time are indicated if jaundice is present. An X-ray chest may show changes suggestive of tuberculosis, mycoplasma, or legionellosis.

In endemic areas, look for malaria (peripheral smear and rapid detection tests), dengue (serology and NS1 Ag), Leptospira (antibody tests), enteric fever (blood culture), typhus (antibody test), and JE (antibody in serum and CSF) as the probable etiology.

TABLE 8: Specific therapy according to the etiology of acute febrile encephalopathy

Diagnosis	Specific therapy
Herpes simplex virus	Acyclovir-DOC, valacyclovir, foscarnet
Varicella zoster	Acyclovir
Human herpes virus 6	Foscarnet, ganciclovir
Cytomegalovirus	Ganciclovir
Enterovirus	Pleconaril
Rickettsia	Doxycycline, erythromycin
Mycoplasma	Azithromycin
Leptospirosis	Penicillin
Tuberculosis	Antitubercular drugs
Pyogenic meningitis	Ceftriaxone + vancomycin
ADEM	Steroids, IVIG

ADEM, acute disseminated encephalomyelitis; IVIG, intravenous immunoglobulin; DOC, drug of choice.

KEY POINTS

Baseline investigations recommended in acute febrile encephalopathy

- ☞ Complete blood count with platelets, peripheral smear
- ☞ Blood glucose
- ☞ Blood culture, urine examination
- ☞ Liver function tests, renal function tests, electrolytes
- ☞ Coagulation parameters, chest X-ray
- ☞ Arterial blood gas measurement, lactate, ammonia.

Tests which may be done in endemic areas

- ☞ Malaria (peripheral smear and rapid antigen test)
- ☞ Dengue (serology and nonstructural protein 1 antigen)
- ☞ Leptospira (antibody tests)
- ☞ Enteric fever (blood culture)
- ☞ Typhus (antibody test)
- ☞ Japanese encephalitis (antibody in serum and cerebrospinal fluid).

TABLE 9: Diagnostic criteria used for some common etiologies of acute febrile encephalopathy

Diagnosis	Criteria
HSV encephalitis	• Nonspecific prodrome, exanthem ± • Fever with altered sensorium, focal signs +, neck signs + • CSF cytology (predominant lymphocytes), CSF PCR and serology • EEG: Periodic lateralized epileptiform discharges • MRI/CT: Frontotemporal pathology
Japanese encephalitis	• Disorientation and delirium → somnolence, then progressing to coma • Rapidly changing central nervous system signs, seizures • CSF pleocytosis, PCR, antigen tests • Albuminuria
Pyogenic meningitis	• Fever with altered sensorium, no focal signs, neck signs + • CSF cytology (predominant neutrophils) • MRI/CT: Meningeal enhancement
Tubercular meningitis	• Stage 1: nonspecific signs, stage 2—neck signs, signs of ↑ ICP, cranial nerve palsies, focal signs, stage 3—coma, decorticate/decerebrate posturing • CSF compatible with TBM, isolation of AFB, ADA ↑ • MRI/CT: hydrocephalus, basal exudates, tuberculoma
Cerebral malaria	• Fever with altered sensorium ± focal signs, frequent seizures hypoglycemia • Peripheral smear +, rapid antigen test +
ADEM	• Fever much earlier than the onset of encephalopathy • Cranial nerve palsies, visual loss, ataxia, motor and sensory deficits, bladder/bowel dysfunction, and spinal cord demyelination • CSF compatible (↑ proteins, N sugars, N cytology) • EEG: Generalized slowing, occipital epileptiform discharges • MRI: Diffuse white matter changes
Sepsis associated encephalopathy (SAE)	• Underlying sepsis syndrome • CSF and imaging normal

HSV, herpes simplex virus; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; EEG, electroencephalogram; MRI, magnetic resonance imaging; CT, computed tomography; ICP, intracranial pressure; TBM, tuberculous meningitis; AFB, acid-fast bacilli; ADA, adenosine deaminase activity.

Lumbar Puncture

Urgent evaluation of CSF is required when there is a suspected infection of the CNS; provided the patient is hemodynamically stable, and has no features of raised ICP. A lumbar puncture is recommended in all patients with suspected CNS infections

Box 3: Contraindications of lumbar puncture

Lumbar puncture should be deferred in patients with

- Abnormal breathing patterns
- Shock
- Bradycardia (HR <60)
- Hypertension (BP >95th percentile)
- GCS <8 or deteriorating GCS
- Convulsive SE or NCSE
- Abnormal doll's eye movement
- Dilated pupils
- Impaired pupillary reaction to light
- Abnormal posture
- Features of raised ICP

HR, heart rate; BP, blood pressure; GCS, Glasgow Coma Scale; SE, status epilepticus; NCSE, non-convulsive status epilepticus; ICP, intracranial pressure.

who are febrile, have a GCS less than 12, and are less than an year old [probably with an open atrial fibrillation (AF)], and those who are clinically stable to undergo the procedure. In patients who are not stable, a neuroimaging study should be obtained prior to the lumbar puncture (Box 3).

Cerebrospinal fluid should be examined for pressure, gross examination for turbidity, cytology, biochemistry, Gram's stain, Ziehl-Neelsen stain for acid fast bacilli, bacterial culture, latex agglutination, polymerase chain reaction (PCR) for HSV 1 and 2, and IgM antibodies for JE and for dengue virus (if suspected), and additional cultures based on clinical suspicion (fungal or tubercular). Concurrent blood sugar must also be measured to look for the CSF to blood sugar ratio.

Usual CSF findings in viral encephalitis include lymphocytic pleocytosis, mild to moderately elevated protein, and normal CSF sugar. Similar findings may occur in tubercular meningitis and partially-treated pyogenic meningitis; however, the CSF sugar is likely to be low in these situations. Neutrophilic predominance is seen in pyogenic meningitis with high protein levels, and a Gram's stain, latex agglutination test or culture may clinch the diagnosis.

Empirical treatment should be started pending the results of lumbar puncture and/or neuroimaging studies. The CSF analysis is an important investigation in children with AES.

Neuroimaging

Decision for imaging should not delay the empiric therapy. CT scan of the brain is of limited value in a patient with AFE, since it does not definitely indicate either meningeal or parenchymal involvement; however, it may be the only possible option available in an emergency. It is known that CT scan is likely to be normal in many cases of viral encephalitis, especially in the early stages and is more likely to pick up abnormality in the later stages when the pathology is well established. Magnetic resonance imaging is more likely to pick up early lesions in patients with AFE and should be the radiological investigation of choice in such patients as soon as it is available.

Computed tomography (CT): If the child is afebrile and deeply comatose and/or has focal signs, it is preferable to do a CT scan prior to a lumbar puncture. Focal seizures and presence of focal neurological deficits indicate a localized lesion and are expected to be picked up by CT scan. Computed tomography scan may give valuable information such as presence of a bleed, and basal exudates and hydrocephalus in tubercular meningitis. The presence of diffuse edema on CT scan may suggest an underlying parenchymal involvement and focal hypodensities in temporal lobe and basal ganglia or thalamus may point towards a possible diagnosis of viral encephalitis (HSV or JE). Computed tomography may also show brain herniation, effacement of cisterns, and infective collections such as brain abscesses and subdural empyema. Computed tomography should be performed immediately when the examination suggests increased ICP (papilledema, bulging fontanel in infants, or bradycardia with hypertension) or a transtentorial herniation syndrome (Box 4).

Magnetic resonance imaging (MRI): If possible, an MRI should be obtained, as soon as the patient is stable. Magnetic resonance imaging is known to be superior in picking up subtle changes and is likely to be more helpful in establishing a diagnosis by picking up characteristic pattern of gray matter involvement and meningeal enhancement. Magnetic resonance imaging is more sensitive for early evidence of viral encephalitis and may show frontotemporal pathology in HSV infection, thalamic involvement in JE, and midbrain and pons involvement in enterovirus infection. It also picks up infarction, diffuse axonal injury from head injury, petechial hemorrhages, cerebral venous thrombosis and necrotizing lesions in acute necrotizing encephalopathy. Magnetic resonance imaging is also useful for diagnosing alternative etiologies such as ADEM (evident as demyelination on MRI), and antibody associated encephalopathies. Magnetic resonance imaging may also offer information regarding prognosis in patients with anoxic or traumatic coma.

Magnetic resonance imaging is not needed if the etiology is clear by other investigations, e.g., cerebral malaria, pyogenic meningitis; or if suggestive changes are seen on CT; or in epidemic situations where the likely etiology is already known. In all other patients, MRI provides useful information regarding the etiology and alternative diagnoses. However, the availability, cost, and difficulties in transporting sick and unstable patients for MRI may be limiting factors (Box 5).

Box 4: Indications of computed tomography

- Intracranial bleed
- Basal exudates and hydrocephalus (tuberculous meningitis)
- Herniation syndromes
- Brain abscess
- Subdural empyema

Box 5: Indications of magnetic resonance imaging

- Frontotemporal lesions (herpes simplex virus)
- Thalamic involvement (Japanese encephalitis)
- Midbrain and pons (enterovirus)
- Demyelination (acute disseminated encephalomyelitis)
- Infarction, cerebral venous thrombosis

Clinical Pearls

- Empirical treatment should be started pending the results of lumbar puncture
- Decision for imaging should not delay the therapy
- Magnetic resonance imaging is preferable to computed tomography, if available and affordable.

Step 4: Initiate Empiric Therapy

Empiric antimicrobial treatment is recommended when the diagnosis of bacterial meningitis or herpes encephalitis is strongly suspected, as early treatment improves prognosis of these conditions. Treatment may impair the diagnostic sensitivity of CSF cultures but should not affect other tests (total cell count, Gram's stain, or PCR). The recommended empiric therapy in a case of AFE is a combination of a third-generation cephalosporin, acyclovir and an antimalarial.

A broad-spectrum antibiotic such as ceftriaxone must be given in a dose of 100 mg/kg/day, which can be stopped if no evidence of bacterial meningitis is evident in the subsequent CSF analysis or imaging.

Acyclovir must be started according to age-specific doses, in all cases of suspected viral encephalitis, as HSE is a treatable disease, and can be stopped if the HSV PCR in CSF is negative or the MRI findings are not suggestive of the same. Children beyond the neonatal group should be treated with intravenous acyclovir in a dose of 10 mg/kg every 8 hours given as a 1-hour infusion. A positive MRI scan and EEG have 95% sensitivity in the diagnosis of HSE. However, if the CSF PCR for HSV or MRI have been performed very early after the symptom onset (within 48 hours), these may be falsely negative. Hence, these studies should be repeated before stopping acyclovir if the clinical suspicion of HSE continues to be high.

Empirical antimalarials must be started if there is a suspicion of cerebral malaria. The recommended antimalarial therapy is an artemisinin-based combination therapy consisting of artesunate + sulfadoxine-pyrimethamine or artemether + lumefantrine. Alternatively, quinine may be used with strict monitoring of blood sugar levels and ECG. This should be stopped if the peripheral smear and rapid diagnostic tests are negative.

KEY POINTS

Recommended Empiric therapy for AFE

☞ Ceftriaxone + Acyclovir + Antimalarial.

Step 5: Send Specific Investigations and Treat the Cause

When the etiology is not clear, other microbiological investigations must be obtained. These samples include urine, throat swab, nasopharyngeal aspirate, serum, and swab from vesicles or rash, if present. In patients having unexplained encephalopathy with fever and rash, testing for rickettsial infections (Weil-Felix test, and rickettsial serology) must be performed. HIV testing should be performed in children with unexplained encephalitis, as rarely, meningoencephalitis may be a presenting feature of primary HIV infection.

Additional studies may be indicated if there are clinical clues suggestive of particular infections. These may include HSV whole blood PCR in suspected cases of disseminated HSV infection and serologic testing for measles, mumps, arboviruses, varicella, EBV, syphilis, and Lyme disease.

Identifiable causes like DKA and hypertensive encephalopathy should be treated according to the recommended protocols. The clinician should always be alert to the possibility of child abuse in an infant/toddler with sudden unexplained altered consciousness.

In suspected cases of opioid ingestion, naloxone should be administered; atropine and pralidoxime should be given in suspected organophosphorus poisoning and flumazenil should be given for benzodiazepine overdose. Antivenom is recommended in cases of envenomation.

Other Tests

An EEG must be performed in all children with unexplained altered sensorium to look for suspected NCSE. Periodic epileptiform discharges may occur in NCSE but also in underlying brain injury without seizures. Diffuse theta and delta activity, absence of faster frequencies, and intermittent rhythmic delta activity are characteristic of severe encephalopathies. Periodic lateralized epileptiform discharges suggest herpes encephalitis or infarction. Multifocal or generalized periodic discharges can also be seen with metabolic and infectious etiologies and are characteristic of subacute sclerosing panencephalitis. Triphasic waves indicate a hepatic or uremic encephalopathy. Nonepileptiform features of the EEG, such as slowing or asymmetry, are largely nonspecific findings, but can sometimes provide diagnostic or prognostic information. Continuous EEG can be used to assess and titrate the depth of sedation in patients placed under anesthesia for control of status epilepticus or increased ICP. Electrocardiogram may also be helpful in patients with subtle and doubtful seizures, to guide antiepileptic drug management.

In cases of suspected metabolic abnormalities and unexplained or recurrent encephalopathy, blood ammonia, urine and blood samples for amino and organic acid disorders, free fatty acid and carnitine levels should be obtained before starting treatment and stopping feeds. Hyperammonemia may be caused by some inborn errors of metabolism, Reye's syndrome, liver failure, or valproate toxicity. Blood tandem mass spectroscopy, urine gas chromatography-mass spectroscopy can detect common causes of intoxication and drug abuse, and specific drug levels (suspected antiepileptic toxicity) should be obtained if specific ingestions are suspected. In selected cases, a urine toxicology screen, thyroid function tests and thyroid autoantibodies (Hashimoto's encephalopathy), cortisol levels, carboxyhemoglobin levels (carbon monoxide poisoning), autoimmune screen (cerebral vasculitis), and coagulation studies (coagulopathy) are recommended.

Step 6: Supportive Care

After stabilization of the airway, breathing, and circulation, other supportive care measures must be instituted along with the empirical treatment as mentioned above. Timely and appropriate supportive care is of paramount importance to reduce the mortality and morbidity associated with viral encephalitis. Patients with GCS less than 8, having features of raised ICP, status epilepticus, and shock should ideally be managed in an intensive care unit. Full sedation, controlled ventilation, and minimal handling with elevation of the head end of the bed at 30°, should be maintained during transport of the child.

Maintenance Intravenous Fluids

Fluid therapy should be targeted to maintain euvolemia and normoglycemia, and to prevent hyponatremia. Children with acute viral encephalitis should receive fluids at the normal daily requirement. Increased fluids and fluid boluses may be indicated for dehydration and hypotension. Serum sodium should be monitored, and abnormalities of serum sodium should be corrected slowly. Rapid correction of hyponatremia may lead to central pontine myelinolysis.

Other Drugs

Corticosteroids: Steroids are indicated in meningococcemia with shock, enteric encephalopathy, ADEM, Hashimoto's encephalopathy, and autoimmune encephalitis. The role of corticosteroids in the treatment of viral encephalitis is not established. However, corticosteroids may be considered along with acyclovir in patients with marked cerebral edema, brain shift or raised ICP. Dexamethasone is recommended prior to antibiotics in *H. influenzae* B meningitis, as it reduces the incidence of deafness and neurological handicap. However, this benefit is not certain for meningitis due to other organisms like *Pneumococcus*.

If metabolic causes have been identified, e.g., DKA, hepatic encephalopathy, uremia, or hyperammonemia, these should be treated appropriately. Concurrent bacterial infections like pneumonia should be appropriately treated. Haloperidol and phenergan may be used to combat the abnormal or psychotic behavior. Dopamine receptor blocking agents are used to control the choreoathetosis, and muscle relaxants and anticholinergics may help in the management of dystonia.

Step 7: Prevention/Treatment of Complications and Rehabilitation

The clinical course of the child should be monitored closely and documented on a daily basis. Particular attention should be paid to changing level of consciousness, fever, seizures, autonomic nervous system dysfunction, increased ICP, and speech and motor disturbances.

Supportive and rehabilitative efforts are very important after patients recover. Nosocomial infections, aspiration pneumonia, and coagulation disturbances may occur as complications, and should be detected and treated promptly. Motor incoordination, convulsive disorders, total or partial deafness, and behavioral disturbances are commonly seen after viral CNS infections. Visual disturbances due to chorioretinopathy and peripheral amblyopia may also be seen. Myocarditis and pulmonary edema are important complications of enteroviral encephalitis. Subdural effusions develop in 10–30% of patients with meningitis. Other complications include seizures, raised ICP, cranial nerve palsies, stroke, herniation syndromes, and thrombosis of the dural venous sinuses. Pericarditis or arthritis may occur in patients being treated for meningitis, especially that caused by *Neisseria meningitidis*.

Rifampicin chemoprophylaxis is recommended for all close contacts of patients with meningococcal and *H. influenzae* B meningitis. Vaccination for *H. influenzae* B is recommended for all children, and meningococcal and pneumococcal vaccine should be given to the high-risk groups. Vaccination for polio, measles, mumps, rubella and varicella should also be instituted. Control of insect vectors by suitable spraying methods and eradication of insect breeding sites reduces the incidence of arboviral infections and malaria.

Regular posture change must be done to prevent the development of bed sores. The patient should be started on early physiotherapy, to prevent the development of contractures. Neurodevelopmental and audiologic evaluations should be a part of the routine follow-up of children who have recovered from viral meningoencephalitis. Metabolic causes may need long-term dietary treatment. Psychological support needs to be rendered to the patient and family.

PROGNOSIS

The outcome of a child with an AFE depends on the etiology, and the depth and duration of impaired consciousness, the specific cause and the age of the child. Prolonged coma after a hypoxic-ischemic insult carries a poor prognosis. Most children surviving infectious encephalopathies have a comparatively better outcome, often surviving with mild or moderate difficulties only. Outcome has been shown to be worse for patients who were younger, had a lower GCS score on presentation, or had absent brainstem reflexes, poor motor responses, hypothermia, or hypotension. These children should be followed up for early identification of developmental disabilities, learning and behavior problems, as well as other neurological sequelae such as motor, visual, or hearing deficit and seizure disorder. Acute complications like motor deficits and cortical blindness improve with time.

CONCLUSION

Diagnostic approach to a child presenting with an AFE poses a real challenge, especially when the history is not reliable and the clinical findings are not contributory towards a specific etiology. A high index of suspicion should be maintained for a diagnosis in these patients as time is the essence in the management strategy. A systematic approach to the history, thorough physical examination and appropriate investigations aimed at recognition of the etiology could aid in the diagnosis. Early stabilization and institution of nonspecific-supportive

measures remain the cornerstone of management, and identification of the cause and its appropriate treatment need to be instituted in order to ensure the survival and also to prevent long-term sequelae, neurological or otherwise.

KEY POINTS

- ☞ Acute febrile encephalopathy is an altered mental state manifested by fever, coma, seizures, and/or decerebration
- ☞ Central nervous system infections are the most common cause of acute febrile encephalopathy in children
- ☞ A definitive diagnosis may not be possible even after a detailed diagnostic workup
- ☞ Early recognition, efficient decision making and institution of therapy can be lifesaving.

SUGGESTED READINGS

1. American Heart Association. 2005 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: pediatric basic life support. Pediatrics. 2006;117:e989-e1004.
2. Bansal A, Singhi S, Singhi P, Khandelwal N, Ramesh N. Non traumatic coma. Indian J Pediatrics. 2005;72:467-73.
3. Bauer T. Non-convulsive status epilepticus and coma. Epilepsia. 2010;51:177-90.
4. Bhalla A, Suri V, Singh P, Varma S, Khandelwal NK. Imaging in adult patients with acute febrile encephalopathy. Journal of Acute Disease. 2012;1:7-12.
5. Bhalla A, Suri V, Varma S, Sharma N, Mahi S, Singh P, et al. Acute febrile encephalopathy in adults from Northwest India. J Emerg Trauma Shock. 2010;3:220-4.
6. Chandran A, Herbert H, Misurski D, Santosham M. Long-term sequelae of childhood bacterial meningitis. Pediatr Infect Dis J. 2011;30:3-6.
7. Charles G. Prober,LauraLe Dyner: Viral Meningoencephalitis. In: Kliegman RM, Stanton BM, St. Geme J, Schor N, Behrman RE (Eds). Nelson Textbook of Pediatrics, 19th ed. Saunders Elsevier; 2011. pp. 2095-7.
8. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis. 2006;43:1565-77.
9. Grimwood K, Andersen P, Andersen V, Tan L, Nolan T. Twelve year outcomes following bacterial meningitis: Further evidence for persisting effects. Arch Dis Child. 2000;83:111-6.
10. Hazarika D. Approach to a child with fever and altered sensorium. Indian J Pract Pediatr. 2011;13:193-206.
11. Karmarkar SA, Aneja S, Khare S, Saini A, Seth A, Chauhan BK. A study of acute febrile encephalopathy with special reference to viral etiology. Indian J Pediatr. 2008;75:801-5.
12. Kirkham FJ. Non traumatic coma in children. Arch Dis Child. 2001;85:303-12.
13. Klig JE, O'Malley PJ. Pediatric office emergencies. Curr Opin Pediatr. 2007;19: 591-6.
14. 0Kneen R, Jakka S, Mithyantha R, Riordan A, Solomon T. The management of infants and children treated with acyclovir for suspected viral encephalitis. Arch Dis Child. 2010;95:100-6.
15. Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Pediatric Allergy Immunology and Infection Group National Guidelines. J Infect. 2012;64:449-77.
16. Koelfen W, Freund M, Gückel F, Rohr H, Schultze C. MRI of encephalitis in children: Comparison of CT and MRI in the acute stage with long-term follow-up. Neuroradiology. 1996;38:73-9.
17. Kothari VM, Karnad DR, Bichile LS. Tropical infections in the ICU. J Assoc Physicians India. 2006;54:291-8.
18. Logan SA, MacMahon E. Viral meningitis. BMJ. 2008;336:36-40.
19. Mikati MA. Status epilepticus. In: Kliegman RM, Stanton BM, St. Geme J, Schor N, Behrman RE (Eds). Nelson Textbook of Pediatrics, 19th ed. Saunders Elsevier; 2011. p. 2038.
20. Modi A, Atam V, Jain N, Gutch M, Verma R. The etiological diagnosis and outcome in patients of acute febrile encephalopathy: A prospective observational study at tertiary care center. Neurol India. 2012;60:168-73.
21. Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. Pediatrics. 2002;110:e21.
22. Parke JT. Acute encephalopathies. In: McMillan JA, Feigin RD, DeAngelis C, Jones MD (Eds). Oski's Pediatrics: Principles and Practice, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 2258.
23. Prober CG, Le Dyner L. Acute bacterial meningitis beyond the neonatal period. In: Nelson Textbook of Pediatrics, 19th ed. Saunders Elsevier; 2011:595:2087-2095.
24. Sankhyan N, Vykunta Raju KN, Sharma S, Gulati S. Management of raised intracranial pressure. Indian J Pediatr. 2010;77:1409-16.
25. Saunders M, Gorelick MH. Evaluation of the sick child in the office and clinic. In: Kliegman RM, Stanton BM, St. Geme J, Schor N, Behrman RE (Eds). Nelson Textbook of Pediatrics, 19th ed. Saunders Elsevier; 2011. pp. 275-8.
26. Schor NF. Acute disseminated encephalomyelitis (ADEM). In: Kliegman RM, Stanton BM, St. Geme J, Schor N, Behrman RE (Eds). Nelson Textbook of Pediatrics, 19th ed. Saunders Elsevier; 2011. pp. 2079-80.
27. Sharma S, Kochar GS, Sankhyan N, Gulati S. Approach to the child with coma. Indian J Pediatr. 2010;77:1279-87.
28. Sharma S, Mishra D, Aneja S, Kumar R, Jain A. For the expert group on Encephalitis, Indian Academy of Pediatrics: Consensus Guidelines on Evaluation and Management of Suspected Acute Viral Encephalitis in Children in India. Indian Pediatrics. 2012;49:897-910.
29. Shaw DW, Cohen WA. Viral infections of the CNS in children: imaging features. Am J Roentgenol. 1993;160:125-33.
30. Singh RR, Chaudhary SK, Bhatta NK, Khanal B, Shah D. Clinical and etiological profile of acute febrile encephalopathy in eastern Nepal. Indian J Pediatr. 2009;76:1109-11.
31. Stevens RD, Bhardwaj A. Approach to the comatose patient. Crit Care Med. 2006;34:31-41.
32. Taylor DA, Ashwal S. Impairment of consciousness and coma. In: Swaiman KF, Ashwal S, Ferriero DM (Eds). Pediatric Neurology: Principles and Practice, 4th ed. Philadelphia: Elsevier Publications; 2006. p. 1379.
33. Tenembaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. Neurology. 2007;68:S23-S36.
34. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guideline for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267-84.
35. Yeolekar ME, Trivedi TH. Febrile encephalopathy: challenges in management. J Assoc Physicians India. 2006;54:845-7.

CHAPTER 34

Management of a Child with Respiratory Distress

Sanjay M Bafna, Kochurani Abraham

INTRODUCTION

Respiratory distress (RD) is a manifestation of variety of pulmonary and extrapulmonary conditions. Prompt recognition and early intervention prevent progression of RD to respiratory failure (RF) and cardiorespiratory arrest.

This chapter describes general management approach to RD with main focus on emergency room management. Detailed specific management of conditions causing RD is discussed elsewhere in the book.

DEFINITIONS

Respiratory distress is a clinical state characterized by abnormal respiratory rate or effort. It commonly manifests as tachypnoea and increased work of breathing.

A child with neurological illness usually has abnormal pattern of respiration and/or bradypnoea.

Respiratory failure is defined as a clinical state of inadequate oxygenation or ventilation or both. It is often the end stage of RD.

PATHOPHYSIOLOGY

Most important function of respiratory system is oxygenation and ventilation. Impaired oxygenation in lungs results in hypoxemia. This may occur due to alveolar hypoventilation, V/Q mismatch or right to left shunt.

Tissue oxygenation depends on oxygenation in lungs, cardiac output, hemoglobin concentration, and tissue perfusion. Impairment of any of these would result in tissue hypoxia.

Inadequate ventilation is seen in airway disease, lung parenchymal disease, and central hypoventilation. This results in hypercarbia.

Conditions causing tissue hypoxia or hypercarbia result in RD as a compensatory mechanism to maintain adequate gas exchange.

When these compensations fail, child develops RF.

INITIAL EVALUATION AND STABILIZATION

The first priority is evaluation and stabilization of airway, breathing, and circulation.

Airway

The airway is assessed to see if it is patent or obstructed. This is done by "look, listen, and feel" for air movement. Abnormal airway sounds and/or poor air entry may indicate obstructed airway.

The airway can be clear, maintainable or not maintainable.

Clear Airway

Allow the child position of comfort.

Maintainable airway

This essentially means that the airway may be partially obstructed but is maintainable by simple maneuvers like positioning, suctioning, removal of foreign body, or use of airway adjuncts.

- Head tilt/chin lift: if the airway is blocked by the falling back of the tongue, it may be opened by this maneuver. The rescuer places one hand on the forehead and applies pressure to tilt the head back gently, to achieve neutral position in an infant and sniffing position in a child. Two to three fingers of the other hand should then be placed under the chin to lift it upwards. The thumb of this hand may be used to part the lips to keep the mouth open
- Jaw thrust: this is used in suspected cervical spine injury as head tilt-chin lift is contraindicated. This is achieved by placing two or three fingers under the angle of the mandible bilaterally, and lifting the jaw upwards.

Not maintainable airway

It may need one of the following advanced airway interventions:

- Endotracheal intubation
- Laryngeal mask airway in unconscious patient

- Application of continuous positive airway pressure (CPAP)
- Cricothyrotomy/tracheostomy
- Endoscopic removal of foreign body.

Breathing

This can be supported by administration of oxygen or by assisted ventilation. It is important to differentiate RD from RF at initial evaluation. Child with RF has features of hypoxemia and hypercarbia.

Clinical Pearl

- Respiratory failure is a clinical diagnosis. Arterial blood gas is done for confirmation and monitoring.

In a child with RD, maintenance of airway, administration of oxygen, etiological management, and monitoring may suffice. But in a child with RF, one must take total control of airway and breathing.

Oxygen Delivery

In a child with RD, proper administration of high concentration of oxygen is the mainstay of therapy. Oxygen is given in a nonthreatening manner to a child with RD, avoiding agitation as far as possible, as this increases the work of breathing and makes the flow of air turbulent thereby increasing the resistance to air flow. Taking the mothers help to provide oxygen goes a long way in decreasing the child's agitation. Nasal prongs and a simple face mask do not provide a high concentration of oxygen and are unreliable for use in the emergency room. The devices which can be used are a nonrebreathing mask with a flow rate of 10–12 L/m, an oxygen hood in infants with a flow of 10–15 L/m or a flow inflating bag with a flow rate of three times minute ventilation.

Assisted Ventilation

Child with severe RD or RF will need advanced airway measures and assisted ventilation. Assisted ventilation can be provided by bag-mask ventilation (BMV), noninvasive ventilation or endotracheal intubation and mechanical ventilation.

In most emergencies, effective BMV usually provides adequate oxygenation and ventilation until definite control of airway can be achieved. BMV can be as effective as ventilation through endotracheal (ET) tube for short periods of time and may be safer when provider is inexperienced in insertion of advanced airway.

Table 1 summarizes the initial management of child with RD.

ASSESSMENT TO DETERMINE THE SEVERITY AND TYPE OF RESPIRATORY PROBLEM

Severity

Once oxygenation and ventilation are stabilized, the severity is identified as respiratory distress or failure.

TABLE 1: Initial management of respiratory distress/respiratory failure

Evaluate	Interventions
Airway	• Support an open airway or if necessary, open the airway with ○ Head tilt-chin lift ○ Jaw thrust without head tilt if cervical spine injury is suspected. If this maneuver does not open the airway, use the head tilt-chin lift or jaw thrust with gentle head extension. • Clear the airway if indicated by suctioning or removal of visualized foreign body • Consider an oropharyngeal airway (OPA) or nasopharyngeal airway (NPA)
Breathing	• Monitor O_2 saturation • Provide humidified O_2. Use a high concentration delivery device like nonrebreathing mask for treatment of severe respiratory distress • Administer inhaled medication (e.g., salbuterol, epinephrine) as needed • Assist ventilation with bag mask device and supplementary O_2 if needed • Prepare for endotracheal intubation if indicated
Circulation	• Monitor heart rate, rhythm and blood pressure • Establish vascular access

Type

Respiratory problem is categorized as one of the following:

- Upper airway obstruction (UAO)
- Lower airway obstruction (LAO)
- Lung tissue disease
- Disordered control of breathing.

TARGETED INTERVENTIONS

Targeted intervention includes:

- General measures as per the type of respiratory problem
- Specific measures as per the etiology.

Following sections describe important emergency room measures in a child with RD. The specific measures depend on the underlying etiology, which are mentioned here briefly. The detailed description is given elsewhere in this book.

UPPER AIRWAY OBSTRUCTION

Acute UAO is an obstruction of large airways outside the thorax.

General Management

The most important priority in UAO is to open and maintain a patent airway. The measures needed to do so are described in table 1.

- When UAO is severe, call for help of a person with expertise in airway management
- In less severe UAO, children may benefit from insertion of an oropharyngeal airway (OPA) or nasopharyngeal

airway (NPA), which may relieve the obstruction caused by the tongue
- Use OPA only in comatose child
- A child with intact gag reflex may tolerate an NPA
- Child with redundant tissues or tissue edema may benefit from application of CPAP.

Clinical Pearl

- Failure to aggressively treat a partial upper airway obstruction can lead to complete airway obstruction and cardiac arrest.

Specific Management

Apart from initial interventions mentioned in table 1, additional measures as per etiology focus on relieving the obstruction. Table 2 summarizes the clinical features of various UAO

Foreign Body Aspiration

Management depends upon degree of obstruction.

Incomplete obstruction

(Child is breathing, coughing, and able to make sounds).
- Position of comfort
- Supplemental oxygen
- Rigid bronchoscopy.

Clinical Pearl

- Do not perform blind finger sweep, it may push the foreign body further into the airway.

Complete obstruction

(No sound, unable to cough, and unable to breathe adequately). Perform following maneuvers:
- Less than 1 year: five back blows followed by five chest thrusts
- More than 1 year: heimlich maneuver (abdominal thrust)

One of the given outcomes may follow:
- Relief from obstruction: evaluation
- Incomplete obstruction: managed as above
- Child becomes unresponsive: start cardiopulmonary resuscitation (CPR). Before you deliver a breath, look into the mouth. If you a see a foreign body that can be easily removed, remove it.

Angioneurotic Edema

Steps in management of anaphylaxis are summarized in box 1.

Clinical Pearl

- Hyperacute onset of breathlessness in an alert child should arouse suspicion of foreign body aspiration or anaphylaxis.

Acute Laryngotracheobronchitis

Treatment of child with acute laryngotracheobronchitis depends upon severity as described in table 3.

Box 1: Management of anaphylaxis

- Administer adrenaline 1:1,000 IM 0.01 mL/kg, repeated every 10–15 minutes as needed
- Treat bronchospasm with salbutamol metered-dose inhaler or nebulization
- For severe respiratory distress, anticipate further airway swelling and prepare for endotracheal intubation
- To treat hypotension:
  - Place the child in Trendelenburg position as tolerated
  - Administer normal saline bolus 20 mL/kg (repeat as needed)
  - Consider adrenaline drip for hypotension unresponsive to above measures
- Administer diphenhydramine and H_2 blocker
- Administer methylprednisolone or equivalent corticosteroid IV

TABLE 2: Differential diagnosis of acute upper airway obstruction

Etiology	Fever	Cough	Voice	Stridor	Dysphagia	Others
Epiglottitis	+++	Ineffective	Hot potato	Soft	+	Drooling of saliva Thumb sign on X-ray
Diphtheria	±	–	Normal to hoarse	In laryngeal involvement	+	Pseudomembrane, toxicity
Retropharyngeal abscess	+++	Ineffective	Muffled	Soft	+	Drooling of saliva, neck stiffness, soft tissue swelling on X-ray
Foreign body	–	Sudden choking	Hoarse	Depends upon level of obstruction	±	–
ALTB	+/–	Brassy	Hoarse	Harsh	–	Steeple sign on X-ray
Angioedema	–	Dry staccato	Hoarse	Varies	±	Swelling of lip, tongue, mucous membrane
Bacterial tracheitis	+++	Brassy	Hoarse	Harsh	–	Purulent tracheal secretions

ALTB, acute laryngotracheobronchitis.

TABLE 3: Management of croup

Mild	• Careful observation, monitoring. • Consider oral dexamethasone.
Moderate	• Administer humidified oxygen • Administer nebulized epinephrine • (1:1,000 solution at a dose of 0.5 mL/kg—max 5 mL) • Administer dexamethasone oral/IM/IV • (0.15–3 mg/kg) or budesonide 2 mg nebulization • Observe for at least 2 hours after nebulized epinephrine to ensure continued improvement.
Severe	• Administer high concentration of oxygen • Assist ventilation if necessary • Administer dexamethasone IV/IM • Perform endotracheal intubation if indicated • Prepare for surgical airway if needed.

Clinical Pearl

- In upper airway obstruction with signs of severe obstruction, place an advanced airway early even if SpO_2 is normal, as it drops much later.

LOWER AIRWAY OBSTRUCTION

General Management

- The most important priority is to maintain adequte oxygention and ventilation
- The aim is to maintain SpO_2 above 94%
- Use appropriate oxygen delivery device with optimum flow rate
- In severe RD, administer oxygen by nonrebreathing mask to provide 100% oxygen
- If assissted ventilation is required, perform BMV at relatively slow rate.

Clinical Pearl

- Ventilating at slow rate in lower airway obstruction reduces the risk of air trapping and complications of high airway pressure.

Specific Management

Common causes of LAO are asthma and bronchiolitis.

Management of Bronchiolitis

- Management is mainly supportive
- Administer humidified O_2
- IV fluids
- Suction oral and nasal secretions
- Trial of bronchodilators: continue only if favorable response is noted
- Severe cases need intensive care unit (ICU) care. Assess and provide ventilatory support if needed

TABLE 4: Management of acute asthma

Asthma severity	Interventions
Mild to moderate	• Salbutamol MDI with spacer +/– mask or nebulized salbutamol every 20 minutes—total three doses. • Administer oral prednisolone
Moderate to severe	• Hospitalize and start oxygen • Continue salbutamol nebulization 1–4 hourly or continuously • Administer steroids PO/IV • Add ipratropium bromide nebulization every 20 minutes for three times followed by 6 hourly • Consider magnesium sulfate • Perform diagnostic tests
Impending respiratory failure	• Consider adding following measures: ○ Start on terbutaline infusion and/or aminophylline infusion ○ In case of poor response or red flag signs: – Consider BiPAP in alert child – ET intubation and mechanical ventilation

MDI, metered-dose inhaler; BiPAP, biphasic positive airway pressure; ET, endotracheal.

- Hypertonic saline, steroids, ribavirin: conflicting reports, variable response. None have proven benefit.

Table 4 summarizes acute asthma treatment in emergency room.

LUNG TISSUE DISEASE

Common causes of lung tissue disease are:

- Pneumonia
- Cardiogenic pulmonary edema
- Acute respiratory distress syndrome (ARDS).

General Management

Initial interventions are listed in table 1.

In children with refractory hypoxemia, consider CPAP, noninvasive ventilation or mechanical ventilation with positive end-expiratory pressure (PEEP).

Clinical Pearl

- Saturated oxygen of arterial blood less than 90% on 100% oxygen is an indication for assisted ventilation.

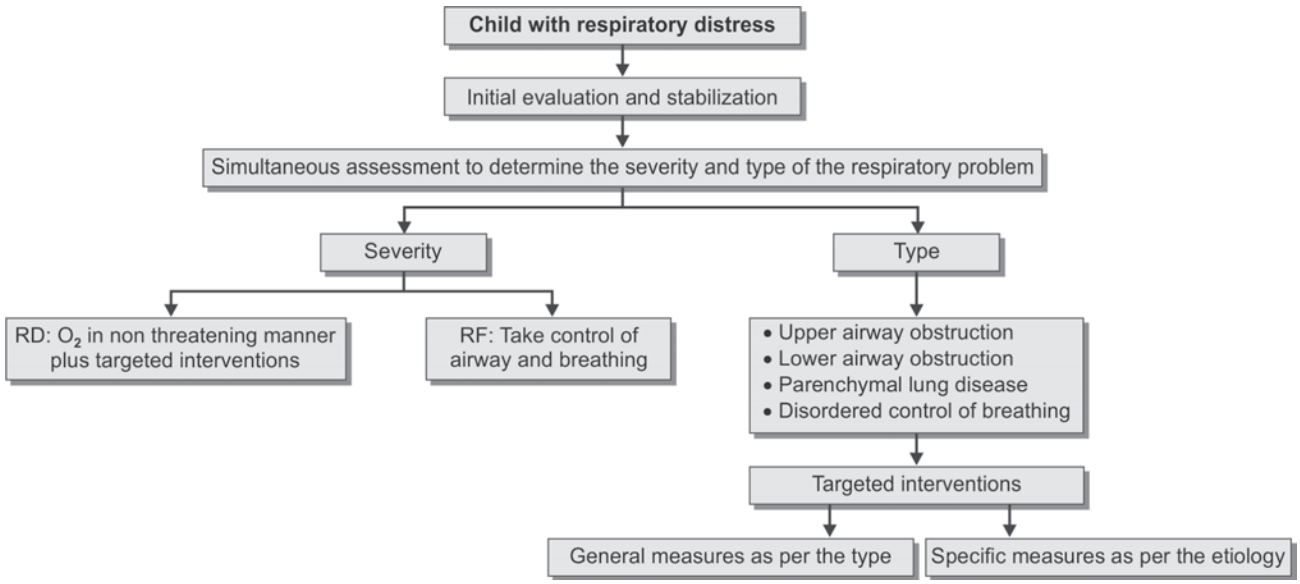
Specific Management

Acute Infectious Pneumonia

- Perform diagnostic tests—e.g., complete blood count (CBC), chest X-ray (CXR), blood culture, etc. as indicated
- Administer antibiotic therapy
- Treat wheezing with bronchodilators
- Consider using CPAP or noninvasive ventilation. Severe cases need intubation and mechanical ventilation
- Supportive measures: antipyretics, IV fluids, etc.

ALGORITHM 1

Step-wise management of a child with respiratory distress



RD, respiratory distress; RF, respiratory failure.

Cardiogenic Pulmonary Edema

The most common cause of acute cardiogenic pulmonary edema in children is left ventricular myocardial dysfunction.

- Provide ventilatory support as needed
- Consider diuretics to reduce left atrial pressure
- Inotropic infusions and afterload-reducing agents to improve myocardial function
- Obtain expert consultation.

Acute Respiratory Distress Syndrome

Early recognition and treatment of bacteremia, shock and RF may help prevent progression to ARDS.

- Obtain laboratory studies—CBC, ABG, serum electrolytes, blood culture etc. as indicated
- Provide ventilatory support as needed
- Indications for ventilator support:
  - Worsening clinical and radiological lung disease
  - Hypoxemia refractory to high concentrations of fraction of inspired oxygen.

DISORDERED CONTROL OF BREATHING

It results from affection of central control of respiration or neuromuscular weakness.

Important Aspects of Treatment

- Airway management
- Management of raised intracranial pressure (ICP)
- Treatment of the cause.

KEY POINTS

- ☞ The first priority in the management of a child with respiratory distress (RD) is to stabilize airway, breathing and circulation
- ☞ As this is being done, simultaneously the child is assessed to determine the severity and type of respiratory problem
- ☞ Subsequently, detailed evaluation (including investigations) is required to determine the underlying etiology of RD
- ☞ Treatment of RD consists of general measures depending upon the type of the problem and specific-targeted intervention as per the etiology
- ☞ Early recognition and a systematic approach to management are crucial for better outcome.

SUGGESTED READINGS

1. Agarwal R, Singh V, Yewale V (Eds). RTI facts; bugs, drugs and you. IAP Consensus Guidelines on Rational Management of Respiratory Tract Infections in Children. IAP Action Plan, 2012.
2. Everald ML. Acute bronchiolitis and croup. Pediatr Clin North Am. 2009;56:119-31.
3. Global Strategy for Asthma Management and Prevention—revised 2012. [online] Accessed from www.ginasthma.org. [Accessed December, 2015].
4. Helfaer MA, Nichols DG (Eds). Roger's Handbook of Pediatric Intensive Care, 4th edition. Lippincott Williams & Wilkins; 2010.
5. PALS Provider Manual. American Academy of Pediatrics and American Heart Association. 2011.
6. Subramanyam L. Essentials of Paediatric Pulmonology, 3rd edition. PPFI; 2008.
7. Wilmott RW, Boat TF, Bush A, Chernick V, Deterding RR, Ratjen F (Eds). Kendig and Chernick's Disorders of the Respiratory Tract in Children, 8th edition. Saunders; 2012.

CHAPTER 35

Hypovolemic Shock

Parmanand GK Andankar

INTRODUCTION

Circulatory shock is a common emergency encountered in pediatric practice. Shock has been defined as a pathophysiological state in which there is an inadequate supply or inappropriate use of metabolic substrate (particularly oxygen) by peripheral tissues. It is often classified as hypovolemic, cardiogenic, obstructive, or distributive.

CAUSES (BOX 1)

Hypovolemic shock is caused by a loss of intravascular fluid which is usually whole blood or plasma.

Whole blood loss (hemorrhagic): Blood loss may occur from an open wound or from concealed hemorrhage in the abdominal or thoracic spaces (e.g., hemothorax, lacerated liver, spleen or kidney, gastrointestinal hemorrhage), in retroperitoneal tissues (with ruptured aorta or coagulation abnormality) or in tissues surrounding bony fractures.

Plasma loss (nonhemorrhagic): Intravascular volume depletion due to excessive extracellular fluid loss with or without loss of plasma protein. For example, pancreatitis, peritonitis, burns, crush syndrome, and anaphylaxis tend to have a high plasma protein loss, whereas vomiting, diarrhea, excessive nasogastric/fistula/enterostomy losses, sodium-losing nephropathy, and diuretic therapy are usually associated with low, plasma-protein losses.

Box 1: Hemorrhagic and nonhemorrhagic causes of hypovolemic shock

Hemorrhagic	Nonhemorrhagic
• Gastrointestinal bleeding	• Heat stroke/water deprivation
• Surgery	• Vomiting/diarrhea
• Trauma	• Pharmacologic (e.g., diuretics)
• Hepatic or splenic rupture	• Burns
• Major vessel injury	• Nephrotic syndrome
• Intracranial bleeding	• Pancreatitis
• Long bone fractures	• Diabetes mellitus
	• Diabetes insipidus

Clinical Pearl

- Hemorrhage can be concealed in the abdominal or thoracic spaces, in retroperitoneal tissues or in tissues surrounding bony fractures.

CLINICAL FEATURES

The clinical features of hypovolemic shock are the same as those of shock (in general), i.e. tachycardia, poor peripheral pulses, delayed capillary refill time, cool extremities, pallor, and poor urine output. In addition, the child may have hypotension, dyspnea, and change in sensorium.

It is the history which provides specific clues to the shock being hypovolemic.

INVESTIGATIONS

Complete blood count, electrolyte levels (Na^+, K^+, Cl^-, HCO_3^-), blood urea nitrogen, creatinine, glucose levels, prothrombin time, activated partial thromboplastin time, arterial blood gases, and urinalysis.

Blood should be typed and cross-matched.

TREATMENT AND MANAGEMENT

Prehospital Care

- Prevent further injury
- Transport the patient to the hospital as rapidly as possible
- In patients with acute gastroenteritis with dehydration, start oral rehydration solution at home and during transport for hospitalization.

Prevention of Further Injury

- Cervical spine must be immobilized
- Splinting of fractures.

General Shock Management

Position of Child

Stable: Allow to remain with caregiver in a position of comfort.
Unstable: If hypotensive, place in Trendelenburg position unless breathing is compromised.

Airway

- Open, clear, maintained
- Consider intubation.

Breathing

- To optimize arterial O_2 content
- Start oxygen by nonrebreathing mask at flow rate 10–15 L/min
- Assist ventilation if required
- When in doubt, ventilate.

Circulation

- Establish venous access or intraosseous access or central line
- Replace fluid
- Give an isotonic fluid (crystalloid) bolus of 20 mL/kg to restore blood pressure and tissue perfusion
- For trauma and hemorrhage, administer packed red blood cells (PRBCs).

Monitor

- Mental status
- Heart rate
- Respiration
- Blood pressure
- Electrocardiogram
- Arterial oxygen saturation
- Temperature
- Urine output.

Clinical Pearl

- If peripheral access is not readily obtained, intraosseous access may be established quickly and reliably in patients of any age.

Fluid Therapy

Initiate fluid resuscitation as quickly as possible.

Reasons for fluid therapy

- Preserve oxygen delivery to tissues
- Correct hypovolemia
- Maintain cardiac output—Colloids + red blood cells
- Optimize gas exchange
- Replace electrolytes and water—Crystalloids
- Maintain urine output
- Identify the goal and choose the fluid which best achieves the goal.

What fluids?

Three randomized controlled trials compared the use of colloid to crystalloid resuscitation in children with dengue shock. No difference was shown in mortality between those resuscitated with colloid or crystalloid. Similarly, there were no differences in outcome (new organ failure, duration of ventilation, renal replacement therapy, or length of stay) and mortality after albumin administration (versus saline). Albumin and normal saline were equally effective for fluid resuscitation [Saline versus Albumin Fluid Evaluation (SAFE) Study]. Thus, isotonic crystalloid solutions are as effective as colloid solutions for the majority of patients with hypovolemic shock (Table 1).

Dutch Pediatric Society evidence-based clinical practice guidelines recommend that in neonates and children with hypovolemia the first-choice fluid for resuscitation should be isotonic saline.

If loss of protein containing fluids is documented or suspected (clue: low albumin), or if resuscitation is not responding to crystalloids, only then should colloids be administered.

In patients with crystalloid refractory hemorrhagic shock, PRBC 10 mL/kg should be administered promptly.

How much fluid?

Surviving sepsis guideline suggests that initial resuscitation begin with infusion of crystalloids with boluses of 20 mL/kg over 5–10 minutes. The amount of fluid necessary to restore effective circulating blood volume depends on amount of fluid lost and rate of ongoing losses. The volume of fluid required for resuscitation can be 40–60 mL/kg or higher. However, a child with nonhemorrhagic hypovolemic shock should generally respond to 40 mL/kg of crystalloid solution; if a child is unresponsive to this amount of fluid resuscitation, the child must be evaluated for complicating factors causing refractory shock, such as unrecognized pneumothorax or pericardial effusion, intestinal ischemia, sepsis, myocardial dysfunction, adrenocortical insufficiency, and pulmonary hypertension.

TABLE 1: Crystalloids versus colloids

Crystalloids	Colloids
• Includes 0.9% normal saline and RL	• 5% albumin, dextran, hydroxyethyl starch, and blood products
Advantages	
• Availability, low cost, and lack of exposure to blood products	• Maintain or increase oncotic pressure • Significant increase of intravascular volume • Stays in the intravascular compartment longer • Better perfusion • Less tissue edema
Disadvantage	
• Large volumes required	• Pulmonary edema can occur

RL, Ringer's lactate.

How fast?

As fast as possible (5–10 minutes).

How long?

It has been reported that up to 60 mL/kg of fluids may be given in first hour of therapy in shock without increasing risk of pulmonary edema. The rate of fluid administration should be reduced substantially when there are clinical signs of adequate cardiac filling with hemodynamic improvement. The end point of fluid resuscitation is when there is normalization of arterial blood pressure, pulse pressure, and heart rate, and adequate urine output and decrease in metabolic acidosis.

If shock persists, while one may continue with aggressive fluid resuscitation in aliquots of 20 mL/kg, one needs to carefully monitor vital parameters, and also more aggressive monitoring like continuous central venous pressure (CVP), for response of therapy.

In a hypotensive patient with a CVP of less than 10 mm Hg, in absence of pulmonary edema, more fluids can be given to achieve the desired preload.

Inspite of this, if there is no improvement in blood pressure, peripheral perfusion or urine output, the patient's diagnosis should be re-evaluated, and a probable cause of ongoing depletion should be sought. The child must be evaluated for complicating factors causing refractory shock such as unrecognized pneumothorax or pericardial effusion, intestinal ischemia, sepsis, myocardial dysfunction, adrenocortical insufficiency, and pulmonary hypertension.

If CVP is greater than 10 mmHg and shock persists, consider 2D echocardiography to rule out cardiac dysfunction.

In hemorrhagic hypovolemic shock, blood must be transfused if hypotension persists despite adequate crystalloid infusion. It must be noted that hematocrit is a poor indicator of severity of hemorrhage, because it does not decline in the setting of hemorrhagic shock.

Clinical Pearl

- Hematocrit is a poor indicator of severity of hemorrhage, because it does not decline in the setting of hemorrhagic shock.

When to start inotrope?

Fluid administration should be stopped and inotropes should be started when the ventricular filling pressure (CVP and 2D Echo) rises, without evidence of improvement in cardiovascular performance.

Additional/Special Considerations during Management of Hypovolemic Shock in Trauma Patients (Table 2)

Even as the primary assessment is being performed,

- Organize trauma team
- Call the surgeon
- Notify the blood bank.

During Primary Assessment

Airway

- Protect the airway, use adjuncts as required; if unstable—secure airway early
- Protect cervical spine.

Breathing

Provide high flow oxygen, assist ventilation as needed.

Circulation

- Secure two separate venous access with large bore cannula
- Send blood for grouping, cross matching
- Control external bleeding.

Disability

Assess neurological status—alert, voice, pain, unresponsive scale.

Exposure

Undress patient to look for additional injuries.

During Tertiary Assessment

Additional radiology: X-ray chest, pelvis, cervical spine (lateral).

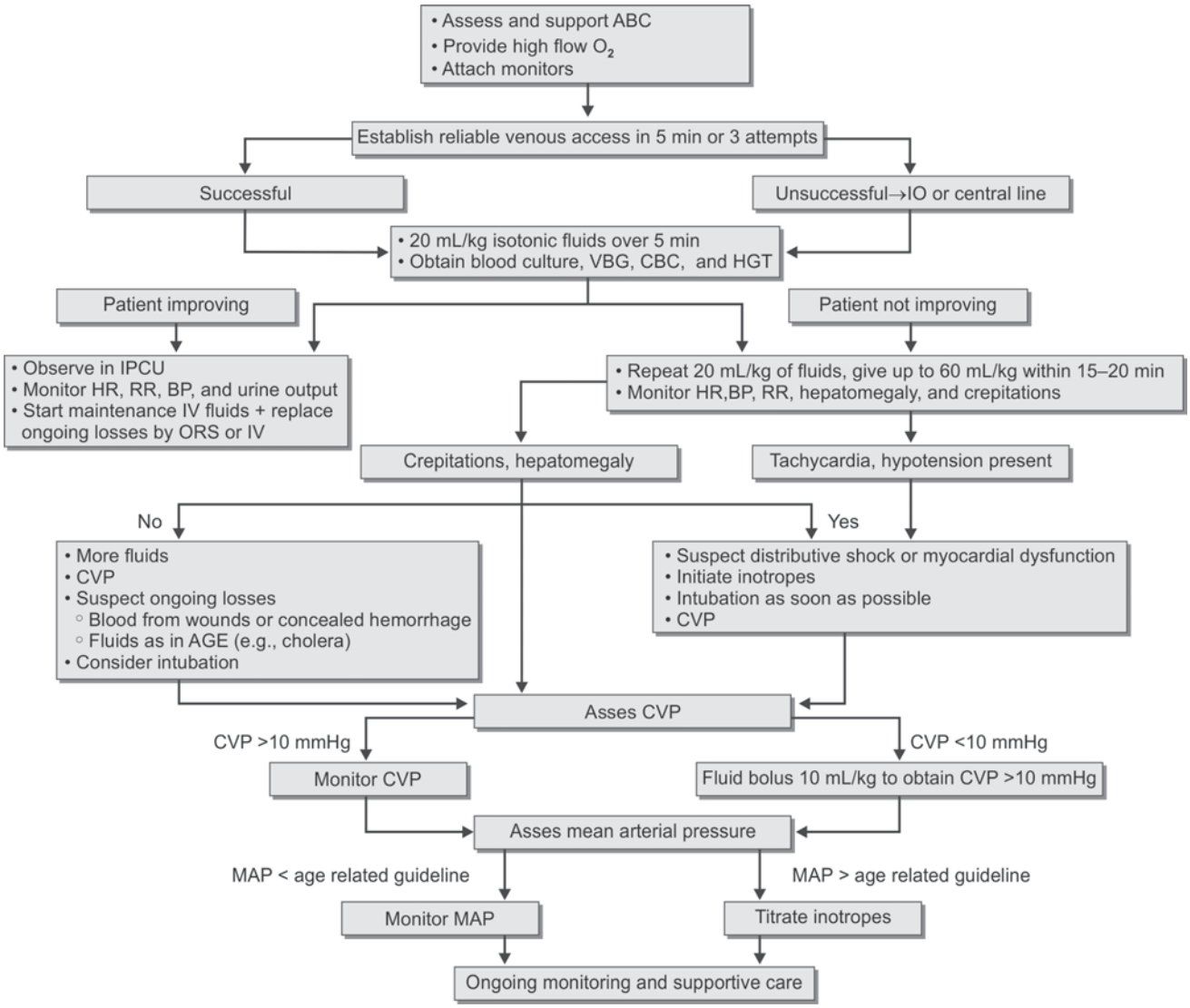
TABLE 2: Identification of source of hemorrhage and interventions

Identify the source of hemorrhage				
External	Long bones	Chest	Abdomen	Retroperitoneum
Careful visual inspection	Careful visual inspection	Chest X-ray	Diagnostic peritoneal tap/(FAST)	Pelvic X-ray
Interventions				
Apply direct pressure, suture lacerations	Splint, reduce fractures	ICD	Emergency laparotomy	Externally stabilize pelvis

FAST, focused abdominal sonography in trauma.

ALGORITHM 1

Algorithm for management of hypovolemic shock



ABC, Airway, Breathing and Circulation; IO, intraosseous; VBG, venous blood gas; CBC, complete blood count; IPCU, Intensive Psychiatric Care Unit; HR, heart rate; RR, respiratory rate; IV, intravenous; ORS, oral rehydration solution; CVP, central venous pressure; AGE, acute gastroenteritis; MAP, mean arterial pressure.

KEY POINTS

- ☞ The clinical signs of hypovolemic shock are the same as those of shock in general. It is the history which provides specific clues to the shock being hypovolemic
- ☞ While the need for fluids is obvious, one must administer oxygen to optimize arterial oxygen content
- ☞ Isotonic crystalloid solutions are as effective as colloid solutions for the majority of patients with hypovolemic shock
- ☞ One may need up to 40 mL/kg of fluid before a child with hypovolemic shock (nonhemorrhagic) responds; additional needs beyond this amount should prompt a review of other possibilities/complications
- ☞ There are additional/special considerations during the management of hypovolemic shock in trauma patients.

SUGGESTED READINGS

1. Fuhrman BP, Zimmerman JJ (Eds). Pediatric Critical Care, 4th edition. Elsevier; 2011.
2. Management of Shock, Pediatric Advanced Life Support.
3. Shaffner DH, Nichols DG (Eds). Roger's Textbook of Pediatric Intensive Care, 5th edition. Wolters Kluwer Health; 2015.
4. Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005;353(9):877-89.
5. Worthley LI. Shock: a review of pathophysiology and management. Part I. Crit Care Resusc. 2000;2(1):55-65.

CHAPTER 36

Approach to Fever in Children

Rhishikesh P Thakre

INTRODUCTION

Fever is one of the most common distressing signs of childhood illness. In majority, the cause is usually viral, self-limited, and benign, but in few it is due to serious underlying illness. The clinician's responsibility is to establish a correct diagnosis in reasonable time and initiate treatment, if indicated. This chapter focuses on approach to acute fever.

RECOGNIZING FEVER

The first step is to reliably document fever by measuring axillary temperature using digital thermometer. Use of oral and rectal routes is not recommended. A temperature above 38°C or 100.4°F is considered as fever.

Identifying "High Risk" for Serious Illness

One should be alert to and identify immediately any life-threatening features, including compromise of the airway, breathing, or circulation, and decreased level of consciousness (Box 1). This identifies seriously-ill children in need for urgent referral or treatment.

ASSESSMENT OF FEVER

The main goal of evaluation of febrile children is to distinguish those with mild self-limiting illness from those with serious bacterial infection (SBI).

An enquiry should be made about the nature of fever, defining when was the child last well, activity, sleep pattern, whether the child is getting better or worse, history of exposure to sick contacts, use of antipyretics or antibiotics (with their doses) taken or previous diagnostic tests done and their results. All efforts should be made to enquire about the oral intake, fluid losses, urination, recent travel, prior hospitalization, and vaccination status (Table 1).

Box 1: Assessing "danger signs" in febrile children

- A—Arousal, alertness, activity
- B—Breathing difficulty
- C—Color and Circulation
- D—Decreased intake and urine output

TABLE 1: Key points on history

Note	Comment
Onset	High fever from the very onset usually suggests viral infection, malaria, or localized bacterial infection at the site of entry of organisms (tonsillitis/UTI)
Duration	Persistent fever beyond day 3 without localizing signs calls for laboratory tests
Progress	Gradually- improving fever by day 3 or 4 suggests self-limiting viral infection, while bacterial infections peak by day 3 or 4
Interfebrile state	Children suffering from viral infection or malaria appear normal between fever spikes. If the child continues to appear sick even between fever spikes, the cause is likely to be a bacterial infection
Response to antipyretic	Poor response to optimum doses of paracetamol or ibuprofen may suggest severe bacterial infection
Accompanying symptoms	Bacterial infection usually presents with localization to a part of a system (such as tonsillitis or pneumonia) while viral infection usually affects the entire system or multiple systems (such as respiratory and gastrointestinal system)
Contact with similar illness	Family member with similar illness suggests airborne viral infection.
Past history of infective focus	Device (shunt, implant), underlying anomaly (CHD, VUR) predispose to early complication and need urgent evaluation

UTI, urinary tract infection; CHD, congenital heart defect; VUR, vesicoureteral reflux.

EXAMINATION

The purpose of examination is directed at locating a source for fever, with specific attention to potential SBI and resultant complications. Ill-appearing children are more likely than well-appearing children to have SBI, and most well-appearing children do not have SBI.

In addition to temperature one should record the heart rate, respiratory rate and capillary refill time as part of the routine assessment (Table 2).

ASSESSMENT FOR LOCALIZING SIGNS

Presence of associated symptoms or signs gives clue to underlying focus of infection (Table 3). Examination of the throat and ear is important and often missed. A systematic examination should then be conducted, including the skin and nails, head and neck, and the cardiovascular, respiratory, abdominal, musculoskeletal, and neurological systems. One should be aware that classical signs of meningitis like neck stiffness are classically seen in older children and are often absent in infants with bacterial meningitis. Hence, one has to have a high index of suspicion and look for subtle signs like bulging fontanel, irritability, high pitched cry, or any other indicator of altered sensorium (Table 4).

TABLE 2: Key points on general examination

Look for	Note
Appearance	Well or sick based on alertness, interaction, tone, cry, activity, and look. Lack of alertness indicates encephalopathy and underlying serious illness
Breathing	Normal or abnormal, apnea, type of breathing—rate and work of breathing. Breathing difficulty with altered sensorium indicates serious illness
Color	Pink color of extremities is assuring. Mottling, cyanosis, and ashen complexion indicate serious illness
Temperature	Degree and severity
Heart rate	Proportionate or disproportionate to temperature
Hydration	Assess the sensorium, skin turgor, eyes, mucous membrane, and urine pattern

TABLE 3: Common causes of fever

Fever with localization (<7 days)	Probable diagnosis
Watery nasal discharge	Viral URI
Purulent nasal discharge, follicles/ exudates on tonsils, petechiae on palate	Bacterial URI
Tachypnea with chest signs	Pneumonia
Watery stools	Viral AGE
Blood-mucus in stools, tenesmus	Bacterial AGE
Urinary complaints	UTI
Splenohepatomegaly	Malaria, typhoid, hepatitis, or infectious mononucleosis

URI, upper respiratory infection; AGE, acute gastroenteritis; UTI, urinary tract infection.

TABLE 4: Pointers to serious bacterial infections in a febrile child

Fast respiration (>60/min), chest indrawing, grunt	Pneumonia
Neck stiffness, bulging fontanel, decreased level of consciousness, convulsive status epilepticus	Meningitis
Unexplained vomiting, poor feeding, lethargy, irritability, abdominal pain or tenderness, urinary frequency or dysuria	Urinary tract infections
Disproportionate tachycardia, cool extremities, prolonged capillary refill (>3 seconds), core axillary mismatch, altered sensorium, oliguria suggests systemic inflammatory response causing shock	Septicemia
Nonblanching rash, particularly with one or more of the following: an ill-looking child, lesions larger than 2 mm in diameter (purpura, capillary refill time of ≥3 seconds, and neck stiffness	Meningococcemia
Swelling of a limb or joint, not using an extremity, nonweight bearing	Septic arthritis/ osteomyelitis

An attempt must be made to ensure that possibility of SBI has been ruled out on clinical grounds.

At times noninfective causes do present with short-duration fever and one should have a high index of suspicion for them (e.g., Kawasaki disease, leukemia).

INVESTIGATIONS

Many infections can be identified by history and examination alone, but some infections may be occult. The most common SBIs in infants that may not be clinically apparent are bacteremia, urinary tract infection (UTI), and pneumonia. Tempo and complexity of workup is decided by the pace of illness. Investigations must be done on all sick children and in those without localization by 72 hours.

- Complete hemogram: A white blood cell (WBC) count of greater than 15,000/mm^3 or less than 5,000/mm^3, a band-to-neutrophil ratio ≥0.2 is considered abnormal. An abnormality is a relatively poor surrogate marker for bacteremia (Table 5)
- Urinalysis (dipstick, urinalysis, microscopy, Gram's stain, culture) must be considered in presence of fever without localization, particularly in younger children or when UTI is suspected. A urine dipstick test positive for nitrite or leukocyte esterase or a finding of greater than 10 WBCs/hpf or organisms seen on Gram's stain is considered abnormal
- Chest X-ray is useful in children with respiratory localization. Chest film should be considered in an infant with an unexplained WBC count of greater than 20,000, or with prolonged fever or cough
- In children with no definitive diagnosis beyond day 3 or where antibiotic is to be initiated, blood culture must be done. It is the gold standard for the diagnosis of bacterial infection
- Cerebrospinal fluid (CSF) examination (cytology, Gram's stain and culture) is mandatory in every suspected case of meningitis and also in all sick infants without localization. CSF fluid with greater than 8 WBC/mm^3 or organisms on Gram's stain is considered abnormal.

TABLE 5: Interpreting hemogram

Hemoglobin	Total leukocyte count	Polymorphs	Lymphocytes	Eosinophils	Platelets	Disease
Normal	+++	+++	–	0	Normal	Acute bacterial infection
Normal	+++	+++	–	+	High	Systemic infection
Low	+++	+	+++	–	Low	ALL
Normal	++	++	–	0	Normal/low	Acute viral infection
Normal	Low	–	++	0	Normal/low	Typhoid
Low	+/–	–	–	+	Low	Malaria
High	+	–	++	–	Low	Capillary leak
Normal	+	–	++	+	Normal	Tuberculosis, chronic infection

No combination of clinical assessment and diagnostic testing will successfully identify all patients who have serious infection at the time of initial presentation; therefore, the importance of timely reassessment with good history, systematic confident clinical examination and intelligent use of laboratory tests, a rational approach cannot be overemphasized.

INDICATIONS FOR HOSPITALIZATION

Most infants and children who have fever and are otherwise healthy, who are well appearing with no localization can be managed on an outpatient basis. The degree of illness should be determined through the child's interactions with the environment; observing their alertness, playfulness and feeding pattern with appearance of any new symptoms (Box 2).

Box 2: Indications for hospitalization

- Febrile neonate
- Toxic child
- Presence of "danger signs"
- Admission for period of observation
- Pre-existing medical problem (congenital heart defect, immunodeficiency, malnutrition)
- Parental preference

MANAGEMENT OF FEBRILE CHILD (ALGORITHM 1)

- Supportive treatment: supportive treatment of fever is symptomatic. Not all fevers need treatment. Primary goal of treating the febrile child should be to improve the child's overall comfort rather than focus on the normalization of body temperature.

  Cooling: involves nursing in cool environment and unbundling the child. Sponging is reserved for patients with hyperthermia (temperature more than 38.5°C) after 30 minutes of antipyretic dose.

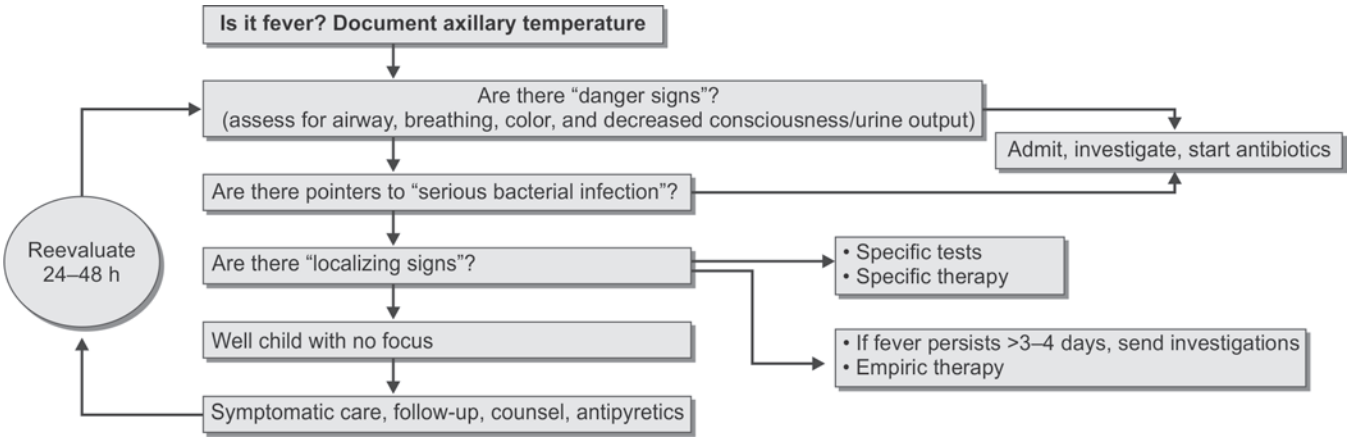
  Antipyretics: the use of antipyretics should be individualized and based on the child's well-being, not temperature alone. Antipyretics should be used as "therapy" for fever rather than "control". Treatment for fever with antipyretic is indicated if the child has discomfort, i.e., irritable, drowsy, greater than 40°C, pain, or excessive crying. Both paracetamol (10–15 mg/kg, 4–6 hourly) and ibuprofen (5–10 mg/kg, 6 hourly) are effective antipyretics.

  Hydration should be ensured for all febrile children by increasing oral intake as for every 1°C rise in temperature the fluid requirement increases by 10%.

  Empiric treatment: empiric treatment is not routinely recommended. It is justified only in toxic children and

ALGORITHM 1

Algorithm for acute fever



neonates and that too, only after sending relevant investigations. It is directed towards the probable underlying cause of illness and most probable organism.

Specific treatment: specific therapy should be directed towards the specific cause identified on evaluation like UTI, pneumonia, etc.

- Follow-up: not all febrile children have a focus identified on first evaluation. All such children should be followed up on outpatient department basis continuing with symptomatic treatment at home. Parents should be made aware about the danger signs and asked to report immediately if there are any concerns or appearance of new symptoms.

SPECIAL CIRCUMSTANCES: FEVER IN NEWBORN (<30 DAYS)

Physical examination has marked limitations to predict accurately a serious infection in neonates. All febrile newborns should be screened for complete blood count, CSF study and for culture of urine and blood. X-ray chest should be done if a respiratory cause is suspected. Febrile neonates should be hospitalized regardless of the results of laboratory studies and given intravenous antibiotics till infection is ruled out.

PARENT EDUCATION: FEVER PHOBIA

Parents should be made aware that fever is a symptom and not an illness. The severity of fever does not necessarily correlate with seriousness of illness. Child's well-being is more important than the height of the fever. The risk of febrile convulsion is less than 5% and it is a benign event.

Clinical Pearls

- Uncommon manifestations of common diseases are more likely than are rare diseases
- Clues to the diagnosis are frequently present in the history and physical examination but are not elicited or unappreciated. Therefore, thoroughness and repetition are vitally important.

KEY POINTS

- ☞ All febrile children should have periodic assessment for "danger signs"; presence of these should lead to prompt interventions
- ☞ Fever without focus in a well child should be treated symptomatically on OPD basis. Such children should be periodically evaluated. Empiric antibiotics should be avoided
- ☞ The emphasis should be on the child and not his temperature. Counseling parents about fever phobia is mus
- ☞ Decision-making in fever should take into consideration the child's age, general well-being, facilities, ease and reliability for follow-up.

SUGGESTED READINGS

1. Chiappini E, Principi N, Longhi R, Tovo PA, Becherucci P, Bonsignori F, et al. Management of fever in children: summary of the Italian Pediatric Society Guidelines. Clin Ther. 2009;31:1826-43.
2. Rapid approach to common symptoms. Standardization of pediatric office practice. Fever, 13-16. Indian Academy of Pediatrics; 2005.
3. Section on Clinical Pharmacology and Therapeutics; Committee on Drugs, Sullivan JE, Farrar HC. Fever and antipyretic use in children. Pediatrics. 2011;127;580-7.

CHAPTER 37

Approach to Poisoning in Children

Somashekhar M Nimbalkar

INTRODUCTION

Data regarding poison exposure is not well maintained in India; but based on global trends it can be assumed with fair approximation that the poison exposure in children in India would range above 8 million at the least.

ETIOPATHOGENESIS

Common causes of poisoning in India vary geographically and are dependent on access to various agents. Healthcare providers should be familiar with common poisonings in their area.

CLINICAL PRESENTATION

Most children present with nonspecific symptoms such as nausea, vomiting, or altered sensorium. However, there are certain toxidromes, which, on recognition, can give us a clinical diagnosis (Tables 1 and 2).

MANAGEMENT OF POISONING

Initial Assessment and Emergency Management

In a responsive patient, initial management in all patients presenting to the emergency is focused on airway, breathing, and circulation.

Airway

Presence of abnormal sounds like stridor, gurgling sounds, or noisy breathing may indicate that the airway is partially obstructed. Altered sensorium indicates that the child's airway is at risk. In such cases, measures to manage airway should be initiated. These may include positioning, oropharyngeal airways, laryngeal mask airways, or endotracheal intubation. Caustic agents, angiotensin converting enzyme inhibitors, and plants containing calcium oxalate crystals can predispose to airway edema and obstruction.

TABLE 1: Clinical manifestations of selected toxic ingestions

Ingestion	Clinical findings
Acetaminophen	• Early: nausea, vomiting, anorexia; jaundice and liver failure occur later
Antihistamines	• Initially CNS depression but stimulation in higher doses (tremors, hyperactivity, hallucinations, seizures)
Aspirin	• Tachypnea, respiratory alkalosis, metabolic acidosis, coagulopathies, slurred speech, tinnitus, seizures
β-blockers	• Bradycardia, hypotension, coma, convulsions, hypoglycemia, bronchospasm
Calcium channel blockers	• Hypotension, bradycardia, junctional arrhythmias, hyperglycemia, metabolic acidosis
Caustics	• Coagulation necrosis with acids or liquefaction necrosis with alkali; burning, scarring/strictures, dysphagia, glottic edema
Digoxin	• Nausea, vomiting, visual disturbances, lethargy, electrolyte imbalance, hyperkalemia, prolonged AV dissociation and heart block
Disk batteries	• Can cause corrosion if there is contact with mucosal surfaces

Continued

Continued

Ingestion	Clinical findings
Ethanol	• Early: nausea and vomiting, stupor, anorexia; late: coma, hypothermia, hypoglycemia • Life-threatening: cardiorespiratory depression if levels above 400–500 mg/dL
Ethylene glycol	• CNS depression, metabolic acidosis, convulsions and coma, renal failure, hypocalcemia, anion gap metabolic acidosis, osmolal gap, oxalaturia
Hypoglycemic agents	• Hypoglycemia, seizures, coma
Iron	• Hemorrhagic necrosis of GI mucosa, hypotension, hepatotoxicity, metabolic acidosis, shock, seizure, coma
Isopropyl alcohol	• Altered mental status, gastritis, hypotension, osmolal gap elevated, ketonuria without metabolic acidosis or hypoglycemia
Lead	• Abdominal pain, constipation, anorexia, listlessness, encephalopathy (peripheral neuropathy), microcytic anemia
Methanol	• CNS depression, delayed metabolic acidosis, optic disturbances, anion gap metabolic acidosis, osmolal gap
Tricyclic antidepressants	• Lethargy, disorientation, ataxia, urinary retention, decreased GI motility, seizures, coma • Cardiovascular alterations: sinus tachycardia, widened QRS complex; may progress to hypotension, ventricular dysrhythmias, cardiovascular collapse

CNS, central nervous system; AV, asterioventricular; GI, gasteointestinal.

TABLE 2: Toxidromes

	Mental status	Heart rate	BP	RR	Pupils	Laboratory and electrocardiographic findings
Acetaminophen	Early: nausea, vomiting Late: confusion, stupor, coma	–	–	–	–	Elevated aspartate transaminase, alanine transaminase, bilirubin after 24 h
Salicylates	Disorientation, lethargy, convulsions, coma	↑	–	↑	–	Respiratory alkalosis, progressive anion gap metabolic acidosis, hyperglycemia or hypoglycemia, electrolyte imbalances
Anticholinergics	Delirium, psychosis, seizure, coma	↑	↑	–	Large, sluggish	Sinus tachycardia (tricyclic antidepressants increase QRS interval)
Benzodiazepines	Drowsy, lethargy, coma	↓	–	↓	–	–
Calcium channel blockers	Drowsy, confusion	↓	↓	–	–	Heart block, metabolic acidosis, hyperglycemia
Stimulants	Agitation, delirium, psychosis, convulsions	↑	↑	↑	Large, reactive	–
Narcotics	Drowsy, coma	↓	↓	↓	Pinpoint	Respiratory acidosis
Organophosphates	Confusion, coma	↓	↓	↑	Small	–
Sedative/hypnotics	Somnolence, coma	↓	↓	↓	Variable	–

Clinical Pearls

- Abnormal sounds suggest partial airway obstruction
- If the patient has altered sensorium, the airway should be managed immediately.

Breathing

Respiratory rate, effort of breathing, retractions, breath sounds, chest expansion, and abdominal excursions are noted for the adequacy of breathing and ventilation. Children presenting with respiratory abnormalities or shock should receive high-flow oxygen through a nonrebreathing mask. Children with decreased consciousness and reduced respiratory effort should receive bag-mask ventilation with 100% oxygen. Bag-Mask ventilation should be done even with adequate saturation as children may have high levels of CO_2.

Circulation

Cardiovascular system is assessed by heart rate, pulse volume, capillary refill, blood pressure, coolness of skin, sensorium, and urine output. Crystalloids should be given to manage

hypovolemia, followed by inotropes and specific antitoxins as these can correct hypotension rapidly. In some poisonings, inotropes can worsen hypotension. In a similar fashion, arrhythmias should be managed with specific antidotes, crystalloids, and antiarrhythmics.

Disability

Neurological function is assessed by measuring consciousness, pupillary size, posture, and presence of convulsive movements. Level of consciousness can be measured by using the AVPU scale. Poisoning with opiates, sedatives, antihistamines, and hypoglycemic agents should be considered in children with lower level of consciousness. Large pupils suggest amphetamines, ecstasy, theophylline and tricyclic-antidepressant poisoning (all of these cause hypertonia) while small pupils suggest opiates and organophosphorus poisonings. Convulsions can be treated by lorazepam or midazolam. Trial of naloxone should be considered in suspected opiate poisoning.

Exposure

The core temperature of the child should be recorded. Salicylates, anticholinergics, sympathomimetics, cocaine, and dissociative drugs such as ketamine can cause a fever. Antipyretics are not effective and external and internal cooling measures should be used to reduce the core temperature to less than 39°C. Benzodiazepines, dantrolene, or paralysis and mechanical ventilation should be used to reduce excessive heat production due to agitation or muscle rigidity.

Monitoring and Investigations

Monitoring includes pulse oximetry, continuous ECG monitoring, noninvasive blood pressure monitoring, and core temperature monitoring. Blood investigations should include arterial blood gases and blood glucose.

Complete blood count, urinalysis, and tests of hepatic and renal function are done. If facilities exist then plasma drug concentrations of a few drugs such as paracetamol, salicylates, iron, lithium, theophylline, methanol, digoxin, ethylene glycol, anticonvulsants, methaemoglobin, and carboxyhemoglobin should be done. However, they should not be part of the general screen; rather they should be done only when suspected, for confirmation of the diagnosis. Usually the results are available later and do not impact initial management. Additionally, interpretation of results should be carefully done in neonates as levels of cholinesterase and carboxyhemoglobin may differ from children. A strip of the child's ECG should be studied, especially if arrhythmias are suspected, and a chest x-ray should be done if there is clinical suspicion of aspiration or pulmonary edema.

Results of investigations can assist in identifying drugs that may have caused the poisoning. Metabolic acidosis is seen with carbon monoxide, iron, methanol, ethylene glycol, tricyclic antidepressants, salicylates, tricyclic antidepressants, and ecstasy. An enlarged anion gap greater than 18 is found in ethanol, iron, methanol, salicylates, and ethylene glycol. Hypokalemia is seen in beta agonist and theophylline poisoning, while hyperkalemia is seen in digoxin ingestion.

Clinical Pearls

- Interpretation of drug concentrations and enzymes in neonates differs from children
- Activated charcoal does not absorb iron, metals, lithium, cyanides, petroleum distillates, and alcohol.

Poison Elimination

Minimizing toxin exposure: this step is especially helpful in cases of topical and inhaled toxin exposure. External toxin decontamination prevents ongoing toxicity to the child and also protects staff from exposure. The child needs to be disrobed including removal of jewelry, watches, etc. and the entire body or exposed area washed, preferably in a suitable area in the emergency room. Ocular exposures should be managed by irrigating the eye with copious isotonic saline (such as normal saline or lactated ringers) for at least half-an-hour or till normal ocular pH is obtained. Prior use of ocular anesthetics such as tetracaine will ensure better irrigation.

Toxin Elimination

The evidence for toxin elimination from the gastrointestinal tract is inconclusive, yet it continues to be used in certain circumstances. In asymptomatic children with nontoxic ingestions, it is not required. However, if the ingestion is recent, the child symptomatic, or there is a possibility of delayed toxicity, then decontamination by various methods is recommended.

Activated Charcoal

Activated charcoal has a surface area of 1,000 m^2/g, is safe and can be used in the dose of 1 g/kg per dose and is capable of binding a number of poisonous substances without being systematically absorbed. It, however, does not absorb iron, metals, lithium, cyanides, petroleum distillates, and alcohol. The dose is generally 10 times the estimated poison dose, and generally children are given 25–50 g. Repeated doses can be used in aspirin, barbiturates, and theophylline as they promote drug reabsorption from the circulation into the bowel and thus interrupt enterohepatic cycling. Charcoal is unpalatable and hence flavoring may be necessary. This does reduce charcoal's activity. Aspirated charcoal can cause lung damage. Usefulness of activated charcoal beyond 1 hour of ingestion is limited but can be considered, if delayed gut absorption is expected.

Emesis

Emesis by administration of ipecac syrup is not recommended for gastrointestinal decontamination.

Gastric Lavage

Lavage is not routinely recommended for decontamination due to variable results, lack of evidence of improved outcomes, and significant adverse effects. Gastric lavage is initiated in children who present within 1 hour. It is contraindicated in poisonings by most hydrocarbons, alkalis, and acids. In children, additional difficulty is encountered as the small size of the lavage tube makes it difficult to remove the toxin. Children often need to be intubated to facilitate the procedure, especially if they have altered sensorium. Most commonly it is effectively used in iron over ingestion and the usual fluid is water or isotonic solution, in aliquots of 10–20 mL/kg. To perform lavage, the child is placed on its left side and a lavage tube is passed into the stomach. Fluid is aspirated and small aliquots of fluid are instilled and reaspirated. This process is continued till the aspirate is clear. After lavage, the tube can be used for instilling specific antidote or activated charcoal.

Whole-Bowel Irrigation

This is not routinely indicated but is used in poisoning by sustained-release or enteric-coated drugs, metals such as iron and lithium, and drug packets that have long absorption time or are not bound by charcoal. A large volume (>1 L) polyethylene glycol electrolyte solution is administered at a fast rate, via nasogastric tube. Effectiveness is seen until about 4 hours after ingestion of enteric-coated tablets and sometimes even until about 12–16 hours after administration of some sustained-release medications. It causes formation of liquid stools and reduces transit time of intestinal contents.

Cathartics

These are of equivocal efficacy. Saccharide (Sorbitol) and saline (magnesium citrate) cathartics have been administered as a single dose.

Clinical Pearls

- Ipecac syrup is not recommended for gastrointestinal decontamination
- Cathartics are of unknown efficacy.

Other Methods of Elimination

Urinary alkalinization by the administration of sodium bicarbonate, effectively increases the elimination of drugs with a low pH such as salicylates and chlorpropamide. Alkalinization increases the ionized fraction of the drug in the tubular lumen, preventing its reabsorption. Hemodialysis is used for salicylates, toxic alcohols, lithium, and theophylline. Charcoal hemoperfusion, plasmapheresis, exchange transfusion and continuous ultrafiltration techniques may also be used.

Specific Antitoxins

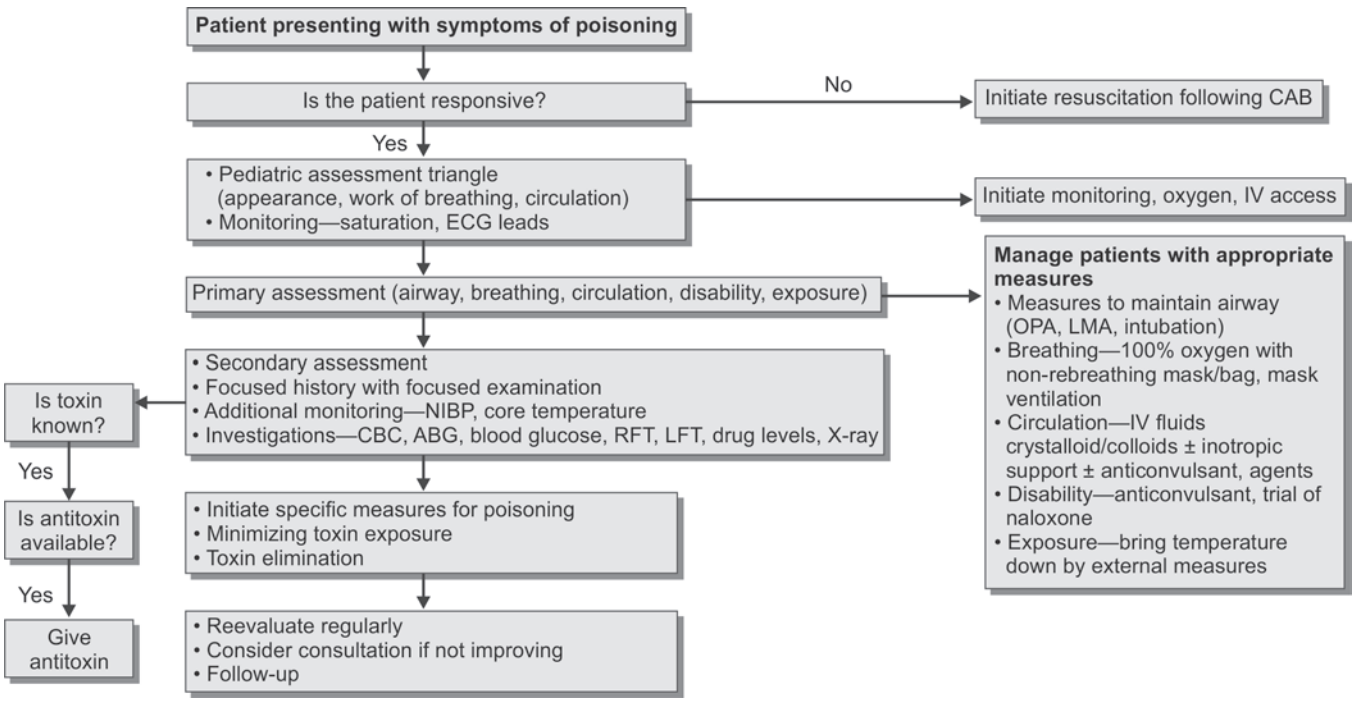
In some poisonings, antidotes which can counter the poison may be available (Table 3).

TABLE 3: Antidotes and management of selected toxic exposures

Ingestion	Potential antidote/Other management
Acetaminophen	N-acetylcysteine, activated charcoal within 4 h
Antihistaminics	Activated charcoal or whole bowel irrigation if extended-release formulations, anticonvulsants, physostigmine
Benzodiazepine	Flumazenil
β-blockers	Glucagon, activated charcoal if early after ingestion, whole bowel irrigation for delayed-release formulations, atropine, IVF, pressors
Calcium channel blockers	Calcium, activated charcoal if early after ingestion, whole bowel irrigation for delayed-release formulations, atropine, IVF, pressors, insulin/glucose
Cholinesterase inhibitors	Atropine, pralidoxime
Digoxin	Digoxin immune fab, activated charcoal, electrolyte management
Iron	Deferoxamine, whole bowel irrigation, hemodynamic support, monitor for possible GI bleed, treat acidosis, hypoglycemia, and hypotension
Isoniazid	Pyridoxine
Opioids	Naloxone
Salicylates	Correct electrolyte imbalance, fluid therapy, urine alkalinizers, hemodialysis
Sulfonylurea	Dextrose, octreotide
Tricyclic antidepressants	Activated charcoal, sodium bicarbonate to reduce cardiotoxicity, pressor support
Cyanide	Ensure airway, breating, circulation, 100% oxygen inhalation, sodium nitrite/sodium thiosulfate or hydroxocobalamin
Carbon monoxide	100% oxygen inhalation or hyperbaric oxygen
Caustic agents	Ensure airway, breating, circulation, steroid use in esophageal burns is controversial; hospitalize the patient to monitor for mediastinitis, pneumonitis, and peritonitis
Disk batteries	Removal if in esophagus; if below esophagus, watch for 3 days for passage with stools, if not passed out, consider surgical removal
Ethanol	Respiratory management, correction of hypoglycemia, temperature control, thiamine (in chronic alcoholism)
Ethylene glycol and methanol	Ethanol or 4-methylpyrazole if level >20 mg/dL, sodium bicarbonate, calcium, pyridoxine, thiamine, folate, hemodialysis
Lead	Chelation with edetate calcium disodium, 2,4-dimercaptopropanol, succimer, and anticonvulsants if required
Agents causing methemo-globinemic	Methylene blue

ALGORITHM 1

Management of poisoning



ECG, electrocardiography OPA,oropharyngeal airway; LMA, laryngeal mask airway; CBC, complete blood count; NIBP, noninvasive blood pressure; ABG, arterial blood gas; RFT, renal function test; LFT, liver function test; CAB, compressions, airway, breathing.

KEY POINTS

- ☞ Providers should be aware of most common poisonings that occur in the area they work
- ☞ Stabilization of the child is of prime importance
- ☞ Awareness of toxidromes will enhance ability to manage complex poisonings
- ☞ Investigations should be tailored to suspected toxins
- ☞ Consultation with a toxicologist is recommended.

Acknowledgement

The author would like to thank Dr Satvik Bansal for drawing the algorithms and Dr Shikha Kothari for editing the manuscript.

SUGGESTED READINGS

1. Abbruzzi G, Stork CM. Pediatric toxicologic concerns. Emerg Med Clin North Am. 2002;20(1):223-47.
2. Clinical Practice Guidelines: Paracetamol Poisoning from The Royal Children's Hospital accessed at http://www.rch.org.au/clinicalguide/guideline_index/Paracetamol_Poisoning/ on 12 Oct 2013.
3. Florin TA, Ludwig S. Poisoning. In: Florin T, Ludwig S, Aronson P, Werner H (Eds). Netter's Pediatrics. Philadelphia, PA: Elseiver/Saunders; 2011. pp. 56-61.
4. Jepsen F, Mary R. Poisoning in children. Current Paediatrics. 2005;15(7):563-8.
5. Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE. Poisonings. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE (Eds). Nelson Textbook of Pediatrics, 19th ed. Philadelphia, PA: Elsevier/Saunders; 2011. pp. 250-70.
6. Penny L, Tony M. Poisoning in children. Continuing Education in Anaesthesia. Critical Care & Pain. 2009;9(4):109-13.
7. Punja M, Hoffman RJ. Approach to poisoning. Critical Care Emergency Medicine. 2011. p. 409.
8. Rezaiyan T. Poisonings. In: Tschudy M, Arcara K (Eds). The Harriet Lane Handbook: a Manual for Pediatric House Officers, 19th ed. Philadelphia, PA: Mosby; 2011. pp. 19-56.

CHAPTER 38

Approach to Burns in Children

Vibha S Bafna

INTRODUCTION

Burn injuries are third leading cause of unintentional deaths in children. Around 90% of these burns are caused by household accidents mostly in the kitchen and mainly by scald injuries. Adolescents are often involved in flame burns, firecracker injuries, and high voltage electrical injuries.

This chapter deals with:

- Modern burn classification system
- Estimation of burnt body surface area
- First aid measures
- The initial triage and management strategy
- Further treatment
- Prevention.

MODERN BURNS CLASSIFICATION

Older descriptions of the burn injuries have now been replaced by superficial, partial thickness (superficial and deep) and full thickness burn injuries (Table 1) (Figs 1 to 4).

ESTIMATION OF BURNT BODY SURFACE AREA

Appropriate burn charts like the Barlow's or Lund and Browder chart, for different age groups should be used to estimate the extent of body surface area burnt (Table 2).

Clinical Pearls

- Accurate estimation of the burnt surface area and depth is required for fluid resuscitation and prediction of eventual morbidity and mortality
- In small burns, less than10% burnt surface area (BSA), the rule of palm may be used, especially in outpatient settings. The palm of the child is roughly 1% of the child's BSA.

FIRST AID MEASURES

- Remove the child from the harmful environment. Extinguish flames by rolling the child on ground, cover him with a blanket or a carpet

TABLE 1: Categories of burn depth

Criteria	1st degree burn (superficial)	2nd degree, or partial thickness burn (superficial and deep)	3rd degree, or full thickness burn
Surface appearance	• Dry, no blisters • Minimal or no edema • Erythematous • Blanches, bleeds	• Moist blebs, blisters • Underlying tissue is mottled, pink and white, fair capillary refill • Bleeds	• Dry, leathery eschar • Mixed white, waxy, khaki, mahogany, soot stained • No blanching or bleeding
Pain	• Very painful	• Very painful	• Insensate
Histological depth	• Epidermal layers only	• Epidermis, papillary, and reticular layers of dermis • May include domes of subcutaneous layers	• Down to and may include fat, sub-cutaneous tissue, fascia, muscle, and bone
Healing time	• 2–5 days with no scarring	• Superficial: 5–21 days with no grafting • Deep partial: 21–35 days with no infection • If infected: converts to full thickness burn	• Large areas require grafting • Small areas may heal from the edges after weeks

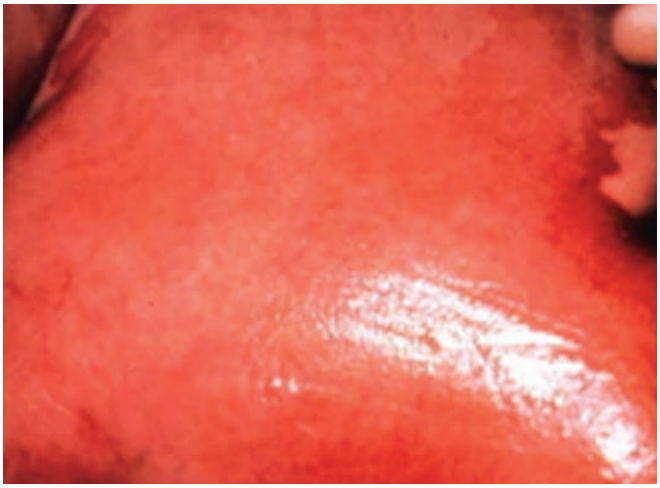


Fig. 1: Superficial partial thickness burn

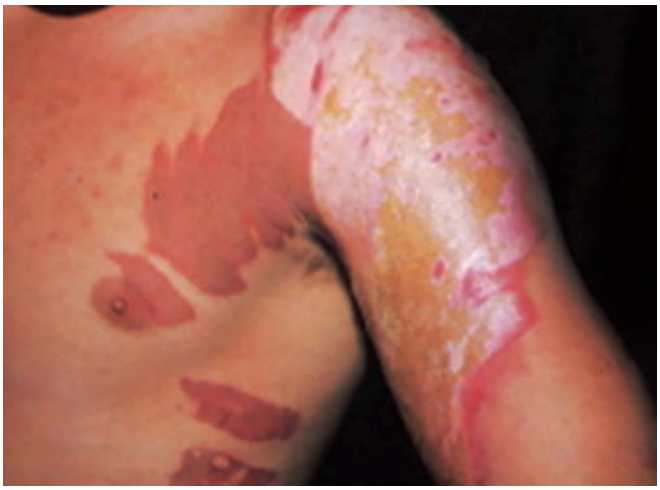


Fig. 2: Deep partial thickness burns

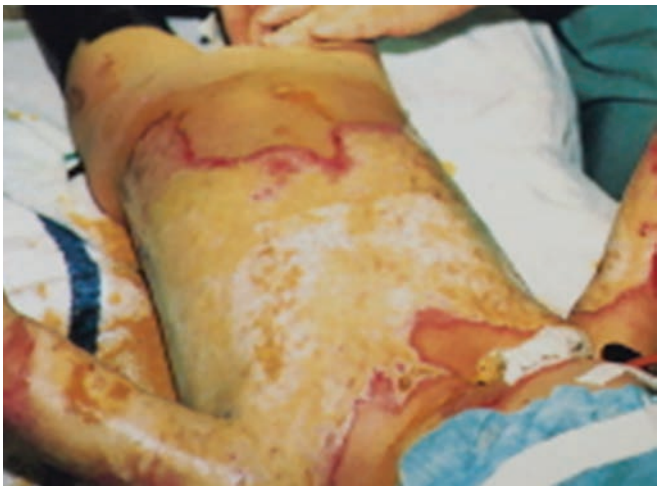


Fig. 3: Full thickness burns

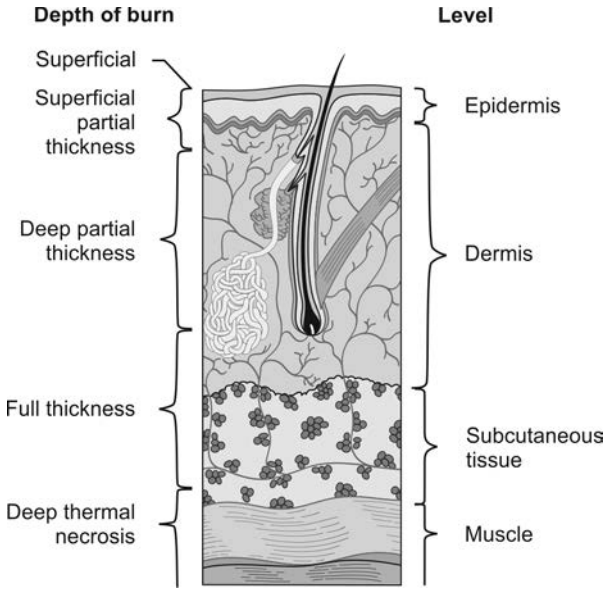


Fig. 4: Depth and level of burn

- Remove smoldering clothing or clothes saturated with hot fluids. Remove all jewelery, especially rings and bracelets to prevent constriction and vascular compromise
- In case of scalds, wash the area with copious water and cover it with cold wet compresses
- In case of chemical injury, brush off any remaining chemical and wash the affected area with water. Consider using a neutralizing agent
- In case of electrical burns, shut off the current before touching the victim yourself
- Administer analgesic medications as feasible
- Arrange for quick and safe transport to nearest adequately equipped medical facility.

INITIAL TRIAGE AND MANAGEMENT STRATEGIES

Rapidly review the cardiovascular and pulmonary status. Document pre-existing conditions like asthma, chronic heart, renal, or hepatic disease, etc.

Airway and Breathing

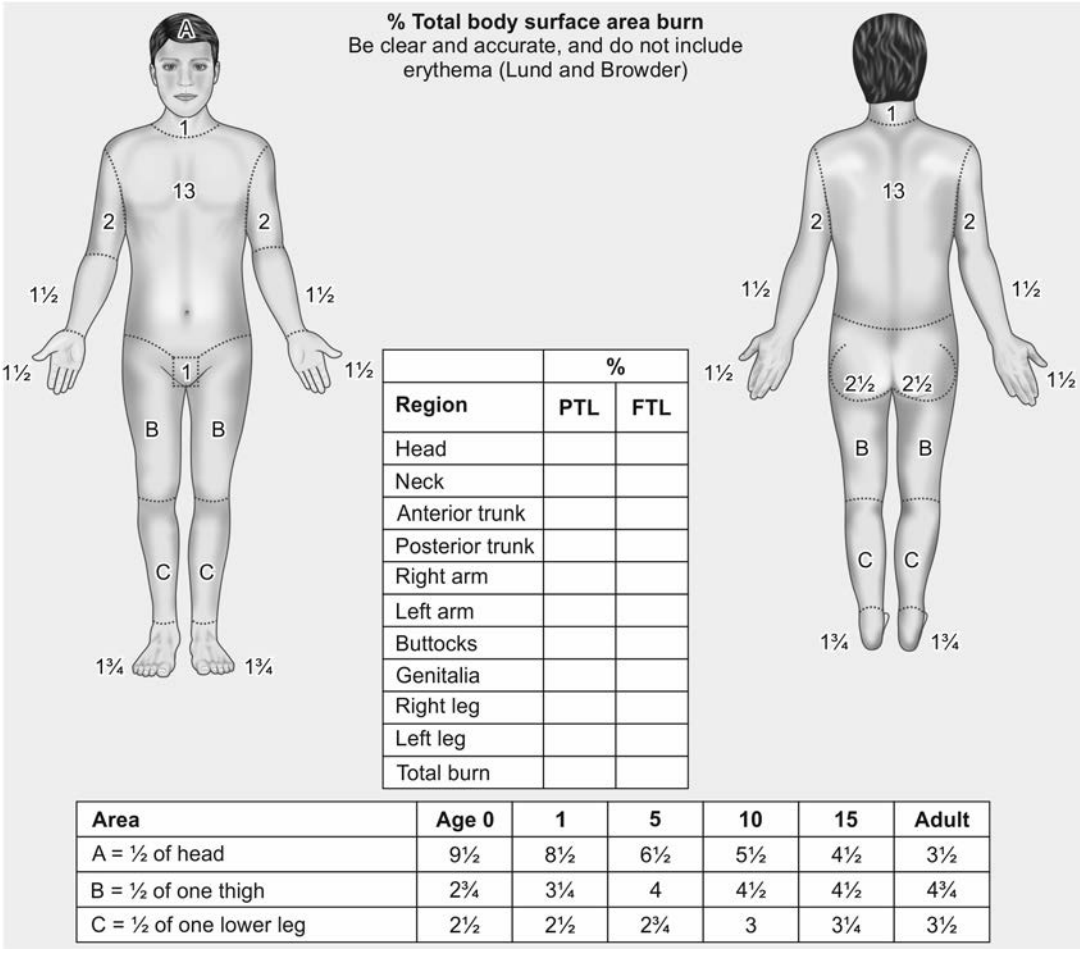
Ensure and maintain adequate airway and provide humidified oxygen. Endotracheal intubation may be required in patients with facial burns or burns in an enclosed space which can cause inhalational injury leading to laryngeal edema. Hypoxia or carbon monoxide poisoning is treated with 100% oxygen.

Circulation

Children with burns more than 15% of body surface area (BSA) require intravenous fluid resuscitation to maintain adequate perfusion. Ringer lactate 10–20 mL/kg/h is initially infused until proper fluid replacement can be calculated. All high tension electrical burns require forced alkaline diuresis to

TABLE 2: Barlow chart for estimating the percentage of burn area

Body part	0–1 yr	1–4 yr	5–9 yr	10–14 yr	15–18 yr	Adult
Head	19	17	13	11	9	7
Neck	2	2	2	2	2	2
Anterior trunk	13	13	13	13	13	13
Posterior trunk	13	13	13	13	13	13
Right buttock	2.5	2.5	2.5	2.5	2.5	2.5
Left buttock	2.5	2.5	2.5	2.5	2.5	2.5
Genitalia	1	1	1	1	1	1
Right upper arm	4	4	4	4	4	4
Left upper arm	4	4	4	4	4	4
Right lower arm	3	3	3	3	3	3
Left lower arm	3	3	3	3	3	3
Right hand	2.5	2.5	2.5	2.5	2.5	2.5
Left hand	2.5	2.5	2.5	2.5	2.5	2.5
Right thigh	5.5	6.5	8	8.5	9	9.5
Left thigh	5.5	5.5	8	8.5	9	9.5
Right leg	5	5	5.5	6	6.5	7
Left leg	5	5	5.5	6	6.5	7
Right foot	3.5	3.5	3.5	3.5	3.5	3.5
Left foot	3.5	3.5	3.5	3.5	3.5	3.5



Region	% PTL	% FTL
Head		
Neck		
Anterior trunk		
Posterior trunk		
Right arm		
Left arm		
Buttocks		
Genitalia		
Right leg		
Left leg		
Total burn		

Area	Age 0	1	5	10	15	Adult
A = ½ of head	9½	8½	6½	5½	4½	3½
B = ½ of one thigh	2¾	3¼	4	4½	4½	4¾
C = ½ of one lower leg	2½	2½	2¾	3	3¼	3½

avoid renal damage due to myoglobinuria caused by muscle injury. There is high risk of arrhythmias in electrical burns, so cardiac monitoring should be started immediately on arrival and cardiopulmonary resuscitation should be instituted promptly if indicated.

Associated Injuries

Evaluate the child for associated internal or external injuries. Cervical-spine injury precautions should be observed until it is ruled out.

Extent and the Depth of Burns

Assess with the help of appropriate charts.

Nil by Mouth

Children with more than 15% burns should not receive oral fluids initially to avoid gastric distension. A nasogastric tube should be inserted to avoid aspiration.

Catheterization

A Foley's catheter should be inserted to monitor urine output in all children who require fluid resuscitation.

Wound Care

All wounds should be wrapped with sterile towels till further plans of treatment are finalized.

Clinical Pearl

- Emergency room management of burns focuses on airway, breathing, and fluid resuscitation.

FURTHER TREATMENT

Outpatient Management of Minor Burns

First and second degree burns of less than 10% of BSA can be treated on an outpatient basis. They do not require tetanus vaccine except if they are unimmunized. Blisters should be left intact and dressed with silver sulfadiazine cream. Debridement of the devitalized skin is required after the blisters have ruptured.

INPATIENT MANAGEMENT OF BURNS (BOX 1)

This includes fluid and electrolyte management, administration of blood products, antibiotics, wound care, pain relief, and nutrition.

Fluid Resuscitation

Modified Parkland formula is most commonly used to calculate the initial fluid requirement.

Box 1: Indications for hospitalization for burns

- Burns affecting >15% body surface area
- Full thickness or third degree burns
- Electrical burns caused by high tension wiring or lightening
- Chemical burns
- Inhalational burns
- Inadequate home or social environment
- Suspected child abuse or neglect
- Burns to face, hands, feet, genitalia, perineum, or major joints
- Burns in patient with significant pre-existing medical conditions
- Associated injuries like fractures

- First 24 hours:
  - 4 mL/kg/% of BSA burn of ringer lactate. The first half is infused over 8 hours and the rest is given over the next 16 hours from the time of burn and not from the time of hospitalization
  - In addition routine maintenance fluids are continued.
- Second 24 hours:
  - Half of the first day's fluid is infused as ringer lactate in 5% dextrose
  - Decrease sodium concentration in fluids in infants if urinary sodium is rising
  - The choice of fluids as colloids or crystalloids is presently controversial. Colloids may be preferred in burns more than 85% BSA, to be started after 8–24 hours of injury.

Assessment and Monitoring

Monitor: vitals, urine output, mental status, acid-base balance, hematocrit, and serum proteins. Adjust fluids according to patient's response.

Catheterization: it should be done in all children needing fluid resuscitation or those with genital/buttock or upper-thigh burns.

IV access: in case of major burns, an adequate central venous access must be secured for fluid replacement and for central venous pressure monitoring in patients with hemodynamic instability. Consider arterial line in patients needing frequent blood gas monitoring.

Initial investigations: hemogram, urine routine, electrolytes, blood sugar level, renal function test, serum proteins, other tests (arterial blood gas, prothrombin time, partial thromboplastin time and cultures, etc. are done as indicated.

Electrolytes

Sodium: supplementation may be required for children with more than 20% burns, if 0.5% silver nitrate solution is used as topical antibacterial burn dressing. Oral sodium chloride, 4 g/m^2 BSA/day is given in 4–6 divided doses to maintain sodium above 130 mEq/L.

Potassium: Maintain levels above 3 mEq/L. Potassium losses are increased with 0.5% silver nitrate solution or in patients on aminoglycosides, diuretics, or amphotericin.

Subsequent Fluids and Feeding

Oral feeding may be started as early as 48 hours after a burn injury with the help of a nasogastric feeding tube. IV fluids are decreased according to the oral feeds tolerated so as to keep the total fluid intake constant.

Blood Products: Indications

Packed red blood cells are infused for Hb of less than 8 g/dL. Consider transfusion in patients with Hb less than 10 g/dL with systemic infection, hemoglobinopathy, cardiopulmonary disease, or anticipated (or ongoing) blood loss when repeated grafting is needed.

Albumin: 5% albumin is infused to maintain a serum albumin level above 2 g/dL. Following amount is infused over 24 hours starting on second day.

Body surface area (BSA)	30–50%	50–70%	70–100%
Albumin (mL/kg/% BSA)	0.3 mL	0.4 mL	0.5 mL

Fresh frozen plasma: it is indicated for a deranged prothrombin time (>1.5 times) or activated partial thromboplastin time (>1.2 times) in children who are bleeding or scheduled for a procedure that could result in blood loss of more than half blood volume.

Prevention of Infection/Role of Antibiotics

The use of prophylactic antibiotics is controversial. Children with more than 30% burns should be treated in a bacteria-controlled segregated unit.

Mortality related to burn injury results from metabolic and bacterial consequences of large open wound, reduction of host defense and malnutrition. Specific sites of infection include wound infection, pneumonia, urinary tract infection and blood stream infection.

Fever alone may not be indicative of infection as it may result from hypermetabolic response. Serial evaluation of burn wound and close monitoring of vitals and other parameters is crucial for early detection of infection. Sepsis screen includes blood cultures, wound swabs, throat swab, sputum, urine, and stool.

An attempt should be made to isolate the organism before starting empirical therapy. Broad spectrum antibiotic with Gram-positive coverage (*staphylococci*) should be used.

Wound Care and Surgical Management

Wound treatment and prevention of wound infection promote early healing and improve aesthetic and functional outcomes.

Topical treatment of burns can be done with silver nitrate, silver sulfadiazine, or mafenide acetate. These agents can penetrate tissue and prevent infection. Wound coverings like Aquacel-Ag (absorptive hydrofiber dressing impregnated with silver) and biobrane (bilaminate membrane with an outer layer of silicone and an inner layer of a nylon mesh impregnated with collagen, induces epithelization and neovascularization) are newer options used in extensive burns. Accuzyme ointment is a topical enzymatic debridement agent useful in deep second degree wounds to remove dead tissue and aid early healing.

Deep 2nd degree and 3rd degree burns should be excised early and grafted. Sequential excision and grafting is often required in deep burns.

Clinical Pearl

- Second and third degree burns need immediate surgical referral.

Prompt excision and wound closure is achieved with autografts. Alternatives for wound closure include allograft, xenografts, and other synthetic skin coverings which may be useful in extensive burns to limit fluid, electrolyte, heat and protein loss, and to reduce pain.

Pain Relief

Adequate analgesia, anxiolytics, and psychologic support is necessary to reduce early metabolic stress and long-term post-traumatic stress disorders. Opiate analgesics like morphine and anxiolytics like lorazepam can be used in conjunction for synergistic effect. Procedures like dressing change and debridement will require adequate sedation and pain relief with same agents used by IV route. Ketamine is another good option for procedural sedation.

Nutritional Support

The burn injury produces a hypermetabolic response causing protein and fat catabolism. Energy expenditure can be curtailed by early excision and grafting, controlling ambient temperature and humidity, thus avoiding cold stress, treating anxiety and pain, and allowing appropriate sleep intervals.

High calorie support consisting of 1,800 cal/m^2/day plus 2,200 cals/m^2 of burn/day and high proteins, i.e., 3–4 g/kg/day reduces metabolic stress. Multivitamins, especially B group, vitamin C, and A, and zinc are also essential.

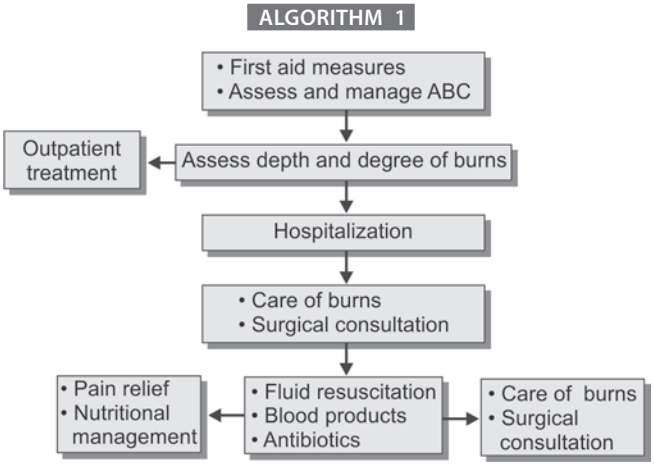
Alimentation should be started as soon as possible, parenterally or enterally to meet the high caloric needs. Parenteral nutrition should be changed to enteral as soon as practical, to decrease infectious complications.

INHALATIONAL INJURY

It should be suspected in case of: (1) exposure to direct heat—e.g., steam burns. (2) Child with acute asphxia. (3) Carbon monoxide (CO) poisoning. (4) Exposure to toxic fumes—e.g., cyanides from combustible plastics.

The consequences of burns with inhalational injury can be:

- Early CO poisoning, airway obstruction, pulmonary edema
- Acute respiratory distress syndrome usually evident at 24–48 hours, although it can occur even later
- Late complications (days to weeks)—pneumonia and pulmonary emboli.



ABC, airway, breathing, circulation.

Treatment

- Maintaining a patent airway by prompt intubation and adequate ventilation and oxygenation
- Beta-agonist aerosols and inhaled corticosteroids are helpful in cases with wheezing
- Carbon monoxide poisoning is treated with 100% oxygen but severe cases may require hyperbaric oxygen therapy
- Patients with severe inhalational injury not responding to conventional ventilation may require high-frequency ventilation, nitric oxide inhalation and finally extra-corporeal membrane oxygenation.

RECONSTRUCTION AND REHABILITATION

Occupational and physical therapy should begin as soon as the initial salvage measures are over and continued throughout the hospital stay. Services of child therapists may be required to ease the early and long-term psychological problems of the child and his care providers.

PREVENTION OF BURNS

Pediatricians can play a major role in preventing the most common burns by educating parent and caregivers.

KEY POINTS

- ☞ Appropriate first aid and initial emergency evaluation and treatment are the keystones in successful management of burn injury
- ☞ The key areas of indoor management of large burns are—fluid and electrolytes balance, wound management, prevention and treatment of infection, pain relief, and adequate nutrition
- ☞ A large number of burns in children can be prevented by simple and effective measures. Education of parents and other care providers plays a very important role in prevention of burn injuries.

SUGGESTED READINGS

1. Antoon AY, Donovan MK. Burn injuries. In: Kliegman, Stanton, St. Geme, Schor and Behrman (Eds). Nelson Textbook of Pediatrics, 19th ed. Elsevier, Saunders.
2. Chugh K (Ed). Management of Burns in Children in Manual of Pediatric Intensive Care & Emergency Medicine, 2nd ed.
3. Gupta RK, Gupta R. Approach to a child with burns. In: Gupte S (Ed). Recent Advances in Pediatrics. Neonatal & Pediatric Intensive Care. New Delhi: Jaypee Brothers; 2011.
4. Lund CC, Browder NC. The estimation of area of burn. Surg Gynecol Obstet. 1944;79:352.
5. Papinir HS. Initial management of a major burn II; assessment and resuscitation. BMJ. 2004:329;101-3.

CHAPTER 39

Approach to Envenomation

Mandar B Patil

INTRODUCTION

Certain reptiles and arthropods secrete and introduce poisonous fluids into the body of their victims by stings and bites. This is known as envenomation.

The most common envenomation encountered is due to snakes and scorpion bites followed less commonly by bee and wasp sting and rarely by lizards.

APPROACH TO SNAKE BITE

India is inhabited by about 244 species of snakes of which 57 are poisonous or harmful. The commonly encountered poisonous snakes in this region include cobra (Naja naja), common krait, Russell's viper, saw-scaled viper, and less commonly sea snakes.

How to Identify Venomous Snake

Diagnosis of the species of the bitten snake is important for optimal clinical management. This is achieved by examining the dead snake or by the clinical examination of the victim.

Commonly encountered poisonous snakes include (Fig. 2):

- *Naja naja*: it is the commonest Indian cobra. It is identified by the famous spectacle mark on the hood. When challenged, cobras rear up, spread a hood, hiss, and make repeated strikes towards the aggressor
- Common krait: it is smooth bluish-black with a rounded head slightly distinct form the neck. There are normally about 40 thin white cross bands. The under surface is white
- Russell's viper: the scales are very rough. The pupil of the eye is distinctly vertical. The body has black edged almond shaped marks. The best recognition characters are the short, fat body, the triangular shaped head and a very regular chain-like pattern. When threatened, it makes a loud and characteristic hissing sound
- Saw-scaled viper: the scales are rough and heavily keeled, eyes are large, and the head is wider than the neck. The body is brown-greyish with a darker zigzag pattern mark on the back and a distinct or lance mark on the head. The under surface is white with brown speckles. When challenged, the grating rasp is both a warning as well as an identifying sound.

TABLE 1: Differences between a poisonous and nonpoisonous snake (Fig. 1)

Poisonous snake	Nonpoisonous snake
Head is triangular-shaped with small scales	Head is rounded with large scales
Pit between the eye and nostril (pit viper)	No pit
Jaw scales: • Third labial touches eye and nasal shields (cobra, king cobra, coral snake) • Central row of vertebral scales enlarged • Four large infralabial scales (krait)	–
Fangs are long and grooved	Short and solid
Teeth have two long fangs	Several small teeth
Belly scales are large and cover entire breadth	Small or large scales but do not cover the entire breadth
Tail is compressed	Not much compressed
Usually nocturnal habits	Not necessarily

CLINICAL FEATURES (ALGORITHM 1)

Clinical features suggestive of nonvenomous snake bite are (also seen in a poisonous snake bite without envenomation or bite through clothing or leather boots) (Fig. 2):

- Universal fear—a state of shock
- Multiple teeth impressions at bite site
- Absence of significant local swelling or pain
- Anxious victims may overbreathe and develop tingling and numbness in the limbs, stiffness or tetany of hands and feet, and dizziness.

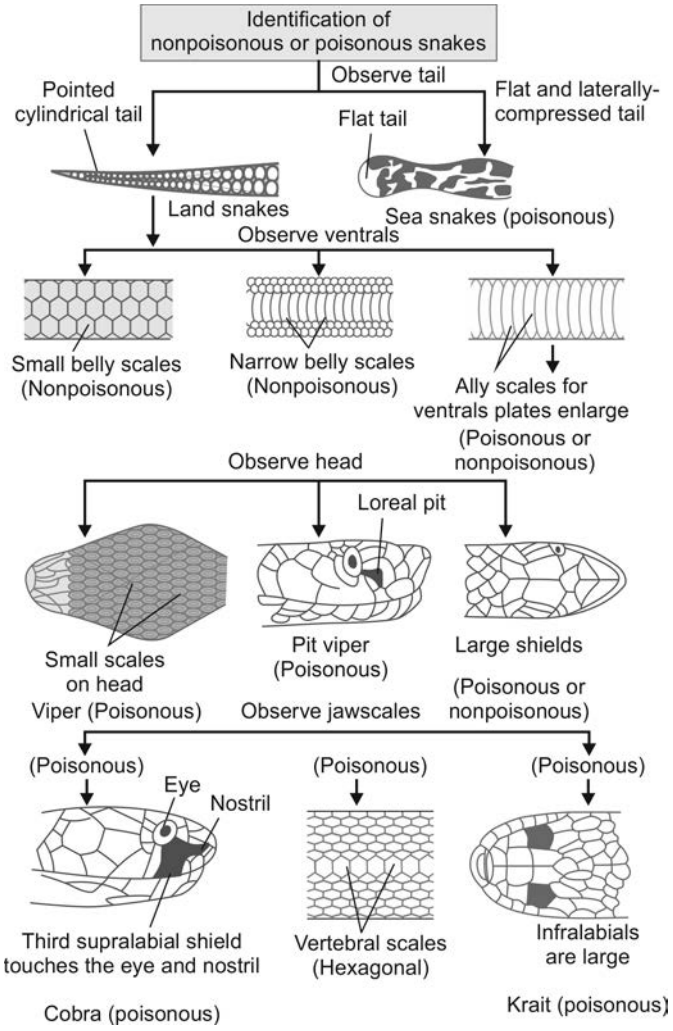


Fig. 1: Examination of bitten snake; poisonous versus nonpoisonous snake

Clinical features suggestive of envenomation:

- *Elapidae* (cobra, krait): neurotoxic
  - Minimum local features at bite site
  - Inability to open mouth
  - Vomiting—earliest symptom
  - Inability to protrude tongue
  - Blurred vision
  - Inability to speak or swallow
  - Ptosis
  - Respiratory paralysis
  - Ophthalmoplegia
- *Viperidae* (vipers):
  - Local:
    - Pain
    - Blistering
    - Swelling
    - Necrosis
    - Bruising
    - Lymphangitis and lymphadenitis
  - Systemic (coagulopathy):
    - Spontaneous bleeding from gums, nose, skin, gastrointestinal tract, and central nervous system
    - Cardiac arrhythmias
    - Persistent shock or hypotension
    - Nephrotoxicity
    - Disseminated intravascular coagulation
    - Abdominal pain
- *Hydrophiidae* (banded sea krait): myotoxic
  - Rhabdomyolysis: myoglobinemia, hypercalcemia, and renal failure
  - Trismus, muscle pain, tenderness with progressive paralysis
- *Crotalidae* (pit viper):
  - Pain swelling, blistering, and regional lymphadenopathy
  - Headache, nausea, vomiting, abdominal pain and chest pain
  - Coagulopathy

ALGORITHM 1

Diagnosis of the snake responsible for the bite

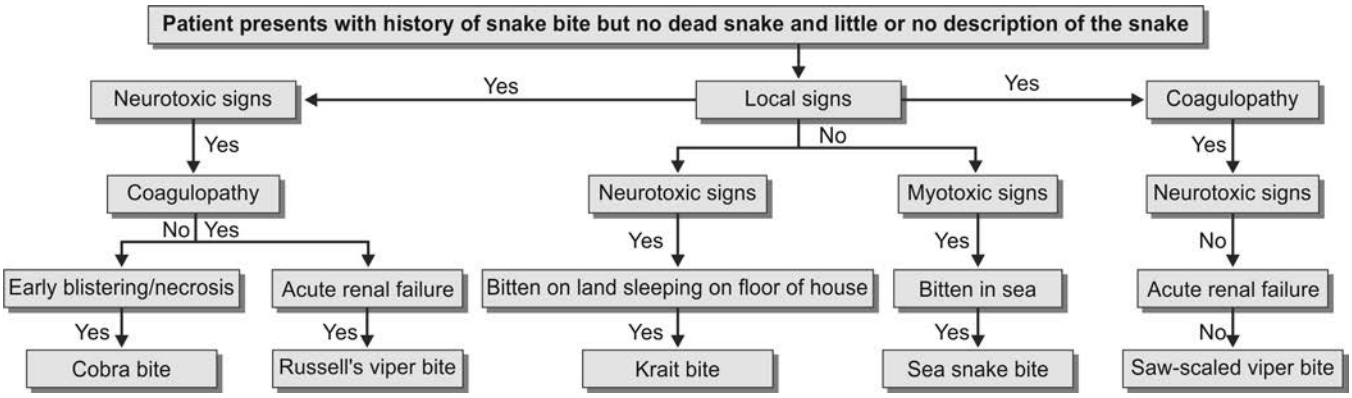


Fig. 2: Poisonous snakes: Cobra, common Krait, Rusell's Viper and Saw- scaled Viper

Clinical Pearls

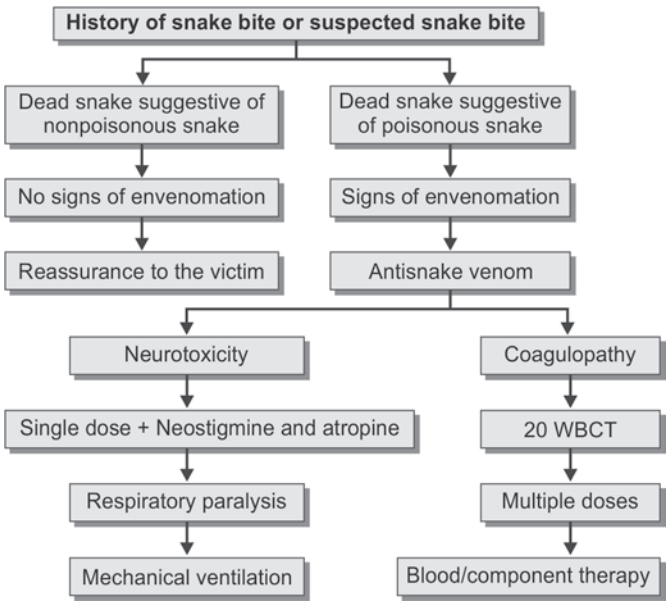
- Venomous snake bite is identified primarily by the clinical signs of envenomation in the victim, although dead snake, if brought and identified, can add to the diagnosis
- Cobra and krait envenomation result in neurotoxicity
- Viper envenomation causes coagulopathy.

MANAGEMENT OF SNAKE ENVENOMATION (ALGORITHM 2)

- First aid: Traditional first aid measures such as incision over bite marks, suction of venom, tourniquets, and local ice packs should be discouraged
  Recommended first-aid measures are:
  - Reassurance to the victim
  - Immobilization of the bitten limb with a splint or sling
  - To avoid interference with the bite wound to prevent introduction of the infection
  - Pressure immobilization is recommended only for bites by neurotoxic elapid snakes, including sea snakes but not for viper bites
- In hospital:
  - Rapid assessment and resuscitation:
    - Rapid assessment of airway, breathing, circulation, and level of consciousness
    - If required, urgent resuscitation for prolonged hypotension and shock, terminal respiratory failure, sudden or rapid deterioration and cardiac arrest
  - Specific therapy:
    - Polyvalent antisnake venom (ASV):
      - Dose of ASV:
        - The dose of the ASV is not determined by the severity of symptoms of envenomation
        - 10 vials of ASV are dissolved in 200 mL of NS and infused over 1 hour

ALGORITHM 2

Management of snake envenomation



20 WBCT, 20-minute whole blood cloting test.

      - Repeat dose of ASV:
        - Hemorrhagic bites: After initial 10 vials of ASV, no dose is given for next 6 hours. Then, 20-minute whole blood cloting test (20 WBCT) is done every 6 hours, and if positive, a repeat dose of 10 vials is given. Occasionally, multiple doses may be required
        - Neurotoxic bites: If the victim does not improve (or worsens) after first dose of ASV and neostigmine over 1–2 hours, another dose of 10 vials is given. After this, the victim will either recover or require mechanical ventilation
      - Management of anaphylaxis due to ASV:
        - ASV can result in anaphylaxis
          - Stop ASV infusion
          - Epinephrine 0.01 mg/kg intramuscularly (IM)
          - Hydrocortisone hemisuccinate 2 mg/kg intravenous (IV)
          - Diphenhydramine 0.2 mg/kg IV
          - After complete recovery, reintroduce ASV, initially slow and then with a normal drip rate
      - 20-minute whole blood clotting test:
        - Between 2–5 mL of victim's blood is taken in a new glass test tube and left undisturbed for 20 minutes
        - The tube is tilted to see if the blood is still liquid (indicating consumption coagulopathy)

- ➢ This test is done to assess effectiveness of ASV and deciding its subsequent doses
- Neostigmine:
  - It is used in victims of postsynaptic type of neuromuscular junction block caused by neurotoxic snake (cobra) bite. Dose is 25–50 µg/kg IM every 4 hourly with 0.05 mg/kg atropine IV till complete neurological recovery
- Mechanical ventilation:
  - It is life-saving in victims of respiratory paralysis due to neurotoxicity by cobra and krait
- Blood transfusion (including component), volume expanders, and peritoneal dialysis are indicated depending upon the clinical situation
  - The bitten limb is nursed in the most comfortable position, preferably slightly elevated
  - Fasciotomy for compartment syndrome.

Note: If dead snake is not brought, snake species could not be identified, directly look for sign of envenomation.

APPROACH TO SCORPION STING

Scorpion sting is an acute life-threatening, time-limiting medical emergency among children, usually in villages.

Out of 89 species of scorpions in India, only two are of medical importance. They are *Mesobuthus tamulus* (Indian red scorpion) (Fig. 3) and *Palamnaeus swammerdami* (Indian black scorpion) (Fig. 4).

Clinical Features (Fig. 5 and Algorithm 3)

The envenomation is classically characterized by "autonomic storm".

Local Manifestations

Soon after sting, the victim experiences severe excruciating radiating pain from sting site, usually toes and fingers. Sudden tap at and around the site of sting induces severe pain and withdrawal—this is the diagnostic sign of sting called "TAP sign". Severe pain without systemic involvement is suggestive of nonvenomous sting.

Fig. 3: Red scorpion

Fig. 4: Indian black scorpion

Systemic Manifestations

Characteristic autonomic storm is divided into four phases:

1. Cholinergic phase
2. Adrenergic-inotropic phase
3. Adrenergic-hypokinetic phase:
   - Left-ventricular dysfunction leading to cardiogenic pulmonary edema
4. Recovery phase.

Other features:

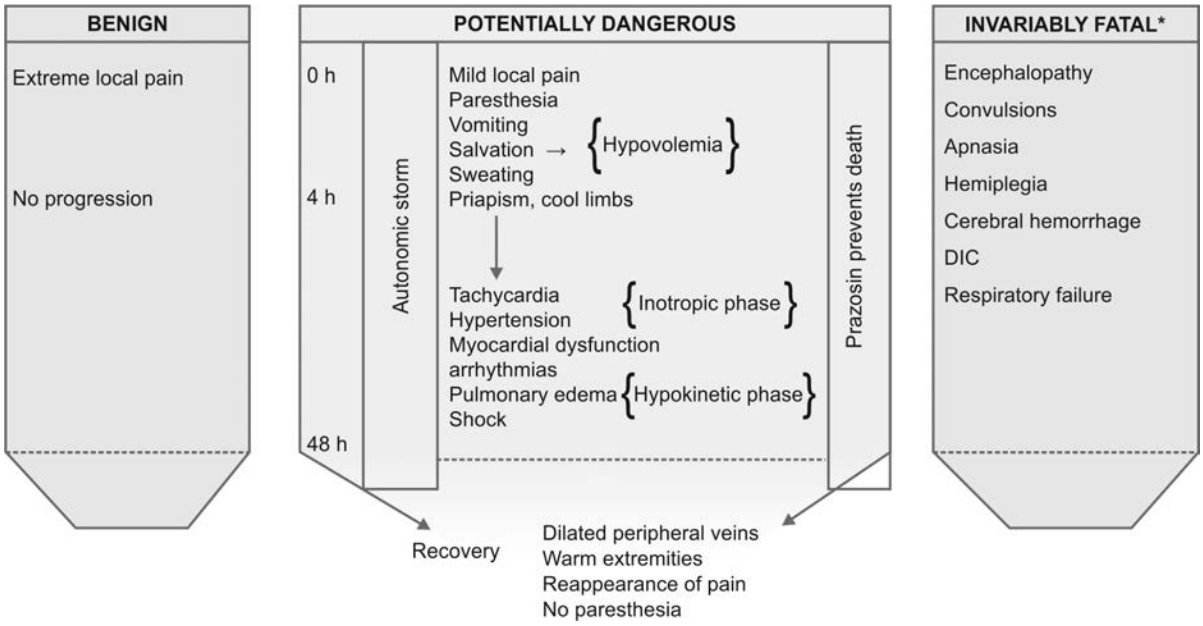
- Central nervous system (encephalopathy, stroke, seizures)
- Disseminated intravascular coagulation (DIC)
- Rarely acute pancreatitis and acute renal failure.

Investigations

- X-ray chest:
  - For evidence of pulmonary edema
- Electrocardiogram (ECG):
  - Sinus tachycardia (most common)
  - Sinus bradycardia
  - Supraventricular tachycardia
  - Peaked (tented) T waves
  - Myocardial infarction pattern
  - Conduction block.

Note: Low voltage complexes throughout the record and left-anterior hemiblock indicate a poor prognosis. All victims with systemic involvement show abnormal ECG.

- Echocardiography:
  - Left-ventricular dilatation
  - Regional-wall motion abnormality
  - Decreased left-ventricular ejection fraction and shortening fraction
- Prothrombin time, activated partial thromboplastin time and fibrinogen degradation products (FDP) with D-dimer for evidence of DIC.

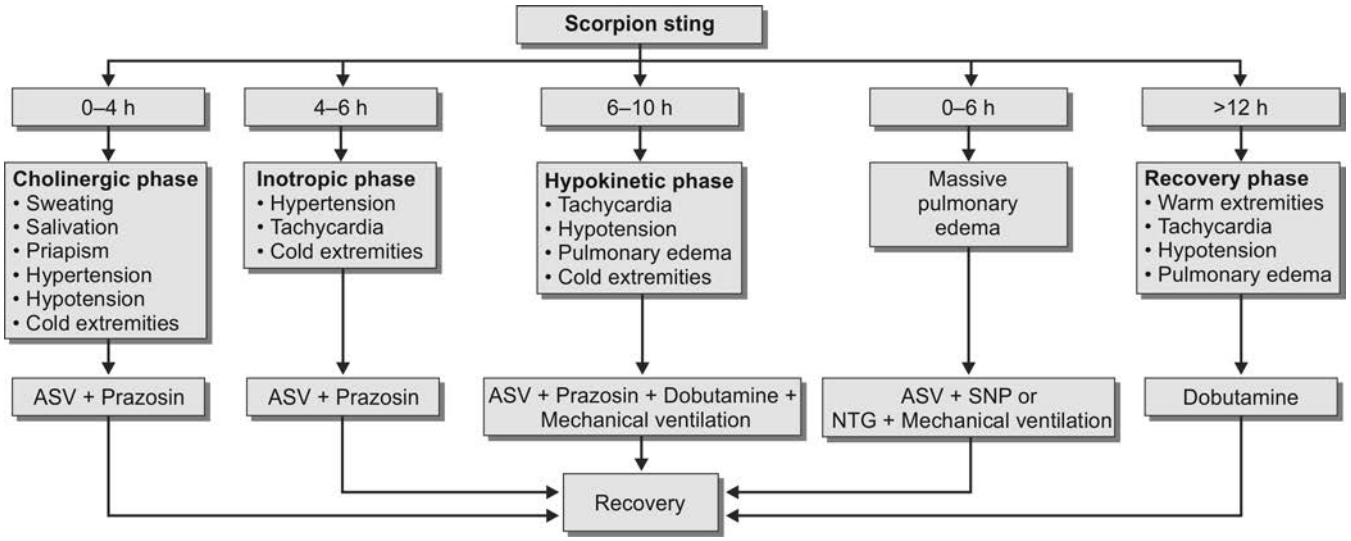


*Aggressive supportive measure may reduce mortality.
DIC, disseminated intravascular coagulation.

Fig. 5: Clinical features (according to time frame) and outcome of *Mesobuthus tamulus* scorpion sting in Indian children

ALGORITHM 3

Management of scorpion sting



ASV, antiscorpion venom; SNP, sodium nitroprusside; NTG, nitroglycerine.

Management (Algorithm 3)

Local pain:
- Mild tolerable pain need not be treated
- Severe pain: oral NSAIDs, local ice pack application and xylocaine (local anesthesia).

Fluid therapy:
- Correction and maintenance of fluid and electrolyte balance.

Scorpion antivenom (SAV):
- Monospecific Fab2 SAV is available for therapeutic use
- Intravenous route
- Administer as early as possible—preferably within first 6 hours of sting
- Dose: 30–100 mL (3–10 vials).

Prazosin:
- Alpha-adrenoreceptor antagonist
- A dose of 30 μg/kg/dose orally or through tube feed

- It is repeated in the same dose at the end of 3 hours and according to the clinical response and later every 6 hours till the extremities are warm, dry, and peripheral veins are easily visible
- The time lag between the sting and administration of prazosin determines the outcome.

Note: Previously used therapies like atropine, steroids, morphine, lytic cocktail, nifedipine, and captopril have proven harmful or deleterious and potentiate the effects of scorpion venom, hence should be avoided.

Clinical Pearls

- Scorpion envenomation is characterized by autonomic storm
- Prazosin—an α-adrenoreceptor antagonist is antidote to envenomation
- Time interval between the sting and administration of prazosin for autonomic storm determines the outcome.

APPROACH TO ENVENOMATION BY BEES AND WASPS

Bees and wasps are stinging insects belonging to the order Hymenoptera.

Allergic Reactions and Anaphylaxis

- Hives
- Loss of consciousness
- Pruritis
- Heart palpitations
- Dyspnea
- Upper airway obstruction.

The most well-known allergic reaction is the type I anaphylactic or immediate hypersensitivity reaction.

Type III (serum sickness) reactions occur 3–14 days after the sting and present with fever, headache, urticaria, lymphadenopathy, polyarthritis, and polyarthralgias.

Mass Stinging Events

Toxicity from massive honeybee envenomation occurs directly from the systemic effects of the venom, as opposed to immune-mediated anaphylaxis. Mass envenomations usually occur when stinging insects respond to an intruder as a threat to their colony.

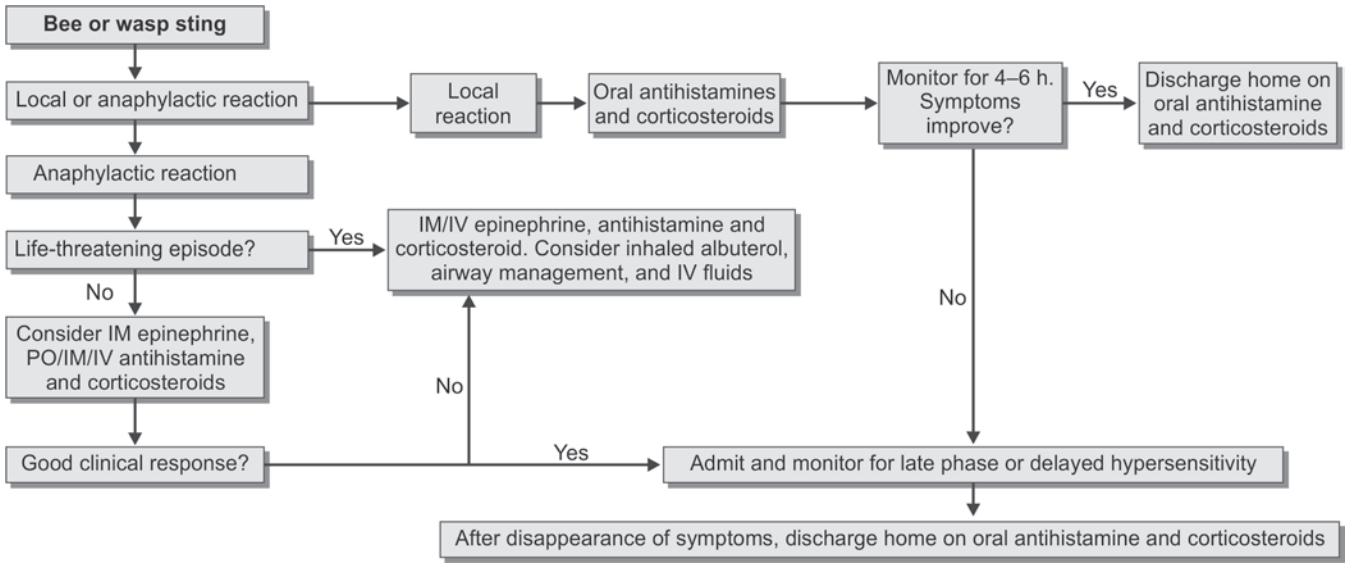
- Generalized edema
- Confusion, coma, seizures
- Hemolysis, thrombocytopenia, DIC
- Fever
- Rapidonset diarrhea
- Rhabdomyolysis, acute renal failure
- Nausea and vomiting
- Tachycardia and hypotension
- Hepatotoxicity

Management (Algorithm 4)

- Removal of stinger from the site of sting in case of bee sting as quickly as possible. Delays in stinger removal cause more venom to enter the wound
- Bee venom is acidic. Hence, neutralize it by applying alkaline solution like soda or methylene blue. Wasp venom is alkaline. Hence, it is neutralized by applying vinegar or lemon juice
- Mild local reactions of pain and erythema are managed with cold compresses and analgesics. Moderate to severe local reactions are managed with oral or paranteral

ALGORITHM 4

Bee and wasp sting management



IM, intramuscular; IV, intravenous; PO, *per os.*

antihistaminics (diphenhydramine 1 mg/kg IV up to 50 mg or hydroxyzine 0.5 mg/kg orally up to 50 mg) and corticosteroids
- Anaphylaxis: IM or SC epinephrine 0.01 mg/kg (maximum dose 0.5 mg) of the 1:1,000 dilution of epinephrine intramuscularly), IV Diphenhydramine, IV hydrocortisone (or methylprednisolone) and adequate IV fluid resuscitation
- Treat hypotension and shock with crystalloids, dopamine, and dobutamine
- Respiratory failure is managed by mechanic ventilation
- Mass stinging: supportive care (correction of hypotension, coagulopathy, and acute renal failure, etc.), no specific antidote or allergy treatment.

KEY POINTS

- ☞ The most common envenomation encountered is due to snakes and scorpion bites followed less commonly by bee and wasp sting
- ☞ The commonly encountered poisonous snakes in this region include cobra, common krait, Russell's viper, saw-scaled viper, and less commonly sea snakes
- ☞ Venomous snake bite is identified primarily by the clinical signs of envenomation in the victim, although dead snake, if brought and identified, can add to the diagnosis
- ☞ Cobra and Krait envenomation result in neurotoxicity. Viper envenomation causes coagulopathy
- ☞ Polyvalent antisnake venom (ASV) is the specific treatment for snake envenomation. The dose of ASV is not determined by severity of symptoms
- ☞ Scorpion envenomation is classically characterized by "autonomic storm"
- ☞ Prazosin is antidote to scorpion envenomation
- ☞ Mass honeybee envenomation usually occurs when stinging insects respond to an intruder as a threat to their colony
- ☞ Mass stinging is treated with supportive care (correction of hypotension, coagulopathy, acute renal failure, etc.). There is no specific antidote or allergy treatment.

SUGGESTED READINGS

1. Bahloul M, Chaari A, Dammak H, Samet M, Chtara K, Chelly H, et al. Pulmonary edema following scorpion envenomation: mechanisms, clinical manifestations, diagnosis and treatment. Int J Cardiol. 2013;162(2):86-91.
2. Bahloul M, Chabchoub I, Chaari A, Chatara K, Jallel H, Dammak H, et al. Scorpion envenomation among children: clinical manifestations and outcome (analysis of 685 cases). Am J Trop Med Hyg. 2010;83:1984-92.
3. Bawaskar HS, Bawakar PH. Efficacy and safety of scorpion antivenom plus Prazosin compared with prazosin alone for venomous scorpion (Mesobuthgus Tamulus) sting: randomized open label clinical trial. BMJ. 2011;342:c7136.
4. Bawaskar HS, Bawaksar PH. Cardiovascular manifestations of severe scorpion sting in India (Review of 34 children). Annal Trop Pediat. 1991;11:481-88.
5. Bawaskar HS, Bawaskar PH. Indian scorpion envenoming. Indian J Pediatr. 1998;65:383-91.
6. Bawaskar HS, Bawaskar PH. Scorpion sting: update. J Ass Phys India. 2012;60: 46-55.
7. Bawaskar HS. Scorpion sting. In: Shah SN (Ed). API Textbook of Medicine. 7th ed. The Association of Physicians of India: Mumbai; 2003. pp. 1282-84.
8. Feng SY, Godo C. Hymenoptera envenomation: bees, wasps & ants. In: Strother C (Ed). Pediatric Emergency Medicine Practice. EB Medicine: 2008;5(6).
9. Kulkarni ML, Anees S. Snake venom poisoning: experience with 633 cases. Indian Pediatr. 1994;31:1239-43.
10. Kulkarni ML. Bee and wasp sting. In: Kulkarni ML, Kulkarni AS, Reddy Pradeep P, Vijay NCD, Kulkarni PM (Eds). Pediatric Toxicology, 1st ed. Hyderabad: Paras Medical Publisher; 2011. pp. 131-53.
11. Kulkarni ML. Scorpion sting. In: Kulkarni ML, Kulkarni AS, Reddy Pradeep P, Vijay NCD, Kulkarni PM (Eds). Pediatric Toxicology, 1st ed. Hyderabad: Paras Medical Publisher; 2011. pp. 131-53.
12. Kulkarni ML. Snake bite. In: Kulkarni ML, Kulkarni AS, Reddy Pradeep P, Vijay NCD, Kulkarni PM (Eds). Pediatric Toxicology, 1st ed. Hyderabad: Paras Medical Publisher; 2011. pp. 131-53.
13. Lovrcchio F, Cannon RD, Algier J, Ruha AM, Curry SC, Wallace KL, et al. Bee swarming in children. Am J Emerg Med. 2007;25:931-3.
14. Natu VS, Kamerkar SB, Geeta K, Vidya K, Natu V, Sane S, et al. Efficacy of antiscorpion venom serum over prazosin in the management of severe scorpion envenomation. J Postgrad Med. 2010;56:275-80.
15. Paul V, Pratibha S, Prahlad KA, Earali J, Francis S, Lewis F. High-dose anti-snake venom versus low-dose anti-snake venom in the treatment of poisonous snake bites a critical study. J Assoc Phys India. 2004;52:14-7.
16. Pramanik S, Banerjee S. Wasp stings with multi-system Dysfunction. Indian Pediatr. 2007;44:788-90.
17. Simpson ID. The pediatric management of snake bite: the national protocol. Indian Pediatr. 2007;44:173-6.
18. Warrell D. Snake bite. Lancet. 2010;375:77-88.
19. Warrell DA. World Health Organization. WHO/SEARO guidelines for the management of snake-bites. Regional office for South-East Asia, New Delhi; 2010.

CHAPTER 40

Recognition and Assessment of Critically Ill Child

Praveen Khilnani

INTRODUCTION

In outpatient practice, pediatric specialist as well as general practitioner comes across common pediatric illnesses frequently. It is important to recognize potentially life-threatening conditions as well as conditions requiring immediate intervention and transfer to a higher-level medical facility.

Besides accidental trauma, poisoning, insect bites, and allergic reactions, common medical problems that bring the child to medical attention are fever, cough, respiratory distress, cyanosis, earache, poor feeding, vomiting, diarrhea, irritability, lethargy, convulsions, and unresponsiveness. Common conditions that require immediate attention are respiratory distress, shock, lethargy, and coma.

Since our main goal as a medical practitioner is to prevent unnecessary mortality and morbidity by prompt and early recognition of potential problems leading to respiratory or cardiorespiratory arrest, it is important to pay attention to the following during history and physical examination done simultaneously.

- Listen carefully to the mother.
- Do not ignore, it will not get better if something is not done.

EVALUATE, IDENTIFY, AND INTERVENE

A carefully performed clinical assessment, including observation, history, and physical examination, will detect serious illness with 90% sensitivity. Each component of the evaluation is effective in identifying serious illness (Fig. 1 and Algorithm 1).

The assessment of a seriously unwell child involves the following:

- Pediatric assessment triangle (initial impression) (Fig. 2)
- Primary assessment: Airway, breathing, circulation, disability, exposure (ABCDE) assessment
- Secondary assessment:
  - Vital signs
  - Focused history
  - Detailed physical examination

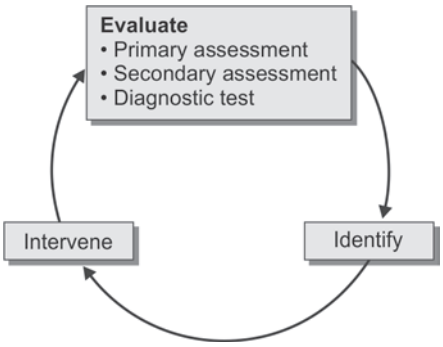
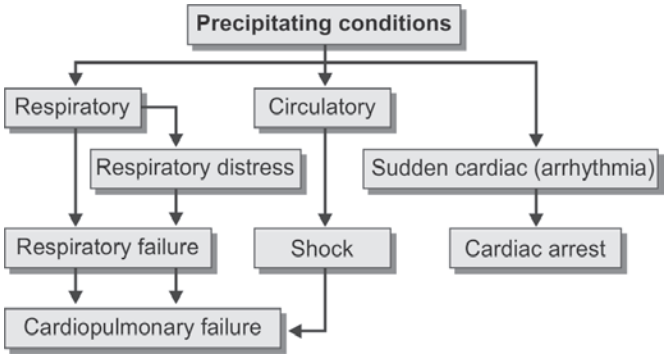


Fig. 1: Action related to pediatric assessment and intervention

ALGORITHM 1

Common conditions precipitating cardiac arrest



- Diagnostic tests:
  - Laboratory and radiological.

Initial Impression

It is the rapid assessment of a child with an emergency condition through visual and auditory evaluation of the child's consciousness, work of breathing, and color. It is "from the

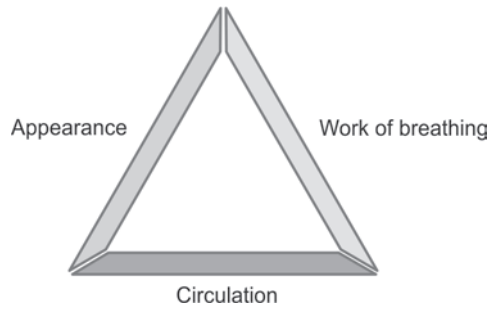


Fig. 2: Pediatric assessment triangle (initial impression)

door" observation to be completed within seconds and no equipment is required. The initial assessment of the child's overall condition is of crucial importance. If the child exhibits abnormal findings, proceed immediately to the primary assessment part of evaluation.

Consciousness

- Reflects the adequacy of ventilation, oxygenation, brain perfusion, body homeostasis, and central nervous system function
- What is the child's state of consciousness: unresponsive, irritable, alert?
- Does the child look ill?

Work of Breathing

- Assess body position, visible movements of chest/abdomen, and breathing pattern
- Listen for abnormal audible airway sounds (snoring, hoarse speech, grunting, and wheezing)
- Look for visual signs of increased work of breathing such as abnormal position or posture (i.e., sniffing position, tripod position, head bobbing), retractions, nasal flaring, grunting, gasping, and tachypnea
- Reflects the adequacy of airway, oxygenation, and ventilation. Are the airways obstructed? Is the child short of breath?

Coloration of Skin

- Assess skin color
- Look at the skin and mucus membranes for abnormal color (pallor, mottling, and cyanosis)
- Reflects the adequacy of cardiac output and perfusion of vital organs. Is the skin unusually pale, mottled, or cyanotic?

The initial impression will help decide if the child problem is life-threatening or not.

Primary Assessment

It uses an ABCDE approach. During the evaluation, primary assessment and management occur simultaneously. The primary assessment should be periodically repeated, particularly after major intervention or when a change in the patient's condition is detected (evaluate, identify, intervene) (Algorithms 2 and 3).

Airway

The goal is to assess if the airway is patent or if there are signs of obstruction (e.g., stridor, dyspnea, and hoarse voice). If the child is unresponsive and cannot talk, cry, or cough, evaluate for possible airway obstruction. Is the airway noisy (e.g., snoring, stridor, wheeze, grunting, or hoarse speech)? Determine if the airway is patent, and able to be maintained with positioning and suction, or not. If cervical spine injury is suspected, manually stabilize the head and neck in a neutral, inline position (jaw thrust without head tilt maneuver to open the airway).

Look in the mouth for blood, broken teeth, gastric contents, and foreign objects. If solid material is visualized, remove it with a gloved finger covered in gauze under direct vision. If a foreign body is suspected but not visualized, a combination of back blows and chest thrusts is recommended in infants. In an older child back blows in a forward leaning position is recommended. Abdominal thrusts in children are not recommended as their effectiveness and safety have not been established.

Insert an airway adjunct (e.g., oropharyngeal or nasopharyngeal airway, or laryngeal mask airway) as needed to maintain a patent airway. If airway patency cannot be maintained, perform tracheal intubation. Rapid sequence intubation should be considered in all patients, except those in cardiac arrest, to provide optimum conditions and to minimize the potential for aspiration. Cricothyrotomy or emergency tracheostomy can be done as a last resort to maintain airway patency. Not many pediatricians would be familiar with performing these procedures, therefore, in anticipation a consult should be obtained from an airway expert such as anesthesia or an ear, nose, throat consultant.

Breathing

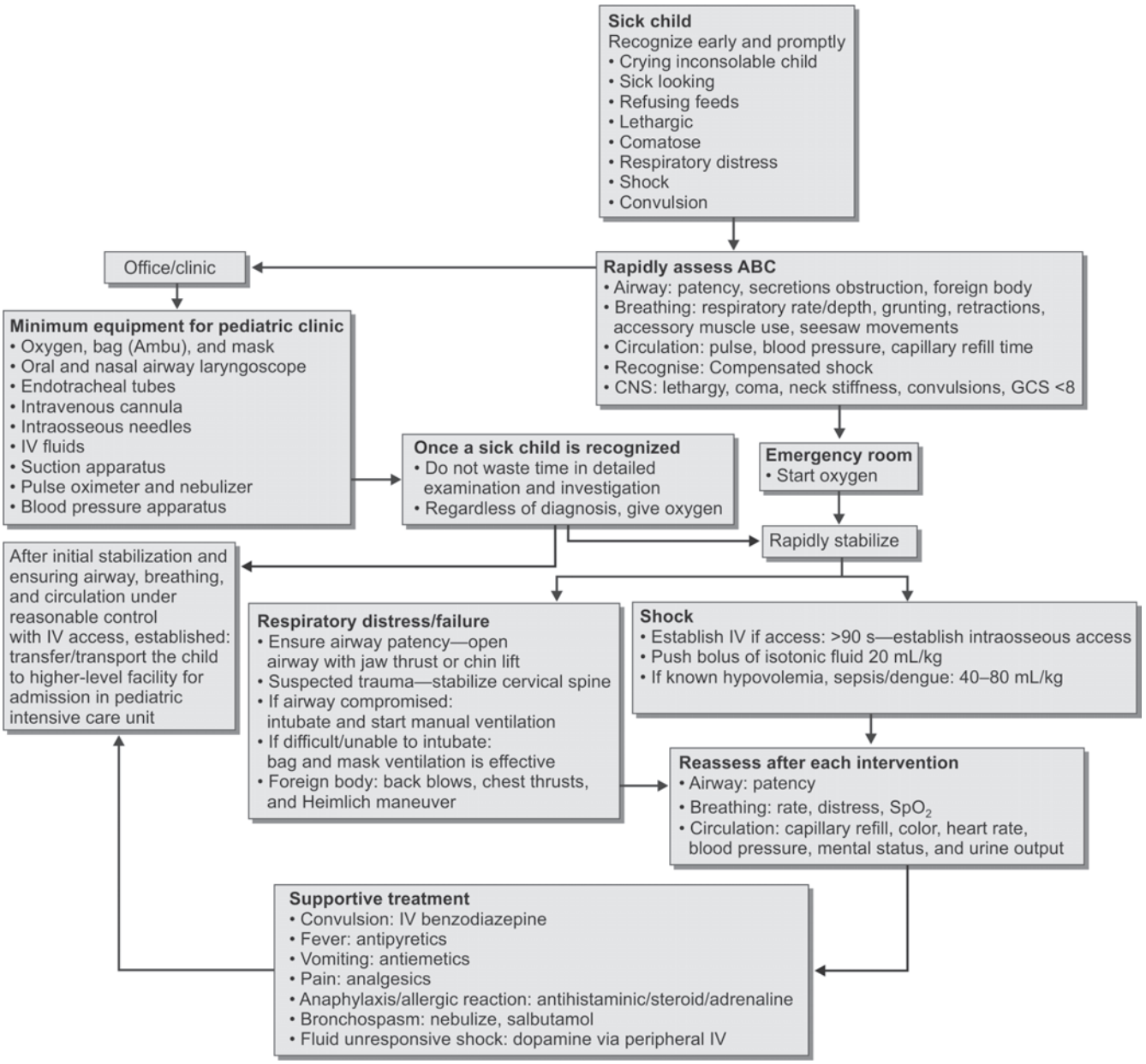
The goal in assessing breathing is to determine whether there is adequate gas exchange.

- Will the child lie flat? Is he in the tripod or "sniffing" position?
- Are accessory muscles being used (head bobbing in infants)? Or is there minimal movement of the chest wall?
- Is there sternal, supraclavicular, substernal, or intercostal recession present?
- Is nasal flaring present?
- Is the respiratory rate fast, slow, or normal?
- Is cyanosis present?
- Is air movement audible on auscultation?
- What is the oxygen saturation (SpO_2)?

Place your cheek near the child's face and mouth and feel/listen for air movement and look at the chest/abdomen for respiratory movement. The child with breathing difficulty often has a respiratory rate outside the normal limits for their age. Normal respiratory rate values according to age are listed in table 1. Initially, the child becomes tachypneic, and as fatigue begins and hypoxia worsens, the child may progress to respiratory failure and bradypnea. On auscultation with a stethoscope over the mid axillary line, try to hear abnormal lung sounds (e.g., wheeze, crackles, and snoring). Palpate the chest for tenderness, instability and crepitations. Table 2 shows types and severity of retractions indicating breathing difficulty.

ALGORITHM 2

Approach to sick child



GCS, Glasgow Coma Scale; ET, endotracheal; CPR, cardiopulmonary resuscitation; PICU, pediatric intensive care unit; IV, intravenous.

Intervention

All children with breathing difficulties should receive high flow oxygen through a face mask oxygen as soon as the airway has been assessed and demonstrated to be adequate. Pulse oximetry is an excellent tool to use in assessing a child's breathing. A pulse oximetry reading above 94% indicates that oxygenation is probably adequate. A reading below 90% in a child with 100% mask oxygen could be an indication for assisted ventilation.

If the child is breathing adequately but is unresponsive, place the patient in recovery position (lateral recumbent) after assessing ABCD with no other abnormal findings. If breathing is absent or the child is hypoventilating (slow respiratory rate or weak effort), respiration should be supported with oxygen via bag-valve-mask device and an airway adjunct needs to be inserted (e.g., laryngeal mask airway, and endotracheal tube).

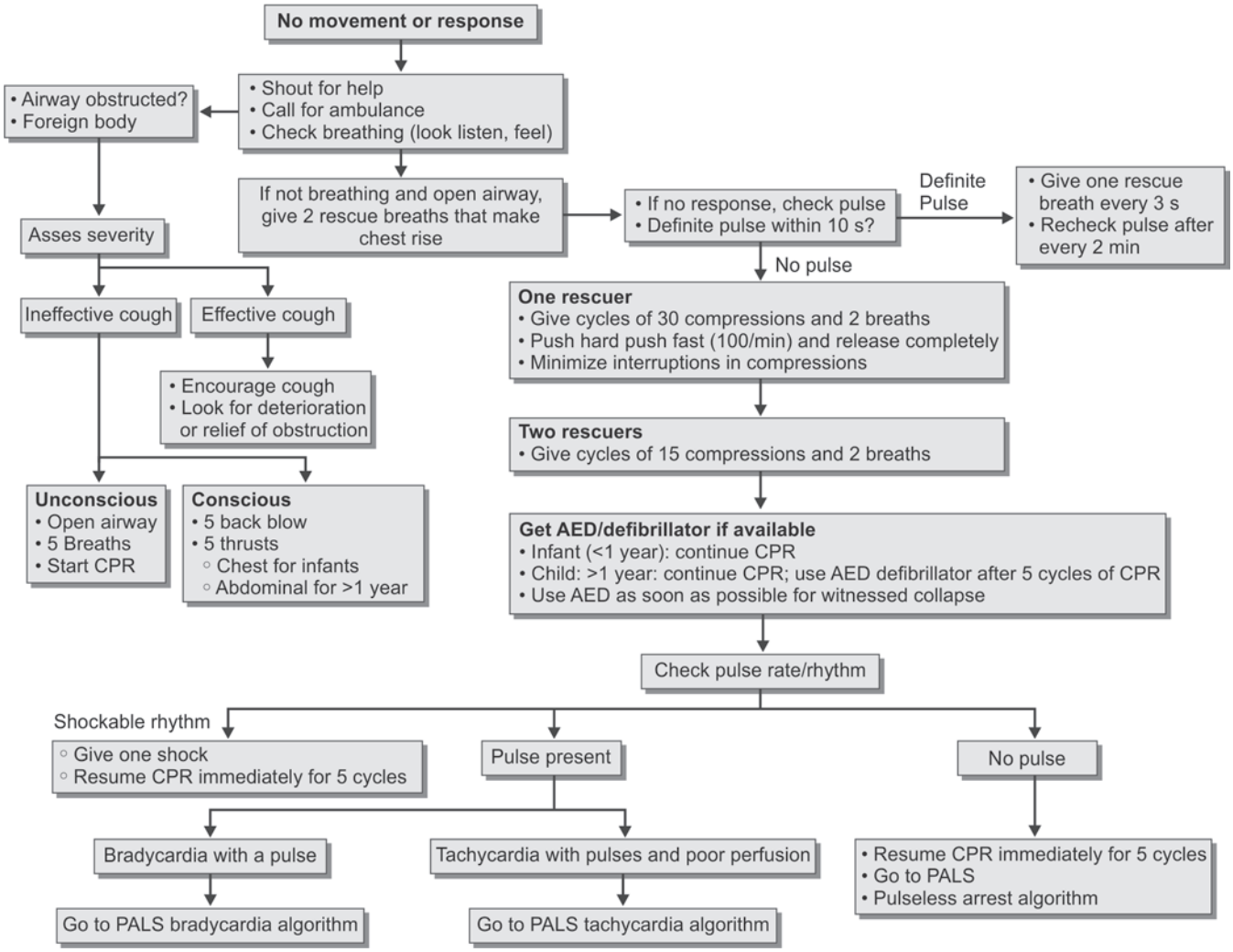
Circulation

The goals are to assess adequate cardiovascular function and tissue perfusion, ensure effective circulating volume, and in trauma, control of bleeding. Look for following points:

- Is skin color normal, or is it pale or mottled?

ALGORITHM 3

Approach to collapsed child



AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; PALS, pediatric advanced life support.

TABLE 1: Normal respiratory rates*

Age	Respiratory rates (breaths per minute)
Infant (<1 year)	30–60
1–3 years	24–40
4–5 years	22–34
6–12 years	18–30
Adolescent (13–18) year	12–16

*>60/min in all ages is abnormal.

- Is there an increased respiratory rate without increased work of breathing?
- Is it cool peripherally but warm centrally?
- Is the pulse rate fast, slow, or normal?
- Is the pulse volume weak or strong?
- Is the capillary refill time (CRT) normal or prolonged?

It is important to determine the heart rate, pulse quality, skin temperature, CRT, and blood pressure. Normal heart rate

TABLE 2: Severity of retractions

Breathing difficulty	Location of retraction	Description
Mild-to-moderate	Subcostal	• Abdominal • Retractions below • Rib cage
	Substernal	• Abdominal • Retractions below • The sternum
	Intercostal	• Retractions • Beetween the ribs
Severe (may include retractions of mild to moderate breathings difficulty)	Supraclavicular	• Reatractions in the neck ablove the clavicle
	Suprasternal	• Restractions just • Above the sternum
	Sternal	• Inward retractions of sternum towards • The anterior spine

varies with age (as noted in table 3); tachycardia can be an early sign of hypoxia or low perfusion, but it can also reflect less serious conditions (e.g., fever, anxiety, and pain). Bradycardia (rate <60/min in children or <100/min in newborns) indicates serious illness and poor myocardial perfusion.

Pulse quality reflects the adequacy of peripheral perfusion. A weak central pulse may indicate decompensated shock, and a peripheral pulse that is difficult to find, weak or irregular suggests poor peripheral perfusion and may be a sign of shock. Check the femoral pulse in infants and young children, or the carotid pulse in an older child or adolescent. If no pulse is felt, and there are no, or minimal signs of life, commenced cardiopulmonary resuscitation.

Next, evaluate the CRT, skin color, and temperature. Normal CRT is less than 2 seconds. The CRT should be done centrally (e.g., on the chest) to minimize the impact of environmental factors. Blood pressure determination and interpretation can be difficult. Normal blood pressure values in children vary according to age and are difficult to remember. Table 4 can be very useful in clinical practice. A low blood pressure indicates decompensated shock.

An easy formula for determining the lower limit of acceptable blood pressure is: minimal systolic blood pressure = 70 + (2 × age in years) (Table 5).

TABLE 3: Normal heart rates (per minute) by age

Age	Awake rates	Mean	Sleeping rate
New born to 3 months	85–205	140	80–160
3 months to 2 years	100–190	130	75–160
2 years to 10 years	60–140	80	60–90
>10 years	60–100	75	50–90

TABLE 4: Normal blood pressure in children by age

Age	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	Female	Male	Female	Male
Neonates (1st day)	60–74	60–74	31–45	31–44
Neonates (4th day)	76–83	68–84	37–53	35–53
Infant (1 month)	73–91	74–94	36–56	37–55
Infant (3 months)	78–100	81–103	44–63	45–65
Infant (6 months)	82–102	87–105	46–66	48–68
Infant (1 years)	68–104	67–103	22–60	20–58
Child (2 year)	71–105	70–106	27–65	25–63
Child (7 years)	79–113	79–115	39–77	38–78
Adolescent (5 years)	93–127	95–131	47–85	45–85

TABLE 5: Definition of hypotension by age

Age	Systolic blood pressure (mmHg)
Term neonates (0–28 days)	<60
Infants (1–2 months)	<70
Children (1–10 years)	70 + (age × 2)
Children >10 years	<90

Hypertension with hemorrhage: >2–25% acute blood loss.

Blood pressure trends are useful in determining the child's condition and response to treatment.

Disability (Mental Status)

Assess the patient by looking at appearance as part of initial impression and at level of consciousness with the AVPU (Alert, response to Verbal stimuli, response to Pain, Unresponsive) scale (Table 6). The pediatric Glasgow Coma Scale (GCS) is a second option (Table 7).

Evaluate the brainstem by checking the responses in each pupil to a direct beam of light. A normal pupil will constrict after a light stimulus. Evaluate the motor activity by looking for symmetrical movement of the extremities, seizures, posturing, or flaccidity.

- What is the child's AVPU score?
- Is the child mobile? Or is there limited movement with poor muscle tone?
- If the child is crying or speaking, is this strong or weak?
- If crying, can the child be consoled?
- Does the child fix their gaze on the carer(s), or does he/she have a glazed appearance?
- Is the child's behavior normal for their developmental age?
- Is the child having convulsions, is he stiff or floppy?

With knowledge of the child's appearance from the initial appearance and AVPU scale, if the disability assessment demonstrates altered level of consciousness, begin with general life support/monitoring with oxygen, cardiac monitoring, and pulse oximetry. Intubation should be considered if GCS is less than 8.

Exposure

Proper exposure of the child is necessary for completing the initial physical assessment. The initial impression using pediatric assessment triangle requires removal of part of the child's clothing to allow careful observation. Be careful to avoid rapid heat loss, especially in infants and children in a cold environment.

- Is there fever?
- Is there a nonblanching rash present?

Secondary Assessment

The secondary assessment focuses on advanced life-support interventions and management. It is important to perform an additional assessment with a focused history and

TABLE 6: AVPU

A	Alert	The chils is awake, active and appropriately responsive to parents and external stimuli, *Appropriate response is assessed in terms of the anticipated response based on the child's age and the setting on situation.
V	Voice	The child responds only when the parents or you call the child's name of speakloudly
P	Painful	The child responds only a painful stimulus, such as pinching the nail bed
U	Unresponsive	The child does not respond to any stimulus

TABLE 7: Glosgow coma scale for adults and modified Glosgow coma scale for infants and children*

Response	Adults	Child	Infants	Coded value
Eye opening	Spontaneous	Spontaneous	Spontaneous	4
	To speech	To speech	To speech	3
	To pain	To pain	To pain	2
	None	None	None	1
Best value	Oriented	Oriented	Coss and babies	5
	Confused	Confused	Irritable, cries	4
	Inappropriate words	Inappropriate words	Cries in response to pain	3
	Incomprehensible sound	Incomprehensible words or nonspecific sounds	Moans in response to pain	2
	None	None	None	1
Best motor response†	Obeys	Obeys commands	Moves spontaneously and purposely	6
	Localizes	Localizes painful stimulus	Withdraws in response to pain	5
	Withdraws	Withdraws in response to pain	Withdraws in response to pain	4
	Abnormal flexion	Flexion in response to pain	Decorticate posturing (abnormal flexion)	3
	Extensor response	Extension to response to pain	Decerebrate posturing (abnormal ectension in response to pain)	2
	None	None	None	
Total score				**3–15**

†If the patient is intubated, unconscious or preverbal, the most important part of this scale in motor response. Providers should carefully evaluate this components.

physical examination in stable patients. Generally, the initial assessment is aimed at detecting immediate life-threatening problems that can compromise basic life functions, as in the primary survey.

The secondary survey is intended to detect less immediate threats to life and has several specific objectives:

- Obtaining a complete history including mechanism of injury or circumstances of the illness. The SAMPLE mnemonic can be helpful:
  - Signs and symptoms
  - Allergies
  - Medications
  - Past medical history
  - Last oral intake
  - Events leading to the injury or illness
- Performing a detailed physical examination

Laboratory and Radiological Diagnostic Testing

- Establishing a clinical diagnosis: obtain a quick random blood sugar
- Performing laboratory investigations and imaging.

Ongoing Assessment

Always reassess the patient; the purpose is to assess the effectiveness of the emergency interventions provided and identify any missed injuries or conditions. This should be performed in every patient after the detailed physical examination and after ensuring completion of critical interventions.

Categorization by Severity

Respiratory Distress

- Tachypnea
- Tachycardia
- Increased respiratory effort
- Abnormal airway sounds
- Pale cool skin
- Changes in mental status

Respiratory Failure

- Early: marked tachypnea/tachycardia
- Late: bradypnea, apnea/bradycardia
- Increased/decreased/no respiratory effort
- Cyanosis
- Stupor/coma.

Shock

Compensated

- Tachycardia
- Cool pale diaphoretic skin
- Delayed CRT (>2 s)
- Weak peripheral pulses
- Narrow pulse pressure
- Oliguria.

Hypotensive

- All features of compensated shock and blood pressure below the 5th percentile
- Change in mental status.

Initial Stabilization

Things required at all practice locations (hospital or private practice clinic):

- Oxygen source and mask
- Bag valve mask device (Ambubag)
- Laryngeal mask airway
- Intubating equipment
- Intraosseous needle
- Intravenous cannula, IV fluids
- Suction
- Pulse oximeter
- Nebulizer.

Common Initial Interventions

Once the critically ill child is recognized, do not waste time in detailed investigations and diagnosis.

Do the following regardless of diagnosis:

- Start oxygen
- If respiratory distress
  - Ensure airway open by head tilt, chin lift, jaw thrust
  - If not maintainable, intubate
  - If cannot intubate, ventilate with bag and mask.
  - If cannot intubate or ventilate, then use laryngeal mask airway and call the best expert in airway management.

Foreign Body Obstruction

If known foreign body obstruction:

- Then back blows, chest thrust, and Heimlich maneuver
- Nebulize as required (adrenaline or β2 stimulant). Monitor oxygen saturation if pulse oximeter is available.

Shock

Establish intravenous/intraosseous access.

- Do not waste more than 90 seconds trying for intravenous access or wasting time with attempting to place a central line
- Intraosseous access can be used in all age groups
- Push fluid bolus 20 mL/kg up to 60–80 mL/kg of isotonic fluid (Normal saline/Ringers lactate).

After each intervention, reassess airway breathing and circulation (capillary refill, color, heart rate, pulse, blood pressure, mental status, urine output).

Other Supportive Therapy

- First dose of antibiotic
- Anticonvulsants: if convulsions, use diazepam IV/rectal, lorazepam, or midazolamiv (caution: respiratory depression/arrest)
  - Phenytoin/phenobarbitone intravenously
- Fever control
- Analgesics, if severe pain: nonsteroidal anti-inflammatory agents/narcotics as necessary
- Antiemetics: if vomiting
- Antiallergics: if allergic reaction/anaphylaxis
- Subcutaneous adrenaline, antihistaminics, steroids.

Transport

After initial stabilization and ensuring airway, breathing, and circulation under reasonable control with established IV access, transfer/transport to a higher-level facility needs to be arranged.

Clinical Pearls

- Cardiac arrest can be prevented in most children if respiratory distress is assessed and treated
- Early rapid cardiopulmonary assessment saves life
- Fluid therapy and antibiotic dose alone can do 80% of the job in a septic child.

KEY POINTS

- ☞ Solve immediate problem
- ☞ Do not waste time in establishing precise diagnosis
- ☞ Recognize critical illness
- ☞ Stabilize
- ☞ Arrange transfer to a pediatric intensive care unit
- ☞ Ensure continued stabilization measures until care is handed over.

SUGGESTED READINGS

1. de Caen AR, Berg MD, Chameides L, et al. Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132:S526.
2. Kleinman ME, de Caen AR, Chameides L, et al. Pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Pediatrics. 2010;126:e1261.

CHAPTER 41

Septic Shock

Vikram Gagneja, Praveen Khilnani

INTRODUCTION

Severe sepsis or septic shock remains a major cause of morbidity and mortality among children, mainly due to acute hemodynamic compromise and associated multiple organ dysfunctions. Emphasis has been on early recognition and early goal-directed therapy of severe sepsis and septic shock by means of aggressive fluid resuscitation (somewhat guarded in malnourished children), use of catecholamines, early antibiotics, and other adjuvant drugs, widely considered of pivotal importance to improve the short- and long-term outcome of these patients. Severe sepsis (septic shock) is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (Boxes 1 and 2) as per Surviving Sepsis Campaign 2012. Sepsis-induced hypotension is defined as blood pressure less than two standard deviation below normal for age with no other causes of hypotension. Normal ranges for pediatric age group are given in table 1.

MANAGEMENT

Airway, Breathing, and Circulation

Patient should be given 100% oxygen by facemask if airway is maintainable or high flow nasal cannula/nasopharyngeal continuous positive airway pressure (CPAP) if there is increase work of breathing to maintain their functional residual capacity. The decision to intubate and ventilate is based on clinical assessment of increased work of breathing, hypoventilation, or impaired mental status. Waiting for confirmatory laboratory tests is discouraged. However, during intubation and mechanical ventilation, increased intrathoracic pressure and drugs used for sedation can reduce venous return and lead to worsening shock if the patient is not adequately volume-loaded. Mechanical ventilation should be done using lung protective strategies (tidal volume 4–6 mL/kg of ideal body weight, plateau pressure ≤30). Appropriate sedation

Box 1: Diagnostic criteria for sepsis

Infection (documented or suspected), and some of the following:

- General variables
  - Fever (>38.5°C)
  - Hypothermia (core temperature <35°C)
  - Heart rate more than two standard deviation (SD) above the normal value for age
  - Tachypnea
  - Altered mental status
  - Significant edema or positive fluid balance (>20 mL/kg over 24 h)
  - Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
- Inflammatory variables
  - Leukocytosis (WBC count >12,000 μL^{-1})
  - Leukopenia (WBC count <4,000 μL^{-1})
  - Normal WBC count with greater than 10% immature forms
  - Plasma C-reactive protein more than two SD above the normal value
  - Plasma procalcitonin more than two SD above the normal value
- Hemodynamic variables
  - Arterial hypotension less than two SD below normal for age
  - Organ dysfunction variables
  - Arterial hypoxemia (PaO_2/FiO_2 <300)
  - Acute oliguria (urine output <0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation)
  - Creatinine increase >0.5 mg/dL or 44.2 µmol/L
  - Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
  - Ileus (absent bowel sounds)
  - Thrombocytopenia (platelet count <100,000 μL^{-1})
  - Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 µmol/L)
- Tissue perfusion variables
  - Hyperlactatemia (>1 mmol/L)
  - Decreased capillary refill or mottling (normal filling in early warm shock)

Box 2: Severe sepsis

Any of the is following thought to be due to infection:

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output <0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation
- Acute lung injury with PaO_2/FiO_2 <250 in the absence of pneumonia as infection source
- Acute lung injury with PaO_2/FiO_2 <200 in the presence of pneumonia as infection source
- Creatinine >2.0 mg/dL (176.8 μmol/L)
- Bilirubin >2 mg/dL (34.2 μmol/L)
- Platelet count <100,000 μL
- Coagulopathy (international normalized ratio >1.5)

and analgesia should be provided to a patient on mechanical ventilation.

Getting intravenous access may be difficult early in the course of shock especially in small children, rapid use of intraosseous access should be utilized which can be used to give any type of medication. Time should not be wasted in attaining central line. Rapid fluid boluses of 20 mL/kg (isotonic crystalloid or colloids) can be administered by push or rapid infusion device (pressure bag) while observing for signs of fluid overload (i.e., the development of increased work of breathing, rales, gallop rhythm or hepatomegaly). In the absence of these clinical findings, repeated fluid boluses can be administered. Children commonly require 40–60 mL/kg in the first hour (some children may require 180–200 mL/kg). Each fluid bolus should be followed by quick assessment of clinical parameters like improvement in heart rate as per age (Table 1), capillary refill time (CRT) (normal CRT <2 s), normal pulses with no differential between peripheral and central pulses, normal blood pressure for age, sensorium, and urine output. Thereafter, central venous oxygen saturation ($ScvO_2$) greater than or equal to 70% and cardiac index between 3.3 and 6.0 L/min/m^2 should be targeted, if facilities for such monitoring are available. Fluid responsiveness techniques can be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables. Noninvasive measures, such as echocardiography, may be utilized to assess for adequacy of fluid resuscitation by assessing inferior vena cava collapse.

Fluid Refractory Shock

If despite of 60 mL/kg of fluid, therapeutics endpoints like CRT less than 2 seconds, threshold heart rates, normal pulses with no differential between the quality of the peripheral and central pulses, warm extremities, urine output more than 1 mL/kg/hour, normal mental status, and blood pressure more than fifth centile for age are not met, shock is defined as fluid refractory and child should be shifted to pediatric intensive care unit (PICU) for further monitoring. Vasoactive drugs can be started through peripheral or intraosseous line till the central line is established. Shock is further defined into warm or cold shock, catecholamine resistant, and refractory shock as shown in table 2. Further management of septic shock in PICU is guided as per algorithm 1.

Antibiotics and Source Control

Broad-spectrum antibiotics should be administered early preferably within first hour of therapy after taking appropriate cultures but should not delay therapy, as each passing hour increase chances of mortality. Antimicrobials can be given

TABLE 1: Heart rates and systolic blood pressure and perfusion pressure (MAP-CVP) for age

Age group	Heart rate (bpm) (Range 5th-95th percentile)	Systolic blood pressure (mmHg), 5th percentile (Perfusion pressure = MAP-CVP)
Up to one month	140 (120–180)	<60 (55)
2 months to 1 year	130 (80–180)	<70 (60)
1–5 years	80 (60–140)	<70 + [2× age in years] (65)
6–10 years	80 (60–130)	<70 + [2× age in years] (65)
>10 years	75 (90–100)	<90 (65)

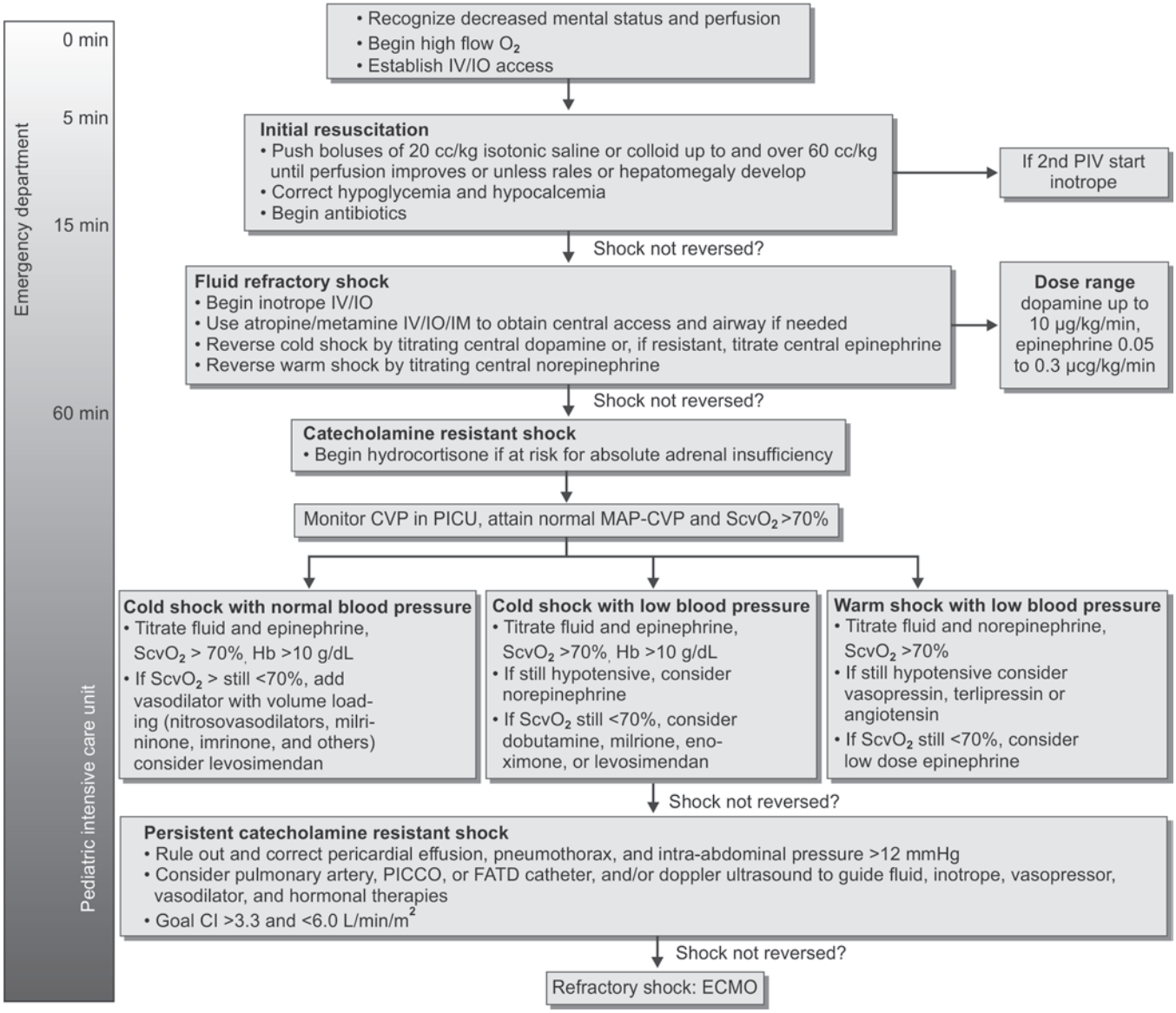
Fifth percentile is the minimum acceptable. MAP (mean arterial pressure) = diastolic pressure + 1/3 pulse pressure (mmHg)

TABLE 2: Hemodynamic definitions of shock as per American College of Critical Care Medicine

Cold or worm shock	Decreased perfusion manifested by altered decreased mental statue, capillary refill >2 s (cold shock) or flash capillary refill (warm shock), diminished (cold shock) or bounding (warm shock) peripheral pulses, mottled cool extremities (cold shock), or decreased urine output <1 mL/kg/h
Fluid-refractory/dopamine-resistant shock	Shock persists despite ≥60 mL/kg fluid resuscitation (when appropriate) and dopamine infusion to 10 μg/kg/min
Catecholamine-resistant shock	Shock persists use of the direct-acting catecholamines; epinephrine or norepinephrine
Refractory shock	Shock persists despite goal-directed use of inotropic agents, vasopressors, vasodilators, and maintenance of metabolic (glucose and calcium) and hormonal (thyroid, hydrocortisone, insulin) homeostasis

ALGORITHM 1

Algorithm for time sensitive, goal-directed stepwise management of hemodynamic support in infants and children. Proceed to next step if shock persists. 1) First hour goals—Restore and maintain heart rate thresholds, capillary refill ≤2 seconds, and normal blood pressure in the first hour/emergency department. Support oxygenation and ventilation as appropriate. 2) Subsequent intensive care unit goals—If shock is not reversed, intervene to restore and maintain normal perfusion pressure (mean arterial pressure-central venous pressure) for age, central venous oxygen saturation >70%, and CI >3.3, <6.0 L/min/m^2 in pediatric intensive care unit.



CI, cardiac index; FATD, femoral arterial thermodilution; Hb, hemoglobin; IM, intramuscular; IO, interosseous; IV, intravenous; PIV, peripheral intravenous; PICCO, pulse contour cardiac output; CVP, central venous pressure; MAP, mean arterial pressure.

intramuscularly or orally (if tolerated) until intravenous line access is available. Antibiotics should be chosen based on suspected community acquired or hospital-acquired infection, local resistance pattern of organism, site of infection, and whether immune-compromised or immune-competent and past history of chronic illness. The choice of empiric drugs should also take into consideration the ongoing epidemic and endemic (e.g., H1N1, methicillin-resistant *Staphylococcus aureus*, chloroquine-resistant malaria, and penicillin-resistant pneumococci). Clindamycin, to decrease toxin production and intravenous immunoglobulin in refractory toxic shock syndrome may be considered. Any site of localized pus collection or any other source of infection should be taken care of once child is stable enough for procedure. Antibiotics may de-escalated later according to culture sensitivity report.

Steroid Therapy

If a child is at risk of suspected or proven absolute adrenal insufficiency (random cortisol level <18 µg/dL) or adrenal pituitary axis failure (e.g., purpura fulminans, congenital

adrenal hyperplasia, prior recent steroid exposure, hypothalamic/pituitary abnormality) and remains in shock despite epinephrine or norepinephrine infusion, then hydrocortisone can be administered. Hydrocortisone may be administered as an intermittent or continuous infusion (preferable in view of decrease incidence of hyperglycemia and hyponatremia) at a dosage of 50 mg/m^2/24 h titrated to reversal of shock and tapered once vasopressor support is not required.

Glycemic Control

Hypoglycemia should be prevented by providing appropriate glucose delivery rate to the child. Associations have been reported between hyperglycemia and an increased risk of death and longer length of hospital stay. Two consecutives values of more than or equal to 180 mg/dL should be managed with insulin infusion in addition to glucose to avoid hypoglycemic episodes.

Blood Products and Plasma Therapies

Packed cell transfusion may be given to maintain hemoglobin of 10 gm/dL if child is hemodynamically unstable ($ScvO_2$ <70% during resuscitation) and target of 7–9 g/dL is reasonable after stabilization and recovery from shock and hypoxemia. Fresh-frozen plasma may be used as infusion not as bolus, if international normalized ratio is prolonged and bleeding tendency is present. In patients with severe sepsis, platelets be administered prophylactically when counts are less than or equal to 10,000/mm^3 (10 × 109/L) in the absence of apparent bleeding, as well when counts are less than or equal to 20,000/mm^3 (20 × 109/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥50,000/mm^3 [50 × 109/L]) are advised for active bleeding, surgery or invasive procedures.

Nutrition

Providing early enteral nutrition to maintain gut integrity and to prevent gut translocation of bacteria should be the goal once hemodynamic stability is achieved. Partial or complete total parenteral nutrition can be given, where enteral feeding cannot be established.

Protein C and Activated Protein Concentrate

No benefit of recombinant human activated protein C in patients with septic shock.

Deep Vein Thrombosis and Stress Ulcer Prophylaxis

There is no role of deep vein thrombosis and stress ulcer prophylaxis in prepubertal children with severe sepsis. However, stress ulcer prophylaxis is commonly used in children who are mechanically ventilated and high risk for bleeding with H2-blockers or proton pump inhibitors, although its effect is not known.

Diuretics and Renal Replacement Therapy

Fluid overload in severe sepsis has been associated with increased risk of mortality, so effort to reverse fluid overload with diuretics when shock has resolved and if unsuccessful, then continuous venovenous hemofiltration or intermittent dialysis to prevent greater than 10% of total body weight fluid overload has met with improved survival in severe sepsis.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation may be used to support children and neonates with septic shock or sepsis-associated respiratory failure. The survival of septic patients supported with ECMO is 73% for newborns and 39% for older children, and is highest in those receiving venovenous ECMO. Forty-one percent of children with a diagnosis of sepsis requiring ECMO for respiratory failure survive to hospital discharge. Venoarterial ECMO is also useful in children with refractory septic shock, with one center reporting 74% survival to hospital discharge using central cannulation via sternotomy. ECMO has been used successfully in critically ill H1N1 pediatric patients with refractory respiratory failure.

CONCLUSION

Optimum treatment of severe sepsis or septic shock is a dynamic and evolving process. Early diagnosis, allowing rapid therapeutic intervention, is essential in improving the outcome of these patients. Current treatment includes early fluid resuscitation, early appropriate antibiotics, tailored use of inotropes and vasopressors, lung protective strategy for acute respiratory distress syndrome, and use of adjuvant treatments such as low-dose hydrocortisone (Table 5). Early recognition of organ failure and supportive therapy especially renal replacement therapy to prevent further injury helps in reversal of organ dysfunction.

TABLE 5: Summary of pediatric recommendations of surviving sepsis guidelines 2012

A. Initial resuscitation	• For respiratory distress and hypoxemia, start with face mask oxygen, or if needed and available, high flow nasal cannula oxygen or nasopharyngeal continuous positive airway pressure. For improved circulation, peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation • Initial therapeutic endpoints of resuscitation of septic shock: capillary refill of ≤2 s, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL/kg/h, and normal mental status. Central venous oxygen saturation ≥70% and cardiac index between 3.3 and 6.0 L/min/m^2 should be targeted thereafter

Continued

Continued

	• Follow American College of Critical Care Medicine-Pediatric Life Support guidelines for the management of septic shock • Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock
B. Antibiotics and source control	• Empiric antibiotics be administered within 1 h of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible but this should not delay administration of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (e.g., H1N1, MRSA, chloroquine resistant malaria, penicillin-resistant pneumococci, recent ICU stay, and neutropenia) • Clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension • Early and aggressive source control (grade 1D) • Clostridium difficile colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease
C. Fluid resuscitation	• In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids or albumin with boluses of up to 20 mL/kg crystalloids (or albumin equivalent) over 5–10 minutes, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales exists then inotropic support should be implemented, not fluid resuscitation. In nonhypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises) blood transfusion is considered superior to crystalloid or albumin bolusing
D. Inotropes/ vasopressors/ vasodilators	• Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation • Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure be given vasodilator therapies in addition to inotropes
E. Extracorporeal membrane oxygenation (ECMO)	• Consider ECMO for refractory pediatric septic shock and respiratory failure
F. Corticosteroids	• Timely hydrocortisone therapy in children with fluid refractory, catecholamine resistant shock, and suspected or proven absolute (classic) adrenal insufficiency
G. Protein C and activated protein concentrate	No recommendation as no longer available
H. Blood products and plasma therapies	• Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (<70%), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, a lower target >7.0 g/dL can be considered reasonable • Platelet transfusion targets as described in text • Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura
I. Mechanical ventilation	• Lung-protective strategies during mechanical ventilation
J. Sedation/analgesia/ drug toxicities	• We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis • Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events
K. Glycemic control	• Control hyperglycemia using a similar target as in adults ≤180 mg/dL. Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant
L. Diuretics and renal replacement therapy	• Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration or intermittent dialysis to prevent >10% total body weight fluid overload
M. Deep vein thrombosis prophylaxis	• No recommendation on the use of deep vein thrombosis prophylaxis in prepubertal children with severe sepsis
N. Stress ulcer prophylaxis	• No recommendation on the use of stress ulcer prophylaxis in prepubertal children with severe sepsis
O. Nutrition	• Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot

Clinical Pearls

- Septic patients may have warm shock or cold shock with or without respiratory distress
- Source control (debridement, drainage) should be considered in all septic patients.
- Isotonic solution such as normal saline or Ringers lactate for all initial fluid therapy
- First dose of antibiotics to be stored in outpatient department and emergency areas
- If persistent hypotension despite fluids and inotropes, one should look for mechanical causes, such as tamponade due to raised intra-abdominal pressure, pleural or pericardial effusion, or tension pneumothorax.

KEY POINTS

- ☞ Early fluid resuscitation, early appropriate antibiotics, tailored use of inotropes and vasopressors, use of hydrocortisone in catecholamine resistant shock, known adrenal insufficiency (chronic steroid therapy, example nephrotic syndrome, autoimmune disorders)
- ☞ Lung protective strategy for acute respiratory distress syndrome should be used
- ☞ Early recognition of fluid overload, organ failure, and supportive therapy, especially renal replacement therapy to minimize fluid overload and further injury helps should be considered in all patients with every sepsis once hemodynamic stability has been achieved
- ☞ Inborn errors of metabolism can mimic sepsis, therefore, anion gap and urine metabolic screen should be considered especially in infants.

SUGGESTED READINGS

1. Amado VM, Vilela GP, Queiroz A Jr, Amaral AC. Effect of a quality improvement intervention to decrease delays in antibiotic delivery in pediatric febrile neutropenia: A pilot study. J Crit Care. 2011;26:103.e9-12.
2. Aneja RK, Carcillo JA. Differences between adult and pediatric septic shock. Minerva Anestesiol. 2011;77:986-92.
3. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med. 2012;13(3):253-8.
4. Branco RG, Garcia PC, Piva JP, Casartelli CH, Seibel V, Tasker RC. Glucose level and risk of mortality in pediatric septic shock. Pediatr Crit Care Med. 2005;6(4):470-2.
5. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009;37:666-88.
6. Dellinger R, Levy M, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637.
7. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis. Crit Care Med. 2004;32:1771-6.
8. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis, International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6:2-8.
9. Khilnani P, Singhi S, Lodha R, Santhanam I, Sachdev A, Chugh K, et al. Pediatric sepsis guidelines: summary for resource-limited countries. Indian J Crit Care Med. 2010;14(1):41-52.
10. Khilnani P. The pediatric BUS has arrived: Is bedside ultrasound in the pediatric intensive care unit a feasible option? Pediatr Crit Care Med. 2011;12(6)681-3.
11. Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. Crit Care Med. 2005;33:855-9.
12. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. Crit Care Med. 2009;37:2448-54.
13. Skinner SC, Iocono JA, Ballard HO, Turner MD, Ward AN, Davenport DL, et al. Improved survival in venovenous vs venoarterial extracorporeal membrane oxygenation for pediatric noncardiac sepsis patients: a study of the Extracorporeal Life Support Organization registry. J Pediatr Surg. 2012;47:63-7.

CHAPTER 42

Status Epilepticus

Soonu Udani

INTRODUCTION

Status Epilepticus (SE) is a brain damaging emergency that needs prompt and targeted therapy in a protocolised manner if good outcome is to be expected. Several algorithms may be available and units must make one most suitable for their setting.

DEFINITION

A seizure is a paroxysmal change in motor activity and or behavior that results from abnormal electrical activity in the brain. There are several proposed definitions for SE.

The classic one is: seizures or repeated seizures lasting for more than 30 minutes without recovering consciousness between seizures.

Recent definition states: status greater than 5 minutes or a continuous seizures or two or more discrete seizure between which there is incomplete recovery of consciousness.

For practical purposes: any child that is brought convulsing to the hospital is said to be in SE.

Defining status in this way allows us to recognize short lasting seizures as relatively benign events not necessarily requiring emergent treatment and gives us strong grounds to treat longer lasting seizures aggressively as true emergencies necessitating strong pharmacologic intervention.

MANAGEMENT OF STATUS EPILEPTICUS

Current management of SE emphasizes a more aggressive approach—initiating first line therapy more rapidly (the longer one waits the longer the seizure takes to come under control).

If the patient is out of hopistal, has no intravenous access, or casualty, consider buccal midazolam 0.3 mg/kg or rectal diazepam 0.3 mg/kg.

1. Intravenous (IV) benzodiazepines: early use gives best results
   - Lorazepam, 0.1 mg/kg IV (maximum, 5 mg) over 1 min, (diazepam can be substituted)
   - Allow 5 minutes to determine whether seizure terminates
   - Give oxygen; stabilize airway, respiration, and hemodynamics as needed
   - Obtain IV access
   - Check bedside glucose
   - Begin electrocardiogram (ECG) monitoring
   - Repeat benzodiazepine administration.
2. Administer fosphenytoin (PHT) 20 mg/kg phenytoin equivalent IV at 2–3 mg/kg/min (maximum, 150 mg/min) (phenytoin needs to be given slower) (Phenobarbitone at 20 mg/kg can be substituted here)
   - If the patient's age is less than 2 years, consider pyridoxine 100 mg IV push
   - Testings:
     - Bedside glucose complete blood count cultures
     - Electrolytes, calcium, magnesium, phosphorus, liver function test, and toxicology if indicated (serum, urine preserve till consultant orders)
     - Antiepileptic drug (AED) levels, prothrombin time, thromboplastin time
     - Support airway, respiration, hemodynamics as needed
     - Continuous vital sign and ECG monitoring.
3. If seizures persist for more than 10 min, repeat dose of PHT 10–20 mg/kg; wait for 10 min if still have seizures

This is now the stage of established SE as two primary drugs have failed.

4. Administer levetiracetam (LEV) 20 mg/kg IV at 5 mg/kg/min (maximum 3 g), continue at 40 mg/kg/day in two to three divided doses.

If contraindication to LEV and no specific concern regarding liver/metabolic/mitochondrial disease, then administer:

- Valproate (VPA) 30 mg/kg at 5 mg/kg/min

OR

- Phenobarbital (PB) 20 mg/kg over 5–10 min.

If seizures persist after 10 min, established RSE and admit to pediatric intensive care unit (PICU).

In patients who had failed first line therapy, additional second and third line therapy adds only marginal benefit (2.3–5%). Given the observation that intermediate steps are time consuming with limited added value and also with increased awareness of the importance of early treatment of seizure, a change to accelerated protocol has been proposed. Lorazepam and phenytoin are given simultaneously, followed by pharmacologic coma (omit phenobarbitone). The application of such treatment has to be balanced with available expertise and infrastructure.

Prepare to secure airway, mechanically ventilate, and obtain central venous access and continuous hemodynamic monitoring through an arterial line.

5. Initiate coma with midazolam 0.2 mg/kg bolus (maximum 10 mg) over 2 minutes, and then initiate infusion at 0.1 mg/kg/h.

If seizures persist for five more minutes after an additional midazolam bolus of 0.2 mg/kg bolus, increase the dose by 0.02 every 5–10 minutes.

One or two extra boluses can be given but they should not be repeated for every increase in infusion rate.

The patient would almost always need intubation and ventilatory support by now. Vasopressor support with norepinephrine (NE) by the central line should be considered

If seizures persist at maximum midazolam (generally 2 mg/kg/h) or midazolam infusion or till hypotension, cardiac instability is seen.

If seizures still persist, with reassessment of cardiovascular status, which may include an echocardiography for contractility, the next step should be pentobarbital coma. An electroencephalogram (EEG)—preferably continuous—should be obtained at this stage, especially if no clinical seizure activity is visible.

6. Thiopental 4 mg/kg load and 1–2 mg/kg/h
   - Increase only on advice of consultant and EEG for burst suppression
   - Warning: cardiodepressive; especially after 3–4 days of continuous use
   - Propofol is another option however, it is not approved in children for use for more than 24 h
   - General anesthesia requires the expertise of an anesthetist and the machine for gas delivery; most PICUs are ill-equipped for the system.
7. Weaning: after a minimum of 24 hours of electrical seizure-free activity, reduce midazolam by 0.05 mg/kg/h every 3 hour, with frequent EEG review.

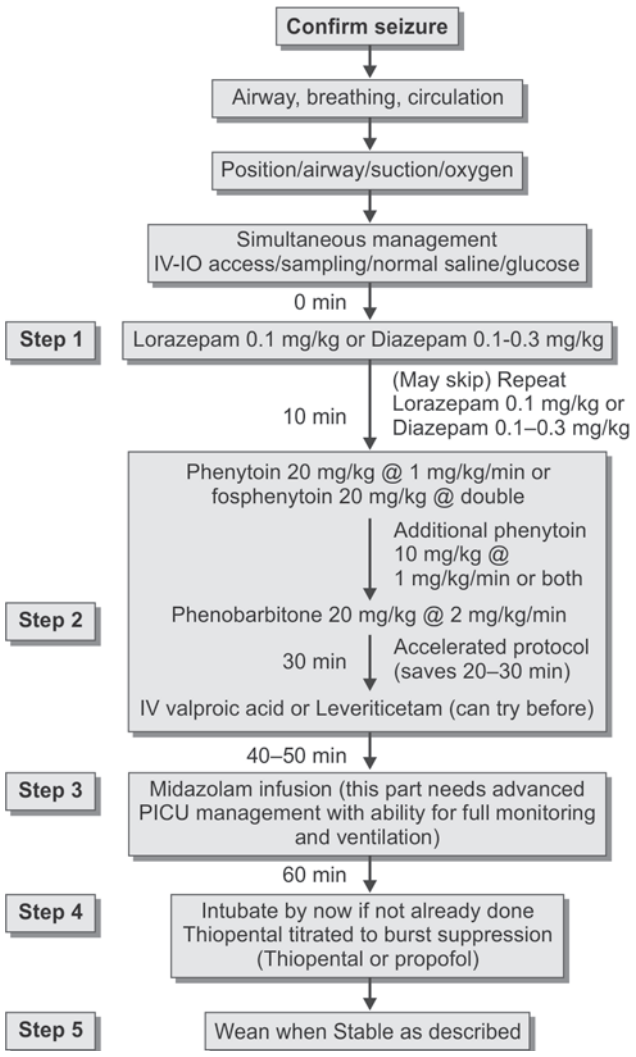
Similar weaning should be done for thiopental, unless abrupt stoppage is required because of severe hypotension uncontrolled by NE. Hypotension will reduce cerebral perfusion pressure and aggravate central nervous injury.

If clinical or subclinical seizures occur, reinstitute coma with midazolam for 24 hours. Similarly for thiopental.

Note: Midazolam does not cause burst suppression, the end point is loss of seizure activity.

ALGORITHM 1

Algorithm of seizure



IV, intravenous; IO, intraosseous; PICU, pediatric intensive care unit.

If no clinical or electrographic seizures, then wean off.

The patient should be monitored for levels of PB, PHT, and VPA when used. The child would be on two to three AEDs by now and these should not be stopped immediately. The rest of the management would depend on the cause and recovery.

Magnetic resonance imaging and etiology seeking tests (as in encephalopathy) should be performed even with the patient on ventilation.

When the patient does not respond, other advanced therapies may be called for which are beyond this discussion.

Clinical Pearls

- Prolonged status injures the brain
- Accelerated protocol saves 20–30 minutes
- Treat within the facility's capabilities and transfer early.

KEY POINTS

- ☞ Attention to airway, breathing, and circulation simultaneously while treating seizures
- ☞ Early treatment aborts status faster and prevents benzodiazepine resistance
- ☞ Do not forget glucose and calcium
- ☞ Strict attention to hemodynamics especially in the stage of refractory status
- ☞ Get expert help as newer drugs and advanced treatments options may exist.

SUGGESTED READINGS

1. Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatr Neurol. 2008;38(6):377-90.
2. Abou Khaled KJ, Hirsch LJ. Advances in the management of seizures and status epilepticus in critically ill patients. Crit Care Clin. 2006;22(4):637-59.
3. Shearer P, Riviello J. Generalized convulsive status epilepticus in adults and children: treatment guidelines and protocols. Emerg Med Clin N Am. 2011;29(1):51-64.

CHAPTER 43

Cardiogenic Shock

Nameet Jerath, Praveen Khilnani

INTRODUCTION

Children with congenital heart disease, cardiomyopathy, various arrhythmias, viral myocarditis,post cardiac surgery or severe sepsis can have severe myocardial dysfunction and cardiogenic shock. It is a commonly encountered problem in pediatric age group and early diagnosis and initiation of treatment can prevent mortality and severe morbidity. This chapter covers algorhithmic approach to a child with cardiogenic shock with systematic differential diagnosis and broad management of various etiologies leading to cardiogenic shock.

DEFINITION

Shock is a state of imbalance between the metabolic supply and demands of the body. Cardiogenic shock is the subset when the cardiac function is responsible for the failure of cardiovascular system to meet the metabolic demands of the body.

Shock on presentation has similar signs and symptoms, like tachycardia, tachypnea, poor perfusion, and decreased urine output with or without drop in blood pressure (hypotension), and it may be impossible to identify shock to be cardiogenic on presentation.

The initial management of any child who presents with shock, irrespective of the etiology, remains the same. The aim is quick identification of shock status and an early appropriate response to improve outcomes.

Cardiac function can be depressed in patients with any type of shock, even of noncardiac origin. Myocardial dysfunction could be responsible for worsening of shock state as in massive sepsis. We shall restrict ourselves to only the cardiac causes of cardiogenic shock in this chapter (Algorithm 1).

PATHOPHYSIOLOGY

It pays to remember the determinants of substrate delivery to the tissues (Algorithm 2). Cardiac output is dependent on heart rate (HR) and stroke volume, and the stroke volume itself is dependent on preload, contractility, and afterload of the heart.

The oxygen content of blood is dependent on the hemoglobin concentration and its oxygen saturation (SpO_2).

Preload, contractility, afterload, hemoglobin, SpO_2, and to some extent, HR can be optimized with drugs or other interventions and help tilting the metabolic balance back to normal.

As the shock progresses, body's compensatory mechanisms, like increase in systemic vascular resistance (SVR) and HR start to kick in. These compensatory responses can be detrimental and can worsen the cardiogenic shock by increasing afterload and worsening cardiac output. As the critical point is reached, patient can switch from a "warm" state of adequate perfusion to a "cold" state. Patients now show signs of poor cardiac output and are tachycardic, hypotensive, diaphoretic, oliguric, acidotic, and poorly perfused. Extremities are cool and mental status is altered. Hepatomegaly, jugular venous distension, rales, and peripheral edema may be observed.

Diastolic Dysfunction

Diastolic dysfunction is poorly understood and often overlooked. It can be associated with normal systolic ventricular function. Impaired myocardial relaxation during diastole increases left ventricular end diastolic pressure (LVEDP). This is transmitted to the lung and results in pulmonary edema and dyspnea. Elevated LVEDP reduces the perfusion pressure in the coronaries which further hampers cardiac perfusion and function.

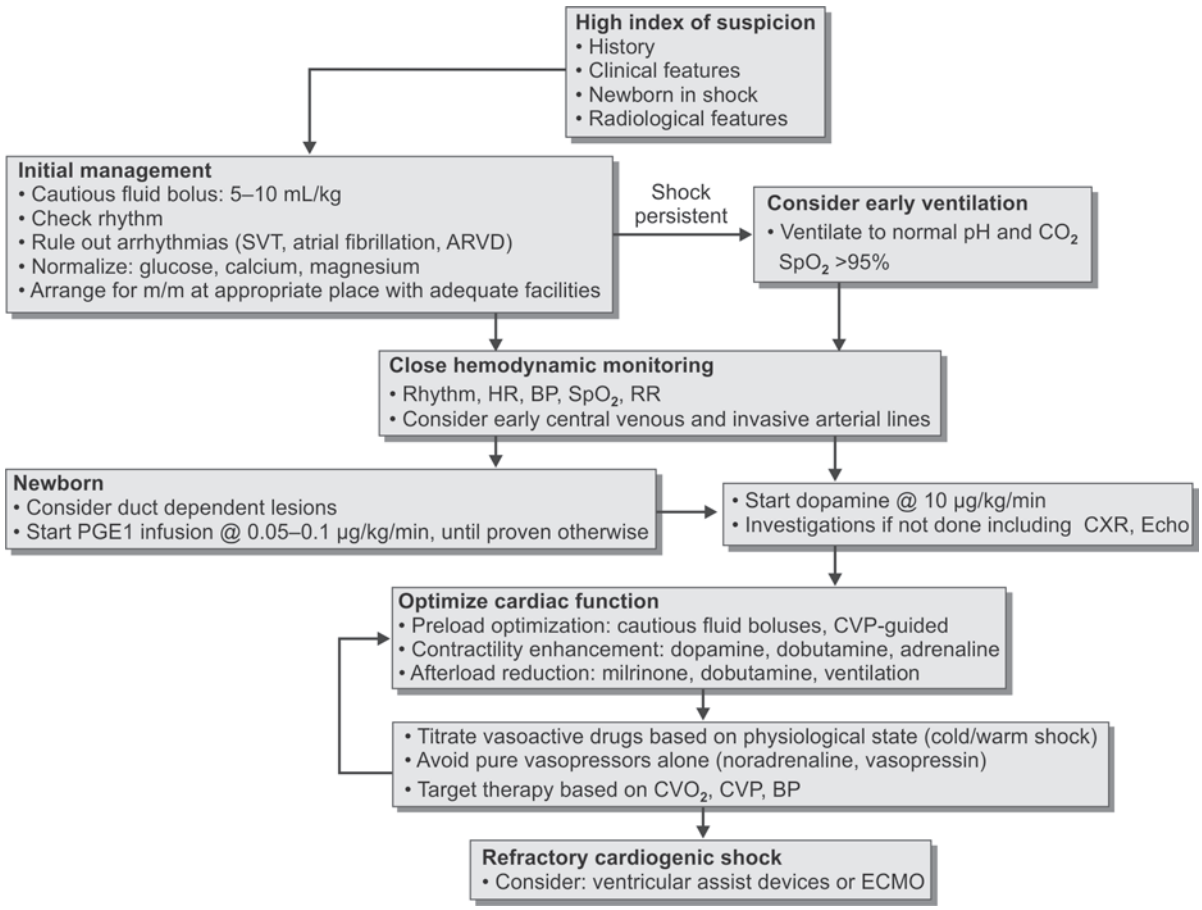
Recognition of Cardiogenic Shock

There are often subtle clues to suggest that the shock could be cardiogenic and it is important to identify such patients, as their management plan would differ from the routine management of shock.

Though there are often overlap of symptoms with other noncardiogenic conditions, the following symptoms should alert one to the possibility of cardiogenic origin of shock:

ALGORITHM 1

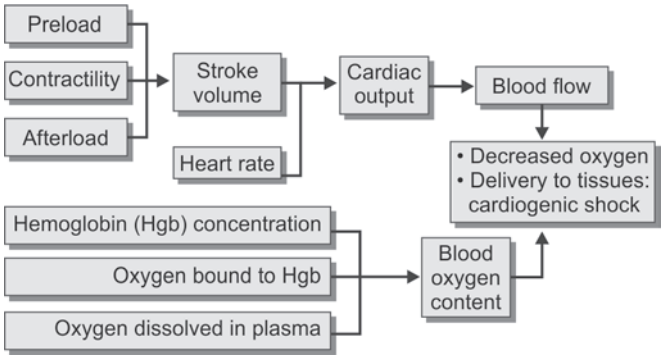
Cardiogenic shock management according to cause



SVT, supraventricular tachycardia; ARVD, arrhythmogenic right ventricular dysplasia; CO_2, carbon dioxide; SpO_2, saturation of peripheral oxygen; HR, heart rate; BP, blood pressure; RR, respiratory rate; PGE1, prostaglandin E1; CXR, chest X-ray; Echo, echocardiography; CVP, central venous pressure; CVO_2, central venous oxygen saturation; ECMO, extracorporeal membrane oxygenation.

ALGORITHM 2

Pathophysiology of cardiogenic shock



- Insignificant fevers compared to the distress, illness
- Excessive sweating
- Excessive irritability
- Breathlessness while feeding
- History of fast breathing at all times
- Dramatic, sudden onset of illness
- Any shock state in an infant
- Central cyanosis.

Often clues towards cardiogenic shock can be found on careful monitoring and trend of vitals and response to interventions during resuscitation. The response to a fluid bolus should be improvement of the HR and improvement in blood pressure as the venous return [and central venous pressure (CVP)] improves. Contrary to expectation, if the HR starts rising and/or the blood pressure drops in response to a fluid bolus, one should be alerted and cautiously review the scenario. Excessive and too fast fluid bolus in a child with cardiogenic shock could worsen the hemodynamic state. Such children may still be hypovolemic and require fluid boluses but these should be slower and in smaller aliquots. The importance of assessment and reassessment after each intervention cannot be overemphasized.

Causes of Cardiogenic Shock

- Arrhythmias: supraventricular tachycardia (SVT), arrhythmogenic right ventricular dysplasia
- Myocarditis/cardiomyopathy: hypoxia, infectious, metabolic, toxic, neuromuscular disorders
- Congenital heart diseases
- Postoperative low cardiac output state (LCOS)
- Trauma.

Neonatal period undergoes significant transitions in pulmonary and systemic circulations immediately to a few weeks after birth. Congenital heart diseases with duct dependent circulations can present dramatically with collapse. Any newborn who presents in shock should be suspected to have a duct dependent circulation.

Congenital heart diseases are a significant group of patients who can present in shock. A chest X-ray can help group them into either well, overly or poorly perfused lung fields. Lesions with generous pulmonary blood flows (like large ventricular septal defect) present with tachypnea and respiratory distress and need measures to restrict the pulmonary blood flow.

Investigations

After initial stabilization, laboratory investigations that may be ordered include complete blood count, arterial blood gas, electrolytes including ionized calcium, renal and liver functions, serum lactate, and cardiac enzymes if indicated.

Once a central venous line is in place, measurement of central venous oxygen saturation (CVO_2) is a good marker of cardiac output. Central venous oxygen saturation measured from superior vena cava reflects the adequacy of oxygen delivery, and therefore, cardiac output (Fick's Principle).

Chest Radiography

The chest radiograph should be evaluated for the size of heart and pulmonary vasculature, both of which provide essential information regarding the possible causes of shock.

Electrocardiography

An electrocardiogram can be diagnostic in certain conditions like anomalous origin of left coronary artery from pulmonary artery. The rhythm on the monitor should be carefully assessed. Long-standing SVT, ventricular tachycardia, atrial fibrillation, or atrioventricular block could be the reason of shock.

Echocardiography

This is the most effective way of a comprehensive assessment of cardiac structure and function. It also helps in the calculation of cardiac output and systemic vascular resistance index. A quick, limited assessment should be in the armamentarium of each critical care specialist.

More specialized tests, like cardiac catheterization or magnetic resonance imaging, are sometimes needed for detailed assessment and management of certain conditions.

Management

Principles of management:

- Minimize myocardial oxygen demands
  - Intubation and mechanical ventilation
  - Reduce agitation, anxiety with judicious sedation
  - Blood transfusion
- Improve myocardial function
  - Optimize preload
  - Augment contractility
  - Reduce afterload (think of ventilation as a modality)
  - Correct rhythm disturbances
- Think of duct dependent states: prostaglandin E1 (PGE1) infusion.

General Measures

The initial management of shock remains the same as outlined in the guidelines elsewhere, as many times it is impossible to discern the cause of shock on presentation. The history, clinical features, and response to resuscitation efforts often have enough clues to primary cardiac involvement. Once cardiogenic shock has been identified, the management should be tailored to the suspected condition.

Fluid boluses should be carefully given in small aliquots of 5–10 mL/kg. Most children will have concomitant dehydration too because of poor oral intake, respiratory losses, and sometimes associated diarrhea and vomiting, and will benefit from fluid boluses. At any stage, if the desired hemodynamic response is not seen, no more fluid boluses should be administered.

Maintain normal sugar levels, temperature, and a calm state by judicious use of sedation to reduce the metabolic demands of the body. The electrolytes including magnesium and calcium should be normalized.

Ventilation should be thought of early in patients with cardiogenic shock. It has the advantages of reducing metabolic demands of the body by reducing the work of breathing, allowing sedation and muscle relaxation, and by reducing afterload. Ventilated patients should be targeted to normal pH and CO_2 with adequate oxygenation.

Monitoring is a vital part of management of cardiogenic shock. Most such children will require invasive arterial pressure monitoring and central venous lines for CVP and for infusion of vasoactive drugs.

CARDIOGENIC SHOCK IN A NEWBORN

The newborn period presents a specific subgroup as this is a period of transition from fetal to extrauterine circulation. Many duct dependent lesions can present with dramatic shock with the closure of the patent ductus arteriosus. All circulatory shocks in newborns should be treated as duct dependent lesion unless proven otherwise and efforts should be targeted to keep the duct patent by PGE1 infusion (0.05–0.1 μg/kg/min).

Preload

Preload assessment and titrating fluid management can be very challenging. The idea is to optimize preload to help the cardiac output by shifting up on the Frank-Starling curve. Judicious small volume fluid boluses are recommended, sometimes as small as 5 mL/kg with subsequent fluid being guided by hemodynamic response. Crystalloids remain the fluid of choice.

In a fluid overloaded child with stable blood pressure, diuretics may be judiciously used later on in the course of the management.

Myocardial Contractility, Inotropic Agents

The choice of vaso-cardioactive drugs will depend on the clinical state and no one prescription fits all.

Dopamine and adrenaline are good inotropic agents and increase the contractile force of the heart pump and increase the SVR. They thus increase the cardiac output and the blood pressure. Both also increase the metabolic demands of the heart.

Dobutamine and milrinone are inodilators that improve the pump function and also cause dilation of systemic vessels [reduced SVR and hence blood pressure (BP)]. The combined effects of improved contractility and reduction in afterload improves cardiac output albeit with some drop in BP. Milrinone and to smaller extent dobutamine has excellent lusitropic effect, which allows for relaxation of heart, improving the diastolic dysfunction.

Noradrenaline and vasopressin are primarily vaso-constrictors and their use alone in a failing heart is not appropriate. They both increase blood pressure but with increased workload (afterload) for the heart. They can help improve coronary perfusion.

Vasoactive Drugs

The clinical effects and recommended doses of few vasoactive drugs are given in table 1.

Diastolic Blood Pressure

The left heart gets its perfusion through coronary arteries during diastole across a pressure gradient (diastolic blood pressure–LVEDP). Maintenance of adequate diastolic blood pressure is, therefore, necessary to maintain the coronary perfusion to fuel the heart.

Afterload Reduction

Positive end expiratory pressure in a child with adequate venous filling has the effects of reducing afterload making it easier for the heart to pump. This, amongst others, is an important reason to consider early ventilation of such children.

Inodilators (dobutamine, milrinone, amrinone) or pure vasodilators (nitroprusside, nitroglycerine) will reduce afterload and may be used to augment cardiac output. They should be avoided as monotherapy in acute early phase of shock due to the risk of uncontrolled hypotension. They are sometimes used together with an inotrope.

SPECIFIC THERAPY

Intravenous immunoglobulin is often used in patients with myocarditis to modulate the immune response. There is not enough literature support for this practice though.

Postoperative LCOS is the state of low cardiac output after cardiac surgeries because of many factors including tissue edema, cytokine release, cardiac stun, etc. This needs careful monitoring and management on the lines described above. Most carefully managed hearts will start showing improvement in about 48 hours.

Surgical Correction

Some congenital heart diseases may need urgent surgical correction. Cardiac lesions with torrential pulmonary blood flow benefit from pulmonary artery banding procedures.

Extracorporeal Cardiac Support

Cardiogenic shock refractory to the above mentioned therapies can be supported on extracorporeal support systems, like ventricular assist devices (e.g., Berlin Heart, Thoratec) or extracorporeal membrane oxygenation. These are used as temporary measures while awaiting spontaneous recovery or as a bridge to transplant.

CARDIAC TRANSPLANT

Heart transplant is the last option for refractory and terminal heart failure. Organ supply remains the biggest hurdle in our country for this option to be exercised.

Clinical Pearls

- Cardiogenic shock in children can present as respiratory distress
- Newborns cardiogenic shock due to congenital heart disease present when ductus closes, as a corollary prostaglandin drip to keep ductus open may be life-saving
- Metabolic/endocrine problems, such as hypoglycemia, hypocalcemia, and hypothyroidism, can present as cardiogenic shock
- Septic shock is an important cause of cardiogenic shock.

TABLE 1: Vasoactive drugs

Drug	Dose	Clinical effect
Dopamine	5–20 μg/kg/min	↑ contractility, vasoconstricts, ↑ heart rate
Dobutamine	5–20 μg/kg/min	↑ contractility, vasodilates
Adrenaline	0.01–1 μg/kg/min	↑ contractility, vasoconstricts, ↑ heart rate
Noradrenaline	0.01–1 μg/kg/min	Vasoconstricts+++, ↑ contractility, heart rate
Milrinone	0.25–0.75 μg/kg/min	↑ contractility, lusitropic
Vasopressin	0.0001–0.008 U/kg/min	Vasoconstricts +++

KEY POINTS

- ☞ Tachycardia and worsening of blood pressure in response to a fluid bolus in any child with shock should alert to a likely cardiogenic cause
- ☞ Central venous oxygenation is a good surrogate for cardiac output assessment
- ☞ Fluid bolus of 5-10 mL/kg should be cautiously used in children suspected to have cardiogenic shock
- ☞ Echocardiography is invaluable in diagnosis of cardiac lesions/conditions
- ☞ All newborns with shock should be suspected to have a duct-dependent lesion
- ☞ Early ventilation should be considered in cardiogenic shock.

SUGGESTED READINGS

1. Arikan AA, Citak A. Pediatric shock. Signa Vitae. 2008;3(1):13-23.
2. Lincoln S Smith, Lynn J Hernan. Shock states. In: Fuhrman BP, Zimmerman JJ (Eds). Pediatric Critical Care. 4th ed. Philadelphia: Elsevier Saunders; 2011. p. 364.
3. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation. 2008;117(5):686-97.
4. Rossano JW, Price JF, Nelson DP. Treatment of heart failure in infants and children: Medical management. In: Nichols DG (Ed). Rogers' Textbook of Pediatric Intensive Care. Lippincott Williams and Wilkins; 2008. p. 1093.
5. Smith KA, Bigham MT. Cardiogenic shock. The Open Pediatric Medicine Journal. 2013;7(Suppl 1: M5):19-27.
6. Woods WA, McCulloch MA. Cardiovascular emergencies in the pediatric patient. Emerg Med Clin North Am. 2005;23(4):1233-49.

CHAPTER 44

Head Injury in Infants and Children

Bhaskar Saikia, Praveen Khilnani

INTRODUCTION

Traumatic brain injury in children is prevalent universally with potentially poor outcomes. Domestic accidents, motor vehicle accidents, recreational injuries, and sports mishaps are the common causes; however, child abuse must be kept in mind in children, especially in toddlers. The reported mortality in developed countries in hospital setting is 9–35%.

The incidence in developing countries is poorly documented, however, mortality is higher in developing countries.

Primary brain injury is the direct result of the physical trauma. It may result in uncomplicated concussion with quick recovery and no residual deficit or in serious hemorrhage, contusion or hematomas. While these are all visible on a computed tomography (CT) scan, diffuse axonal injury can be a severe condition where the initial CT scan may look deceptively benign. Secondary brain injury may occur after the primary event due to potentially preventable causes like hypoxia, hypoperfusion, hypercarbia, and hematoma.

MANAGEMENT

Management of head injury and control of intracranial pressure (ICP) (Algorithm 1) or maintenance of cerebral perfusion pressure (CPP) is to be started right from the site of accident to include prevention of hypotension by active control of bleeding and fluid therapy. Immediate stabilization of the airway, breathing, and circulation (ABC) with cervical spine immobilization should be done followed by detailed evaluation of the following:

- Mode of injury
- Time of injury
- Neurological condition of the child
- Seizures may occur immediately or soon after the injury.

Loss of consciousness of more than 5 minutes warrants imaging and evaluation. Recovery from early loss of consciousness with a secondary lapse may be indicative of extradural hematoma.

Vomiting after even trivial head injury is not uncommon in children, but observation for this is usually advisable.

Neurological deficit may be transient after an impact such as a short seizure. If the child presents with coma, deficit cannot be assessed, a previous observation by parents or doctor is noted and needs to be followed closely.

The AVPU (Alert, Responds to Verbal commands, Responds to pain, Unresponsive) scale can provide valuable information.

Glasgow Coma Scale

The Glasgow Coma Scale (GCS) is used to assess the depth of coma after head injury in adults and children above 5 years of age. In those below 5 years, modified GCS should be used (Table 1).

Classification of head injury using GCS

- 13–15: mild
- 9–12: moderate
- 3–8: severe.

Clinical criteria for discharge from emergency room after 2 hours of observation:

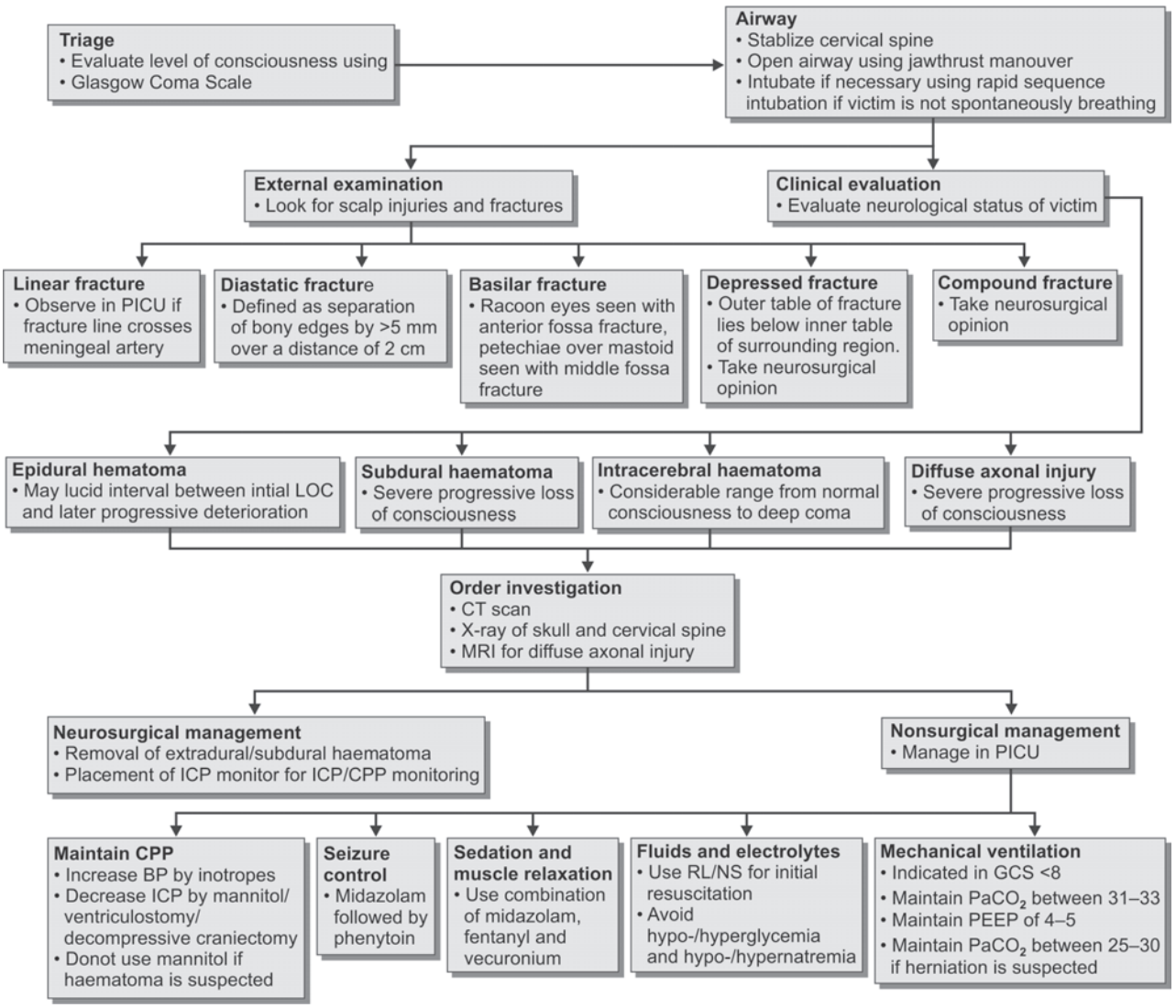
- No loss of consciousness
- No vomiting
- No amnesia
- Normal mental status
- No focal neurological deficit
- No neurological deterioration
- No post-traumatic seizure including impact seizure
- No otorrhea or rhinorrhea or bleeding
- No shock or other organ involvement that would preclude discharge
- No anticoagulant, anti-inflammatory drug, or bleeding diathesis
- No suspicion of child abuse, no matter how trivial the injury
- Radiological criteria for minor head injury
- No intracranial abnormality related to the head injury on CT scan.

Skull fractures are acceptable except:

- Those that cross the middle meningeal artery
- Those that cross the dural sinuses
- Those that are depressed more than the thickness of the adjacent skull.

ALGORITHM 1

Pediatric head trauma



PICU, pediatric intensive care unit; LOC, loss of consciousness; CT, computed tomography; MRI, magnetic resonance imaging; ICP, intracranial pressure; CPP, cerebral perfusion pressure; BP, blood pressure; RL/NS, Ringer's lactate/normal saline; GCS, Glasgow Coma Scale; PEEP, positive end-expiratory pressure; $PaCO_2$, partial pressure of carbon dioxide.

In children fulfilling the above criteria for minor head injury, delayed deterioration is extremely uncommon and can be safely discharged. All other patient should be admitted.

Care upon Admission

Tracheal intubation is indicated for children with GCS ≤8. Children with multi-trauma, inhalation injury, airway/facial injury, and shock with inaccessible head injury should be intubated, especially if at risk for increased ICP from pain and agitation. The cervical spine must be protected.

Pain, fever, and retention of urine should be treated immediately. Constrictive cervical collar or large-bore internal jugular catheter should be avoided. Supine position with the head end elevated to 30° is preferred for adequate venous drainage. All unnecessary touch, rough handling, moving, and noise should be controlled or kept to minimum. Severe hyperglycemia greater than 180 mg/dL and hypoglycemia should be avoided.

Orotracheal intubation is preferred as it is quicker, requiring less manipulation of the neck, avoids aggravating any anterior basilar skull fracture, or introducing infection into the anterior cranial vault.

All patients should be presumed to be full stomach. The jaw thrust maneuver is used during bag mask ventilation and head tilt and chin lift maneuver should be avoided. Common medications used during intubation include thiopentone and lidocaine. It should be emphasized that even comatose patients must have good sedation and muscle relaxant during intubation to avoid sudden rise in ICP.

TABLE 1: Modified Glasgow Coma Scale in pediatrics

Eye opening		**Score**
Spontaneous		4
To verbal stimuli		3
To pain		2
None		1
Verbal response		**Score**
Nonverbal children	***Best verbal response***	
Smiles, oriented to sounds, follows objects, interacts	Oriented and converses	5
Consolable when crying and interacts inappropriately	Disoriented and converses	4
Inconsistently consolable and moans; makes vocal sounds	Inappropriate words	3
Inconsolable irritable and restless; cries	Incomprehensible sounds	2
None	None	1
Motor response		**Score**
Obeys commands		6
Localizes pain		5
Flexion withdrawal		4
Abnormal flexion (decorticate rigidity)		3
Extension (decerebrate rigidity)		2
None		1

Hypotension is common and blood loss should never be attributed to the head injury alone.

A diligent search should be made for the source of bleeding.

Scalp and head trauma can cause hypotension only in children below 2 years of age. Rapid and aggressive treatment is needed to prevent secondary damage from hypoxic-ischemic injury. A low blood pressure at the time of presentation is associated with poor prognosis. Hypotension of neurogenic origin is rare and indicates severe brainstem or cervical spine injury. Hypertension as part of Cushing's triad—hypertension, bradycardia, and hypoventilation—are more common. This indicates raised ICP. Hypertension may mask hypovolemia, therefore, blood pressure measurement alone should not be accepted as a sign of normovolemia. Normal saline is the best choice for initial resuscitation.

Radiological Investigations

There is no real role for skull X-ray in head injury as far as prognostication or severity of injury is concerned. Normal ultrasound cranium in an infant may give false sense of security as it will miss details. Computed tomography scan is very helpful and threshold should be low for ordering a CT in patients with:

- Any focal deficit
- Any history of loss of consciousness more than 5 minutes
- GCS persistent less than 13
- Unable to examine the patient because of sedation, paralysis, or intubation for other reasons
- Pupillary inequality
- Cerebrospinal fluid (CSF) leak
- Depressed skull fracture
- Vomiting more than three times.

It is not necessary to repeat a scan after 24–48 hours if there is no clinical deterioration or change in the GCS.

A quick cross table lateral X-ray can help to visualize at least the top three vertebrae. Cervical spine should also be scanned during the CT head to avoid repeated radiation exposure.

Other associated injuries should be ruled out and should be treated simultaneously if required. The following conditions warrant early surgical intervention:

- Acute extra-axial hematomas of 1 cm or more in thickness
- Subdural or epidural hematomas of more than 5 mm in thickness with midline shift
- Hematomas more than 5 mm with midline shift in patients with moderate brain injury with effacement of the basal cisterns
- Depressed skull fractures.

Cerebrospinal fluid rhinorrhea and otorrhea need conservative approach avoiding packing of ears and nose. Almost all cases resolve spontaneously over 7–10 days. Cerebrospinal fluid leaks less likely to heal are:

- Developing after days or weeks
- Postsurgical repair or accidental trauma
- Massive leaks immediately after surgery
- Gunshot injury
- With normal CSF pressure.

Antibiotic prophylaxis remains controversial.

Intracranial Pressure

Intracranial vault is a closed compartment—although with some potential for expansion in the infant, follows the Monro-Kellie doctrine hypothesis. Intracranial pressure should be monitored in facilities are available. Brief increases in ICP for less than 5 minutes are not associated with significant damage. Sustained increases of more than 20 mmHg that do not return to base line in 5 minutes probably require attention. Most of the evidences in adults and children set the acceptable high ICP level at 20 mmHg. In a study by Esparza, an ICP more than 40 mmHg was associated with a 100% mortality and those between 20–40 mmHg had a 28% mortality, and with 0–20 mmHg had 7% mortality or disability. The current recommendation is to keep the ICP less than 20 mmHg.

Cerebral Perfusion Pressure

This is the critical determinant of cerebral blood flow (CBF) and brain perfusion. It is defined as the difference between mean arterial pressure and the ICP. Studies showing outcomes at various CPP levels confirm that a higher CPP level usually above 60 mmHg is associated with worse outcome. However, there does not seem to be difference of outcome in 40–60 mmHg. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents (2012) recommended CPP of 40 mmHg as the threshold for infants and younger children and 50 mmHg for older children.

Monitoring Devices

Intraventricular catheter, intraparenchymal pressure transducer, and subdural bolt can be used as invasive devices and transcranial Doppler can be used as noninvasive device. Advanced monitoring like jugular venous oxygenation and

brain tissue oxygenation are technologies measuring the adequacy of oxygen delivery to the brain directly. Regional oxygenation can be noninvasively measured with near infrared spectroscopy if available.

Steroids have no benefit in head injury as the edema is cytotoxic in nature.

Hypocapnia reduces the CBF by vasoconstriction and hence reduces ICP. However, it will also reduce CBF to the point of reducing CPP and cause ischemia. Hyperventilation for a brief period of less than 10 minutes may be employed in the setting of a sudden rise in ICP or impending herniation preferably under ICP and CPP monitoring. The goal of therapy is to maintain eucapnia with $PaCO_2$ of 32–35 mmHg.

Mannitol 0.25–1 g/kg is still the most commonly used agent by reducing the blood viscosity reduces the cerebral vasoconstriction, improves the cerebral blood flow, and prevents stasis. This action is immediate and last about 75 minutes. It takes 15 minutes to 6 hours for osmotic reduction of brain water in an intact blood-brain barrier. It may also get deposited in injured brain cells after prolonged use for less than 48 hours, resulting in rebound edema.

Three to seven percent saline has been successfully used in the treatment of traumatic brain injury. The hyperosmolar state induced is more sustained and the reduction in ICP tends to be more sustained with fewer peaks requiring intermittent measures. The exact dosage is still unclear and bolus doses from 6.5 mL–10 mL/kg have been advocated followed by an infusion of 0.1–2.5 mL/kg/h. Serum sodium levels up to 160 mmol/L have been reported with no side effects. Serum osmolarity rather than sodium level should be monitored for effect, with a target osmolarity of 340–360 mOsm/kg. Gradual tapering of about 10% every 6 hours is required if continuous infusion is used for more than 48–72 hours.

Barbiturates are used for reducing the metabolic activity of the brain, thereby its oxygen consumption. Short-acting barbiturates like thiopentone in a loading dose of 4 mg/kg followed by 2–4 mg/kg/h as an infusion is most commonly used. Significant side effect includes hypotension in 54% requiring fluids and vasopressors, anergy, pneumonia, sepsis, and hyponatremia.

Moderate hypothermia with a core temperature of 32–34°C may be useful but did not improve outcome in children.

A seizure does worsen ICP and the severe head injury patient has a high incidence of early symptomatic seizure; prophylactic medication like fosphenytoin, valproate or levetiracetam should be administered. Seizures may occur even in minor trauma. Immediate seizure may occur on impact or within the first 24 hours. Most seizures appear within the first 3 hours, are short-lived, generalized, and without any CT scan abnormality. They do not predict future epilepsy, require no treatment, and bear a good prognosis. If the seizure is complex, prolonged, or localized, further observation and treatment is warranted.

Decompressive craniectomy may be required for severe head injury and medically refractory intracranial hypertension in conditions like:

- Diffuse cerebral swelling on cranial CT imaging
- Sustain ICP more than 40 mmHg before surgery
- Glasgow Coma Scale 3 at some point of subsequent to injury
- Secondary clinical deterioration
- Evolving cerebral herniation syndrome.

Delayed lethargy and behavioral changes may be seen after head injury in a child with normal CT scan and normal neurological examination known as postconcussive syndrome.

Clinical Pearls

- Vomiting, migraine, and cortical blindness can occur with concussion with complete recovery in most cases of closed head injury
- Jaw thrust should be used for cervical spine protection
- Bleeding or clear fluid (cerebrospinal fluid) from ear or nose indicates fracture base of skull
- Persistent hypotension in multitrauma patient may not be due to head injury; look for other causes such as long bone fracture, and abdominal bleeding due to visceral injury.

KEY POINTS

- ☞ All patients with head injuries with loss of consciousness should be admitted for observation
- ☞ Computed tomography head is the investigation of choice in patients with loss of consciousness or neurological symptoms following head injury
- ☞ Glasgow Coma Scale less than 8 is an indication for intubation
- ☞ Hypotension must be treated by control of bleeding and fluid therapy.

SUGGESTED READINGS

1. Adelson PD, Bratton S, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children and adolescents. Pediatr Crit Care Med. 2003;4(Suppl. 3):S72-5.
2. Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med. 2002;30(9):1950-9.
3. Hutchinson JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, et al. Hypothermia therapy after traumatic brain injury in children. N Engl J Med. 2008;358(23):2447-56.
4. Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med. 2009;35(3):471-9.
5. Jagannathan J, Okonkwo DO, Dumont AS, Ahmed H, Bahari A, Prevedello DM, et al. Outcome following decompressive craniectomy in children with severe traumatic brain injury: a 10-year single-center experience with long-term follow up. J Neurosurg. 2007;106(Suppl. 4):268-75.
6. Kochanek PK, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children and adolescents—Second edition. Pediatr Crit Care Med. 2012;13(Suppl. 1):S1-82.
7. McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, et al. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24(2):287-93.
8. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, et al. Adverse effect of prolonged hyperventilation in patients with severe head injury: a randomized control trial. J Neurosurg. 1991;75(5):731-9.
9. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. J Neurosurg. 1983;59(5):822-8.
10. Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2007;24(1):CD001049.

CHAPTER 45

Trauma in Children

Soonu Udani

INTRODUCTION

Polytrauma is defined as trauma to more than one area of the body and the term is usually reserved for moderate to severe injury requiring multiple interventions; e.g., head ± orthopedics ± abdominal ± plastic surgery- and includes burns.

The length should be used for the rapid determination of weight for appropriate drug doses and equipment size.

BE PREPARED !!!

UNIQUE ANATOMY OF PEDIATRIC PATIENTS

- Cranium is larger relatively → more space between brain and bone, hence bridging veins have less support
- Thinner musculature and padding, thus less protection to organs
- Ribs are more flexible, hence less dissipation of energy and lung contusion can occur
- Solid organs are comparatively larger than adults, so, less protected by the rib cage
- Kidney more mobile, hence more commonly injured
- Larger surface area relative to volume predisposes children to thermal evaporative loss. Result is hypothermia and dehydration.

PRIMARY SURVEY (ALGORITHM 1)

Goals of primary survey are:

- Identify immediate/potential threats to life and initiate treatment
- Identify the disposition of the patient (e.g., operating room, intensive care unit, trauma facility)
- Continuous reassessment is essential.

Stabilize and transfer/triage only after the following:

- A—airway
- B—breathing
- C—circulation
- D—disability
- E—exposure

Airway

- Priority → choking will kill faster than anything else
- Assess for obstruction due to position, injury, blood, teeth, vomitus, and foreign object
  - Level of consciousness
  - Maxillofacial injury
  - Stridor or cyanosis.

Hemodynamics → initial fluids: normal saline (NS). Packed cell transfusions if hypotension persists after 2–3 boluses. Attempt to control hemorrhage by bandages.

Breathing Assessment

- Rate
- Chest wall movement: paradoxical breathing; flail segment
- Oxygen status
- Percussion note
- Tracheal deviation
- Crepitus
- Open wounds.

Management will be specific to the findings:

- Warm humidified oxygen
- Gastric decompression
- Appropriate mechanical ventilation → avoid barotrauma and volutrauma
- Chest tube(s) if indicated.

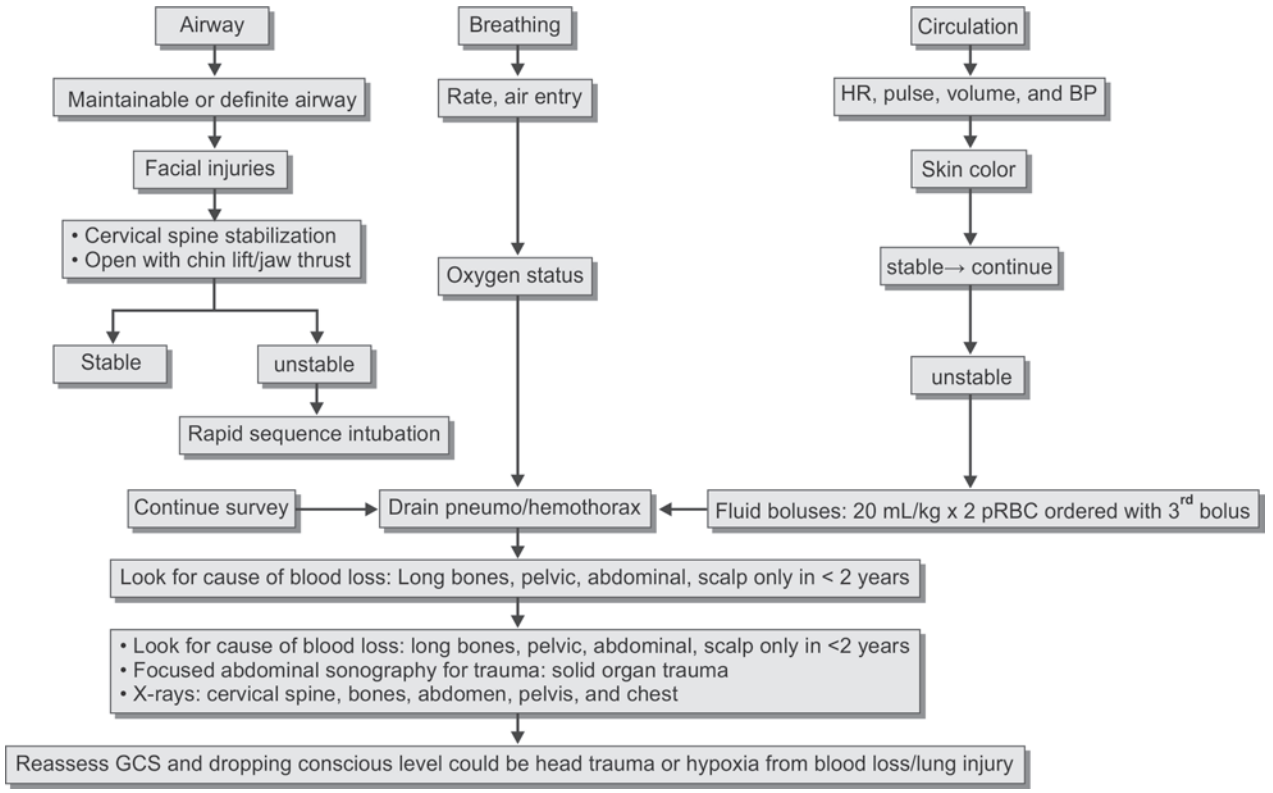
Circulation/Hemodynamics

- Blood volume = 70–90 mL/kg
- Systolic blood pressure (SBP) = 70 + 2 (age in years); In years old, will be 70 + 10 = 80 mmHg
- Diastolic blood pressure = 2/3 SBP

Pediatric vasculature readily constricts and increases systemic vascular resistance to maintain perfusion.

ALGORITHM 1

Primary survey meant to discover life-threatening conditions and stabilize patient



HR, heart rate; BP, blood pressure; GCS, Glasgow Coma Scale; pRBC, packed red blood cells.

Tachycardia and poor skin perfusion may be the only keys to hypovolemia.

Hypotension in a child = decompensated shock and estimated blood loss >/= 45% and may be abruptly followed by bradycardia.

Circulation with Hemorrhage Control

- Heart rate (HR)
- Systolic blood pressure and pulse pressure
- Peripheral pulses
- Skin condition/perfusion/capillary refill
- Sensorium
- Potentially "deadly" bleeding checks.

After initial resuscitation done → reassess

Check for the following:

- Cervical spine must be stabilized
- Chest has to be reassessed
- Fractures long bones and pelvis
- Abdominal injuries
- Bleeding from the ear and nose
- Glasgow Coma Scale (GCS) for improvement or deterioration.

No child should die from lack of vascular access.

Intraosseous access: anything can be given for this site.

- Maximal flow rate: 25 mL/min
- Contraindicated at site of fractures or devitalized limb
- Fluid resuscitation:
  - 20 mL/kg warmed NS = first line therapy
  - Recall the 3:1 rule of crystalloid resuscitation
- Consider packed red blood cells (pRBCs) if
  - Obvious exsanguination injury
  - Initiating third bolus (10 mL/kg of type specific or O negative warmed pRBCs).

Box 1: Structure of the pediatric airway

- Passive flexion due to large occiput → airway obstruction
- Relatively larger tongue → airway obstruction
- Mass of adenoidal tissues → nasopharyngeal (NP) airways difficult to pass
- U-shaped, floppy epiglottis → may necessitate use of a straight blade
- Anterior and cephalad larynx → visualization more difficult
- Airway narrowest at the cricoid ring → uncuffed tubes up to 6 mm or ~ 8 years
- Narrow tracheal diameter and distance between the rings → needle cricothyroidotomy over surgical for a difficult airway
- Short tracheal length (4 cm NB; 8 cm toddler) → RMS intubation and dislodgement
- More narrow large airways → greater airway resistance (R = 1/r4)

Box 2: Indications for a definitive airway

- Lack of a patent/protected airway
- Impending loss of the airway
- Comatose patient Glasgow Coma Scale <9
- Inability to oxygenate
- Inability to ventilate
- Full/impending cardiac arrest
- Head injury

Box 3: Repeatedly check for optimal response to resuscitation

- Slowing of heart rate
- Increased pulse pressure (>20 mmHg)
- Normal skin perfusion
- Improvement in level of consciousness
- Systolic blood pressure >80 mmHg (age based)
- Urine output = 1–2 mL/kg/h

Disability Assessment

- Alert/verbal/painful/unresponsive (AVPU)/modified GCS
- Pupil size and reactivity
- Extremity movement and tone
- Posturing
- Reflexes.

Management: Address findings in keeping with increased intracranial pressure and/or spinal cord injury without radiological abnormality.

Exposure with Environmental Control

- Logroll to examine back
- Look under hair, collar, and splints.
- Survey repeatedly.

SECONDARY SURVEY

This commences once the injured child is stabilized**.**

Goals to identify any new/potential threats to life organ and limb are discussed in box 4.

- Identify injuries that may impact the child later (e.g., minor fractures, dislocations, and lacerations)
- Obtain a more complete history
- Continuous monitoring (HR, blood pressure, T, SaO_2 ± $etCO_2$)
- Achieved through a well organized head to toe examination

Box 4: Check these areas for potential threats to other organs

- Maxillofacial and head
- Cervical spine and neck
- Chest
- Abdomen, perineum, rectum, vagina
- Neurological.

- Placement of Foley catheter with inflatable retaining device only when child > 5 kg
- Secondary survey continued
- Review labs
- Radiology: focused assessment sonography in trauma ultrasound
  - Chest, pelvis, lateral c-spine if not done with primary survey
  - Additional images on the basis of threat to life/limb
- Tetanus toxoid
- Antibiotics
- Analgesia (systemic and local)
- Continuous reassessment; tracking of vitals and urine output.

Head Trauma

- Leading cause of death
- Results in significant morbidity
- Hypotension and hypoxia from concurrent injury adversely affect the outcome from intracerebral injury.

Spinal Cord Injury without Radiological Abnormality

- If spinal cord injury is suspected on the basis of mechanism or clinical examination, do not be dissuaded by normal X-rays
- A normal X-ray and initial exam is not enough
- Be aware of: local pain, torticollis.

Management:

- Avoid secondary and iatrogenic injury
- Corticosteroids are currently not recommended.

Chest and Abdomen

Pliable chest wall so lung contusions may occur without obvious external injury.

Clinical examination improved with gastric and bladder decompression. Clinical findings may underestimate problems. Therefore, diagnostic adjuncts:

- Computed tomography: less sensitive for bowel, spleen, early pancreas, liver
- Ultrasound: good for hepatic and splenic injury.

Visceral injuries specific to the pediatric population:

- Pancreatic injury
- Small bowel perforation (ligament of treitz)
- Mesenteric and small bowel avulsion
- Duodenal hematoma
- Spleen, liver, and kidney disruption
- Bladder injury.

Missed abdominal trauma is the leading cause of preventable morbidity and mortality.

Clinical findings associated with intra-abdominal injury:

- Initial Hct less than 30%
- Abdominal tenderness
- Femur fracture
- AST more than 200 U/L and/or ALT more than 125 U/L
- Urine with more than 5 RBCs/hpf.

INDICATIONS FOR SURGERY

- Hemodynamic instability despite maximal resuscitative measures +/– a positive diagnostic study
- Falling hematocrit
- Transfusion of greater than 50% of total blood volume
- Radiographic evidence of pneumoperitoneum, intraperitoneal bladder rupture, grade V renovascular injury.
- Peritonitis or the development to peritoneal signs
- Evisceration of intraperitoneal contents
- Evidence of fecal or bowel contamination on diagnostic peritoneal lavage.

Nonoperative approach mandates pediatric intensive care unit accessibility.

Clinical Pearls

- Cervical spine should be always taken care of in a child with polytrauma
- Patients with persistent shock despite initial resuscitation may have neurogenic shock, cardiac contusion, or cardiac tamponade
- Multidisciplinary approach with one team leader.

KEY POINTS

- ☞ Trauma is leading cause of morbidity and mortality in developed world
- ☞ Blunt trauma is most common mechanism of injury in children
- ☞ ABCDE sequence of initial assessment should be followed in every child with multiple trauma
- ☞ Continuous monitoring following initial resuscitation is mandatory to detect further deterioration
- ☞ Fatal: Pediatric Trauma Score <0, transport to nearest facility.

SUGGESTED READINGS

1. Nichols DG (Ed). Roger's Textbook of Pediatric Intensive Care, 4th edition. Philadelphia: Lippincott Williams & Wilkins; 2008.
2. The International ATLS working Group. Tchorz, KM. Advanced Trauma Life Support (ATLS®): The Ninth Edition. The Journal Of Trauma And Acute Care Surgery. 2013;74(5):1363.

CHAPTER 46

Poisoning in Children

Pradeep K Sharma, Praveen Khilnani

INTRODUCTION

Various Indian studies report kerosene (30–50%), drugs (11%), pesticides (11%), snakebites (10–20%), corrosives, and household cleaning products as the common substance causing poisonings. Certain household items often ingested by children are proven to be nontoxic and harmless (Box 1). However, ingestion of excessive amount of these substances may lead to toxicity.

EVALUATION OF CHILDREN WITH SUSPECTED TOXIN INGESTION

The acute management generally begins in the emergency department with triage and the determination of appropriate decontamination and treatment regimens. Immediate attention to the patient's airway, breathing, and circulation (ABC) should be done and following the establishment of lifesaving supportive care, a detailed evaluation can be performed (Algorhithm 1).

HISTORY

A comprehensive history may be obtained from witnesses, family members, and friends. Nature of substance ingested, its amount, time of ingestion, circumstances preceding, smells or unusual items, occupation of those in home, and queries regarding the presence of a suicide note is pivotal to management. Obtaining an accurate history in adolescent is especially challenging due to the potential use of multiple substances, possible drug abuse, prolonged time between ingestion and presentation, and attempts at concealing information. Additional information includes the maximum amount of toxin available and the minimum amount per kilogram that produces symptoms. Quantity of liquid toxins swallowed can be estimated as 5–10 mL in a young child and 10–15 mL in an adolescent. Product containers or medication labels are helpful to identify specific toxic contents. A number of medications have been determined to be potentially lethal to a child who weighs 10 kg and ingests just one tablet, capsule, or teaspoonful (Table 1).

Box 1: Nontoxic substances

- Silica gel
- Ball pen inks
- Candle
- Modeling clay
- Crayons
- Lipstick
- Shampoo
- Chalk
- Pencil lead
- Shaving cream and lotions
- Soaps and detergents
- Bath oils
- Thermometer mercury
- Saccharin
- Water colors
- Petroleum jelly
- Toothpaste

PHYSICAL EXAMINATION

A comprehensive physical examination is crucial in determining the involved agents and allows for specific initial treatment. The signs and symptoms that suggest specific classes of poisoning are generally grouped into syndromes and referred to as toxidromes (Table 2). A vitals recording also helps in determining the particular toxidrome (Table 3).

SYSTEMIC EXAMINATION

Frequent neurologic examination is especially important, as many toxins can depress the consciousness. Symmetrical pupillary changes are typical of toxic exposures, with asymmetry most commonly evidencing a structural or focal neurologic abnormality. Detailed general physical and systemic examinations help in pointing to a specific toxin as shown in table 4.

ALGORITHM 1

Approach to a child with poisoning

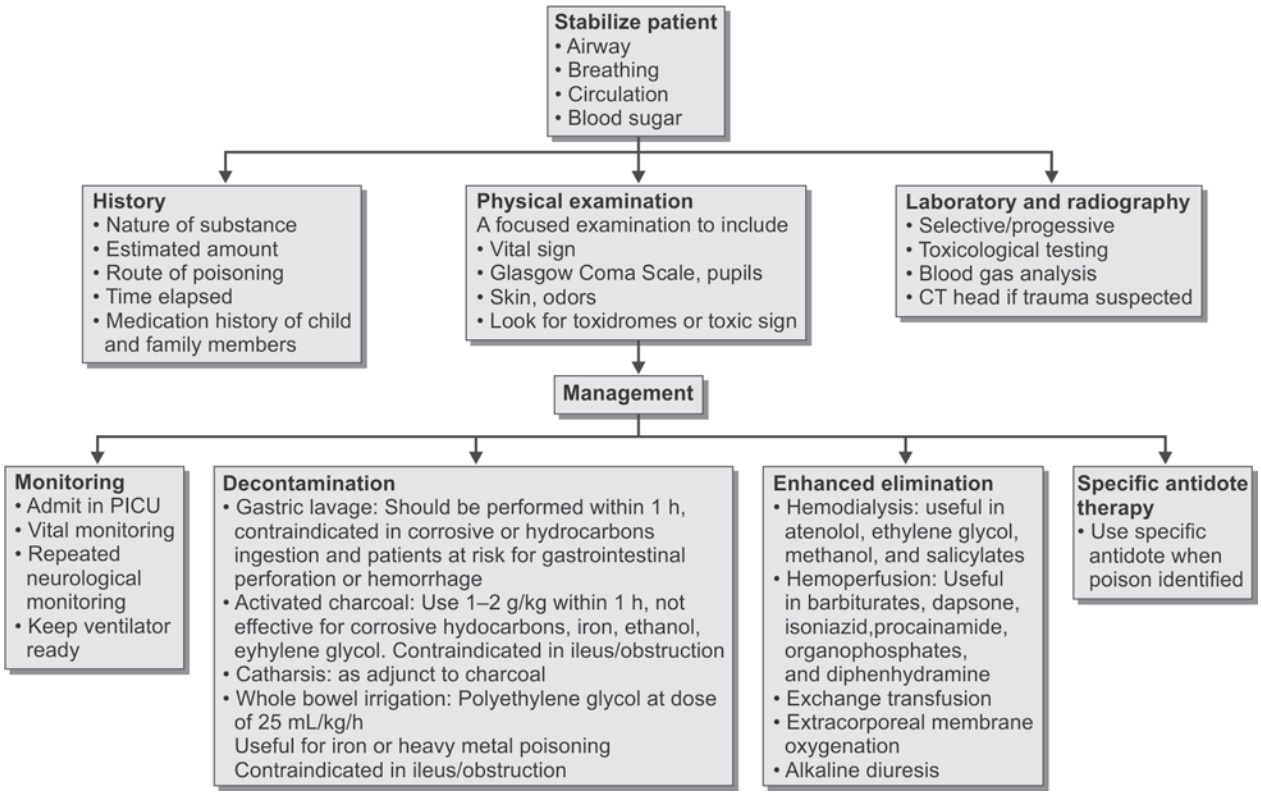


TABLE 1: Toxicity levels of selected medication and medication classes

Agents	Minimum lethal dose	Potential maximum available	Dose potentially fatal units in a 10 kg child
Antimalarial			
Chloroquine	20 mg/kg	500 mg	1
Hydroxychloroquine	20 mg/kg	200 mg	1
Camphor	100 mg/kg	200 mg/mL	5 mL
Imidazolines			
Clonidine	0.01 mg/kg	0.3 mg, 7.5 mg/patch	1
Tetrahydrozoline	2.5–5 mL	0.1%	2.5–5 mL
Methyl salicylates	150–200 mg/kg	1400 mg/mL	1.1–1.4 mL
Sulfonylureas			
Glipizide	0.1 mg/kg	5 mg	1
Glyburide	0.1 mg/kg	10 mg	1

TABLE 2: Toxidromes and agents

Toxidrome	Agents	Clinical manifestations	
Sympatho-mimetic toxidrome*	• Albuterol; amphetamines; caffeine; catecholamines; cocaine; ephedrine; ketamine; lysergic acid diethylamide; methamphetamine; phencyclidine; phenylephrine; phenylpropanolamine; pseudoephedrine; terbutaline; theophylline	• Agitation; seizures; mydriasis; tachycardia • Hypertension • Diaphoresis	• Pallor • Cool skin • Fever

Continued

Continued

Toxidrome	Agents	Clinical manifestations	
Cholinergic toxidrome	• Organophosphate and carbamates • Pesticides, nicotine	• Muscarinic effects (dumbbells) • Diarrhea • Urinary incontinence • Miosis • Bradycardia • Bronchorrhea • Emesis • Lacrimation • Salivation • Nicotinic effects • Fasciculations	• Weakness • Paralysis • Tachycardia • Hypertension • Agitation • Central effects • Lethargy • Coma • Agitation • Seizures
Anticholinergic toxidrome*	• Antihistamines—diphenhydramine, hydroxyzine • Atropine • Benztropine mesylate • Carbamazepine • Cyclic antidepressants • Cyclobenzaprine • Hyoscyamine • Jimsonweed • Oxybutynin • Phenothiazines • Scopolamine • Trihexyphenidyl	• Agitation • Delirium • Coma • Mydriasis • Dry mouth • Warm, dry, flushed skin • Tachycardia • Hypertension • Fever • Urinary retention • Decreased bowel sounds	Associated expressions • "Mad as a hatter" • "Blind as a bat" • "Red as a beet" • "Hot as a hare"
Opioid toxidrome	• Morphine, methadone, dextromethorphan, fentanyl, pentazocine, heroin, codeine	• Central nervous system depression, respiratory depression, coma, miosis, hypothermia, bradycardia, constipation	

*Both have almost similar clinical features except diaphoresis, cool skin, and hyperactive bowel sounds in sympathomimetic toxidrome and warm, dry skin and diminished bowel sounds in anticholinergic toxidrome.

TABLE 3: Common clinical findings in toxidrome

Physical Findings	Sympathomimetic	Anticholinergic	Cholinergic	Opioid	Sedative-hypnotic
Pulse rate	Increased	Increased	Decreased	Decreased	Decreased
Respiratory rate	Increased	No change	No change	Normal/decreased	Normal/decreased
Body temperature	Increased	Increased	No change	Normal/decreased	Normal/decreased
Blood pressure	Increased	No change/increased	No change	Normal/decreased	Normal/decreased
Mental state	Agitated	Agitation/delirium	Depressed	Depressed	Depressed
Pupils	Mydriasis	Mydriasis	Miosis	Miosis	Normal
Mucous membranes	Wet	Dry	Wet	Normal	Normal
Skin	Diaphoretic	Dry	Diaphoretic	Normal	Normal

LABORATORY EVALUATION

The laboratory generally confirms a diagnosis and also based upon quantitative drug or toxin levels helps in deciding about therapy. The drug or toxin levels are available for acetaminophen, ethanol, methanol, ethylene glycol, lithium, salicylates, iron, lead, mercury, arsenic, phenobarbital, carbon monoxide, methemoglobin, and theophylline. A negative toxicology screen by no means excludes the possibility of toxic exposure.

Arterial blood gas analysis evaluates acid-base status and anion gap metabolic acidosis. Agents with elevated anion gap can be summarized by the mnemonic MUDPILES as given below.

MUDPILES: methanol, uremia, diabetic ketoacidosis, paraldehyde and phenformin, isoniazid and iron, lactic acidosis, ethanol and ethylene glycol, salicylates.

Electrocardiogram is invaluable in detecting dysrhythmias and conduction abnormalities. Increased serum osmolality is seen with methanol, ethanol, ethylene glycol, acetone, and isopropanol. Complete blood cell count with platelets and leukocyte differential, prothrombin time, partial thromboplastin time, liver function tests, and electroencephalogram may prove useful. Urine color may be helpful in the identification of a number of toxins. It is important to obtain urine pregnancy tests on patient of childbearing age.

TABLE 4: Clinical manifestations of poisoning

Clinical manifestations	Suspected toxins
Skin	
Cyanosis unresponsive to oxygen	Nitrates, nitrites, phenacetin, benzocaine
Red flush	Carbon monoxide, cyanide, boric acid, anticholinergics
Sweating	Amphetamines, LSD, organophosphates, cocaine, barbiturates
Dry	Anticholinergics
Bullae	Barbiturates, carbon monoxide
Jaundice	Acetaminophen, mushrooms, carbon
Purpura	Aspirin, warfarin, snakebite
Temperature	
Hypothermia	Sedative hypnotics, ethanol, carbon monoxide, phenothiazines, TCAs, clonidine
Hyperthermia	Anticholinergics, salicylates, phenothiazines, TCAs, cocaine, amphetamines, theophylline
Blood pressure	
Hypertension	Sympathomimetics (especially phenylpropanolamine in over-the-counter cold remedies), organophosphates, amphetamines, PCP
Hypotension	Narcotics, sedative hypnotics, TCAs, phenothiazines, clonidine, β-blockers, calcium channel blockers
Pulse rate	
Bradycardia	Digitalis, sedative hypnotics, β-blockers, ethchlorvynol, calcium channel blockers
Tachycardia	Anticholinergics, sympathomimetics, amphetamines, alcohol, aspirin, theophylline, cocaine, TCAs
Arrhythmia	Anticholinergics, TCAs, organophosphates, phenothiazines, digoxin, β-blockers, carbon monoxide, cyanide, theophylline
Mucous membranes	
Dry	Anticholinergics
Salivation	Organophosphates, carbamates
Oral lesions	Corrosives, paraquat, lacrimation
Lacrimation	Caustics, organophosphates, irritant gases
Respiration	
Depressed	Alcohol, narcotics, barbiturates, sedative/hypnotics
Tachypnea	Salicylates, amphetamines, carbon monoxide
Kussmaul	Methanol, ethylene glycol, salicylates
Pneumonia	Hydrocarbons
Pulmonary edema	Aspiration, salicylates, narcotics, sympathomimetics
Central nervous system	
Seizures	TCAs, cocaine, phenothiazines, amphetamines, camphor, lead, salicylates, isoniazid, organophosphates, antihistamines, propoxyphene, strychnine
Miosis	Narcotics (except demerol and lomotil), phenothiazines, organophosphates, diazepam, barbiturates, mushrooms (muscarine types)
Mydriasis	Anticholinergics, sympathomimetics, cocaine, TCAs, methanol, glutethimide, LSD
Blindness, optic atrophy	Methanol
Fasciculation	Organophosphates
Nystagmus	Diphenylhydantoin, barbiturates, carbamazepine, PCP, carbon monoxide, glutethimide, ethanol
Hypertonia	Anticholinergics, strychnine, phenothiazines
Myoclonus, rigidity	Anticholinergics, phenothiazines, haloperidol
Delirium, psychosis	Anticholinergics, sympathomimetics, alcohol, phenothiazines, PCP, LSD, marijuana, cocaine, heroin, methaqualone, heavy metals
Coma	Alcohols, anticholinergics, sedative hypnotics, narcotics, carbon monoxide, tricyclic antidepressants, salicylates, organophosphates, barbiturates
Weakness, paralysis	Organophosphates, carbamates, heavy metals
Gastrointestinal symptoms	
Vomiting, diarrhea, pain	Iron, phosphorus, heavy metals, lithium, mushrooms, fluoride, organophosphates, arsenic
Constipation	Lead, narcotics, botulism
Hematemesis	Aminophylline, corrosives, iron, lead, salicylates

LSD, lysergic acid diethylamide; PCP, phencyclidine; TCA, tricyclic antidepressant.

RADIOLOGIC IMAGING

Radiographic evaluation is useful for certain foreign bodies, radiopaque drugs, metals, and chemicals. Serial chest/abdominal X-rays identify the movement of the disc batteries through the gastrointestinal (GI) tract. Radiopaque compounds may be grouped by the mnemonic "COINS": chloral hydrate and cocaine packets, opiate packets, iron and heavy metals (lead, arsenic and mercury), neuroleptics, and sustained-release or enteric coated tablets.

MANAGEMENT

The approach includes:
- Emergency stabilization
- Decontamination
- Enhanced elimination
- Antidote and poison specific therapy.

Emergency Stabilization

This begins with checking the ABC and stabilization. Because the patient's status can change rapidly, it is essential to

reassess the patient often and monitor the need for ventilator support. Blood glucose should be obtained from patient with ingestion of oral hypoglycemic agents, alcohol, and with altered sensorium. Symptoms of hypoglycemia may be rapidly reversed with intravenous dextrose. Intravenous thiamine (10 mg for infants, 10–25 mg for children) should be given before dextrose administration to prevent Wernicke encephalopathy. Although altered mental status in a child may be presumed to be from poisoning, traumatic head injury should also be considered. Any child with coma, altered sensorium, seizures, agitation, impaired vital parameter—tachycardia/bradycardia, arrhythmia, hypotension/hypertension, respiratory distress or depression, and organ failure should be managed in pediatric intensive care unit.

Decontamination

Decontamination may be individualized, depending upon the type and amount of substance ingested, potential toxicity, time elapsed since ingestion, and the symptoms exhibited.

Gastric Lavage

A mainstay of gastric decontamination, involves insertion of a large-bore orogastric tube into the stomach, followed by repeated administration and aspiration of 10–15 mL/kg saline until aspirates is clear. This can be particularly traumatizing to a young child. Contraindications include compromised upper airway protection, ingestion of corrosive substances or hydrocarbons, and patients at risk for GI perforation or hemorrhage. Possible complications are aspiration, respiratory compromise, mechanical injury/perforation, and electrolyte imbalances. The American Academy of Clinical Toxicology (AACT) and European Association of Poison Centers and Clinical Toxicologists discourage its routine use unless performed within 1 hour of the ingestion.

Syrup of Ipecac

In 2003, the American Academy of Pediatrics released a policy statement advising that syrup of ipecac should no longer be used.

Activated Charcoal

It works by adsorbing the toxin and preventing enterohepatic and enteroenteric recirculation. A charcoal/drug ratio of 10:1 is recommended (1–2 g/kg). Activated charcoal (AC) is helpful in carbamazepine, dapsone, phenobarbital, quinine, theophylline, salicylates, phenytoin, or valproic acid ingestion. AC is unpalatable, messy, and poorly accepted by young children often causing vomiting. AC does not bind well with xenobiotics that are highly ionized (e.g., metals, electrolytes, acids, and alkali). In addition, AC is contraindicated in patients who have ingested corrosives or hydrocarbons, in those with bowel obstruction or perforation, and in patients with a depressed level of consciousness.

The AACT discourages the routine use except within 1 hour of ingestion. The first dose is often given with a cathartic agent, such as sorbitol, to improve taste and transit through the intestinal tract. Multiple doses should not include sorbitol because of possible electrolyte and fluid abnormalities.

Whole-bowel Irrigation

Whole-bowel irrigation (WBI) involves administration of large volumes of polyethylene glycol solution orally to decontaminate the GI tract. The pediatric dose is 25 mL/kg/h, up to 500 mL/h in young children and up to 1 L/h in adolescents. It may be useful when a drug or toxicant does not have an antidote or treatment and the substance ingested is an enteric pill, sustained release preparation, or agents poorly adsorbed by AC. Examples are lithium, iron, and lead. Adverse effects of WBI include vomiting, abdominal cramps, bloating, and rarely, aspiration pneumonitis.

Surgical Decontamination

Surgical intervention is usually indicated for mechanical bowel obstruction or bowel ischemia due to heroin or cocaine drug packets and also for massive iron ingestion with failure to evacuate the GI tract.

Enhanced Elimination

Active elimination techniques should be considered only in ingestion of a potentially lethal dose of toxin, progressive clinical deterioration refractory to aggressive supportive care, and blood concentrations that indicate serious intoxication and impaired organ function. Hemodialysis (HD) is useful for drugs with small volume of distribution, poor plasma protein binding, low molecular weight, and weak lipid solubility, e.g., atenolol, ethylene glycol, methanol, and salicylates. Hemoperfusion, using a charcoal filter in a HD machine, can remove toxins with high molecular weight, e.g., barbiturates, carbamazepine, chloral hydrate, dapsone, isoniazid, procainamide, organophosphates, and diphenhydramine.

Exchange transfusion is an alternative procedure for a small group of children who are not eligible for HD. Beneficial effects are seen with salicylate, theophylline, phenobarbital, chloramphenicol, lithium, aniline, chloral hydrate, salicylate, quinine, and methemoglobinemia. Extracorporeal membrane oxygenation has been used for hydrocarbon-induced lung injury, bupropion, amiodarone, calcium channel blocker overdose, and a severe ibuprofen poisoning.

Diuresis

Drug elimination may be facilitated by ensuring adequate renal flow 2–5 mL/kg/h. Elimination of drugs with pKa values of 3.0–7.2 may be enhanced by alkalinizing the urine, e.g., salicylate, phenobarbital, chlorpropamide, and the chlorophenoxy herbicides. Complications are fluid overload, with cerebral edema, pulmonary edema, and hyponatremia.

Toxin-specific Treatments

If physical examination or laboratory findings suggest a specific toxidrome, then consider toxin specific treatments, such as an antidote (Table 5). Antidotes are usually given after the patient

TABLE 5: Selected antidotes

Antidote	Toxin
Atropine	Organophosphate, carbamate poisoning, bradydysrhythmias
Calcium (chloride or gluconate)	Calcium channel blocker overdose, hydrofluoric acid ingestion/exposure
Cyanide antidote package, Amyl nitrite, Sodium nitrite, Sodium thiosulfate	Cyanide, acetonitrile (artificial nail remover), amygdalin (peach, apricot pits), nitroprusside (thiosulfate only)
Deferoxamine	Iron
Digoxin-specific antibody	Digoxin, digitoxin, natural cardiac glycosides (e.g., oleander, red squill, *Bufo* toad venom)
Flumazenil	Benzodiazepines
Fomepizole	Toxic alcohols (ethylene glycol, methanol)
Glucagon	Calcium channel blocker, β-blocker toxicity
Glucose (dextrose)	Sulfonylureas, insulin, hypoglycemia (multiple toxins)
Hydroxocobalamin (vitamin B12)	Cyanide, acetonitrile, amygdalin, nitroprusside
Insulin (high dose)	Calcium channel blocker, β-blocker toxicity
Methylene blue	Methemoglobinemia
N-acetylcysteine	Acetaminophen, pennyroyal oil, carbon tetrachloride
Naloxone	Opioid toxicity
Octreotide	Sulfonylurea toxicity
Physostigmine	Antimuscarinic delirium (as a diagnostic tool only)
Pralidoxime	Organophosphate poisoning (insecticides, nerve agents)
Protamine sulfate	Heparins
Pyridoxine	Isoniazid, *Gyromitra* mushrooms
Thiamine	Deficiency states (e.g., alcoholism, anorexia nervosa)
Sodium bicarbonate	Sodium channel blocking cardiotoxins, salicylates

is stable, preferably within a few hours of ingestion and may require multiple doses because of short durations of action.

CONCLUSION

Poison prevention remains a challenge and a necessity to prevent the most vulnerable population from becoming exposed to potentially lethal drugs and toxins. The evaluation of a child presumed to have been exposed to a toxic substance should include a precise history of the exposure, a physical examination, and knowledge of current ingestions and recreational practices. Poison centers and medical toxicologists should be consulted to assist with the diagnosis and management of medicinal/drug overdoses.

Clinical Pearls

- Common toxidromes can identify many poisonous substances (Tables 2 and 3)
- Causes of high anion gap—MUDPILES: methanol, uremia, diabetic ketoacidosis, paraldehyde and phenformin, isoniazid and iron, lactic acidosis, ethanol and ethylene glycol, salicylates.

KEY POINTS

- ☞ Precise history is very important in all cases of poisonings
- ☞ Management of most poisonings is supportive
- ☞ Induction of vomiting (syrup ipecac) is no longer recommended due to risk of aspiration in comatose patients and all patients with suspected hydrocarbon ingestion
- ☞ Poison control centers are helpful in guiding therapy and observation period
- ☞ All unknown poisonings or unknown causes of coma are medicolegal cases.

SUGGESTED READINGS

1. American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention. Policy statement: poison treatment in the home. American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention. Pediatrics. 2003;112(5):1182-5.
2. Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC. 2011 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. Clin Toxicol (Phila). 2012;50(10):911-1164.
3. Gupta SK, Peshin SS, Srivastava A, Kaleekal T. A study of childhood poisoning at National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi. J Occup Health. 2003;45(3):191-6.
4. McGregor T, Parkar M, Rao S. Evaluation and management of common childhood poisonings. Am Fam Physician. 2009;79(5):397-403.
5. National Poisons Information Centre (NPIC), All India Institute of Medical sciences. [online] available from http://www.aiims.edu/aiims/departments/pharmacology/NPIC/home.htm [Accessed December, 2015].
6. Nichols DG, Ackerman AD, Argent AC, et al. (Eds). Rogers' Textbook of Pediatric Intensive Care, 4th edition. Philadelphia: Lipincott Williams and Wilkins; 2008.
7. Rathore S, Verma AK, Pandey A, Kumar S. Pediatric poisoning trend in Lucknow District, India. J Forensic Res. 2013;4:179.

CHAPTER 47

Snakebite Envenomation

Soonu Udani, Narendra Rathi

INTRODUCTION

A victim of a snakebite needs to be treated appropriately and rapidly. The outcome can be excellent if a protocolized approach is used.

First aid: many old practices are known to do more harm than good.

- No—incision, suction, ice packs, washing wound, tourniquet
- Reassurance important though neglected step. The sympathetic storm caused by fear and anxiety with pain, is deleterious to the hemodynamics of the patient
- Immobilize bitten part/victim by a splint. Bandage the part by starting distal to the bite and going above the joint
- Carry the child
- Lateral decubitus to prevent aspiration, if weakness should set in and compromise the airway.

TYPE AND SEVERITY OF THE BITE

- Identifying species is not vital as the venom available is trivalent for krait, viper, and cobra
- Take it seriously! Small snake, second bite, severed head are all equally dangerous
- Number of bites. The more the bites, the more the envenomation
- Amount of venom injected for size of patient. The snake injects the same amount of venom and the smaller the size of the patient, the higher the dose

Box 1: Identifying species clinically if possible

- Cobra: local signs + neurotoxic
- Krait: no local signs + neurotoxic
- Viper: local signs + coagulopathy
- Sea snake: no local signs + myotoxic
- "Every snakebite does not need anti-snake venom"
- "Every poisonous snakebite does not need anti-snake venom"

- Neurotoxic and hemorrhage effects. Timing of onset can be variable.

Local signs: Viper versus cobra

- Pain, wheal, swelling, bullae. Regional lymphadenopathy develops rather rapidly
- Blood filled bullae—viper
- Necrosis, gangrene, and anaerobic infections are common.

Neurotoxic Effects

- Neuromuscular blockade: flaccid paralysis
- Ptosis (earliest): inability to look up, external ophthalmoplegia
- Palate, jaw, tongue, larynx, neck, deglutition: ask the child to open mouth and protrude tongue
- Accumulation of secretions: bulbar palsy
- Flaccid quadriplegia.

It lasts 2–4 days and recover over next 2–5 days, but the timings can be variable and effects may last for several days. [anti-snake venom (ASV) will have no effect on already fixed toxin].

Hemorrhagic Effects

- Bleeding from fang marks and injection sites.
- Blood filled bullae locally
- Bleeding gums
- Epistaxis
- Gastrointestinal tract bleed
- Intracranial hemorrhage.

The 20-minute whole blood clotting time (WBCT), a simple, bedside, reliable method to diagnose hemorrhagic effects, monitor ASV effectiveness, and control its administration. Also, helps hemorrhagic effects of venom from disseminated intravascular coagulopathy from sepsis.

Put 2–5 mL blood into a dry, clean, new test tube, leave undisturbed for 20 minutes and check for clotting by gentle movement.

Test to be done on admission and 6 hourly.

TREATMENT

Supportive Therapy

- Rapid assessment of airway, breathing, and circulation
- Open airway, oxygenate if needed
- Cardiopulmonary resuscitation, if needed
- Tetanus toxoid
- Intravenous (IV) fluids, antibiotics with anaerobic coverage
- Blood components readied
- Mechanical ventilation.

Specific Therapy

It includes ASV and neostigmine.
Indications of ASV:

- Signs of local envenomation
  - Swelling involving greater than ½ bitten limb
  - Rapid extension of swelling beyond joint
  - Regional lymphadenopathy
- In absence of tourniquet
- Signs of systemic envenomation
  - Neurotoxic signs
  - Hemorrhagic signs
  - Cardiovascular: shock, arrhythmia, electrocardiogram abnormalities
  - Acute renal failure
  - Hemoglobinuria, myoglobinuria
  - Polymorphonuclear leukocytosis.

Anti-snake venom dose: symptomatology is not useful for dose. The same dose applies to adults and children as it is to neutralize the poison and that quantity remains the same. Table 1 shows the dose relationship and the rationale of using a standard 8–10 + 5–10 vial dosage regimen.

Neurotoxic: if no response to first dose of ASV and neostigmine in 2 hours, then second dose of ASV is to be used. If there is no response to the second dose, then start/continue ventilation.

Neostigmine: it is useful for neuromuscular junction blockade caused by neurotoxic snakebites. It is useful only for postsynaptic type of blockade (occurring with cobra bites) and not for presynaptic block (krait bites cause both pre- and postsynaptic blockade).

TABLE 1: Snakes with venom yield, lethal dose, and antivenom neutralizing dose

Snakes	Venom yield per bite (g)	Lethal dose for man (g)	1 mL of antivenom neutralized (mg)
Cobra	0.2	0.12	0.6
Krait	0.022	0.06	0.45
Russell's viper	0.15	0.15	0.6
Saw-scaled viper	0.0046	0.08	0.45

- Select the objective measure of impairment like single breath count or length of time upward gaze can be maintained and establish the value
- Give intramuscular (IM) neostigmine 25–50 μg/kg with 0.05 mg/kg atropine IV every 10 minutes till the objective measure is reassessed
- Improvement should become evident after 20 minutes.

Hemorrhagic: repeat 20-minute WBCT after 6 hours, if positive give second dose of ASV.

Support with fresh frozen plasma (FFP), platelets and packed red blood cells as needed. Dialysis may be needed for renal failure.

Anti-snake venom administration: Only IV, not IM/SC

- No sensitivity testing is advocated. As soon as possible,, if signs of envenomation
- Not useful to prevent local tissue necrosis, so there should be no local infiltration
- 8–10 vials dissolved in 200 mL normal saline over 1 hour. Repeat in 2–6 hours. (hematotoxin requires more dosing than neurotoxin as it is in the circulation and can be neutralized).

If anaphylaxis occurs:

- Stop immediately if pruritus, urticaria, fever, vomiting, diarrhea, hypotension, bronchospasm
- Intramuscular adrenaline (epinephrine) (0.01 mg/kg)
- Intravenous hydrocortisone (2 mg/kg)
- Intravenous antihistamine (avil 0.2 mg/kg)
- Second dose of epinephrine if no improvement/deterioration in 15 minutes → starts an infusion
- Restart ASV: after complete recovery, slow infusion for 15 minutes, close supervision, after 15 minutes, resume normal drip rate.

Mechanical ventilation: even when ASV not available, mechanical ventilation is life saving.

Indication: respiratory paralysis, inability to handle secretions.

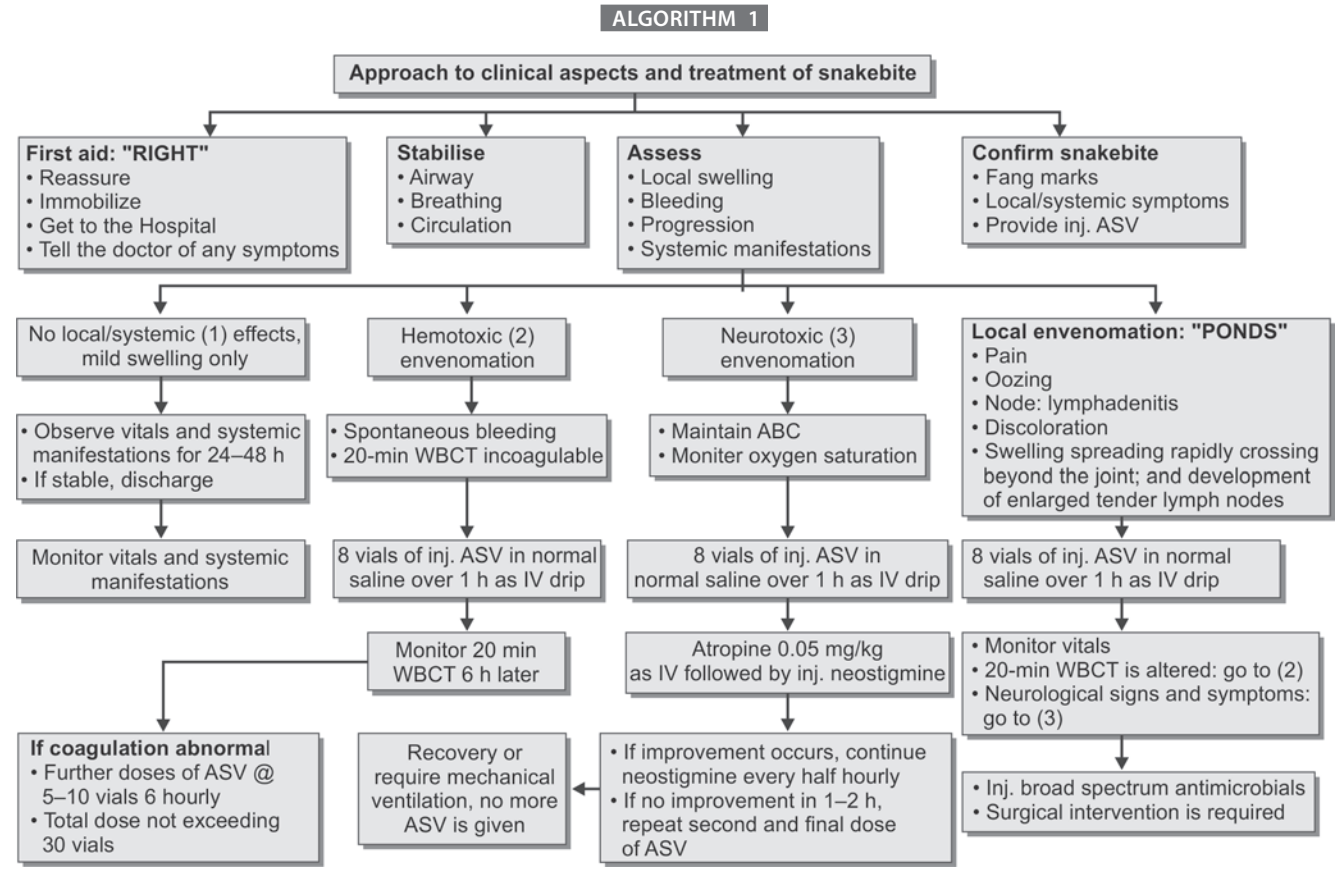
Local therapy, like debridement and incision drainage, should be done only after

- ASV is given
- Do not underestimate the necrosis that can occur—the need for amputation is not uncommon
- Elevation of bitten part
- Aspiration of bullae, only if tense.

Debridement, dressing, grafting: avoid fasciotomy as it may spread the venom again.

Clinical Pearls

- Snakebite is like poisoning
- Call up an expert or check the books for details
- Do not transport unstable patients
- Supportive management can save a life even without anti-snake venom, especially in neurotoxic bites.



ABC, airway, breathing, and circulation; ASV, anti-snake venom; inj., injection; 20-min WBCT, 20-minute whole blood clotting test; IV, intravenous.

KEY POINTS

- ☞ History of snakebite and fang marks are not a must to diagnose snake envenomation (e.g., kraits and sea snakes)
- ☞ In areas known for krait bites, when a perfectly normal person sleeping on floor reports early morning with vomiting, abdominal pain, and bulbar palsy, it should be diagnosed as krait envenomation, unless proved otherwise
- ☞ All snakebites do not need anti-snake venom (ASV). Dose remains the same for all
- ☞ The 20-minute whole blood clotting test is simple, cheap, reliable, and bedside tool in hands of clinician for diagnosing coagulopathy of viper bites
- ☞ Endotracheal intubation and mechanical ventilation are of utmost important in saving a child with neurotoxic respiratory paralysis in isolation and in combination with ASV
- ☞ Do not ignore bite by small snakes, bite after eating prey, or bite after several strikes—all such bites are capable of severe envenomation.

SUGGESTED READINGS

1. Bawaskar HS, Bawaskar PH. Profile of snakebite envenoming in western Maharashtra, India. Trans R Soc Trop Med Hyg. 2002;96(1):79-84.
2. Philip E. Snake bite and scorpion sting. In: Srivastava RN (Ed). Pediatric and Neonatal Emergency Care. New Delhi: Jaypee Brothers Medical Publishers; 1994. pp. 227-34.
3. Simpson ID. The pediatric management of snakebite the national protocol. Indian Pediatr. 2007;44(3):173-6.
4. WHO/SEARO guidelines for the clinical management of snake bites in the Southeast Asian region. Southeast Asian J Trop Med Public Health. 1999;30(Supp 1):1-85.

CHAPTER 48

Initial Approach to a Comatose Child

Soonu Udani

INTRODUCTION

Whatever the initiating event that results in altered sensorium, it is the "secondary injury" (which results from hypoxia and hypoperfusion), that has huge impact on the eventual outcome. The approach to a child with altered sensorium, therefore, focuses on the efforts to prevent or limit this secondary injury, while trying to offer specific treatment.

Rapidly evaluate the appearance, breathing, and circulation. Confirm the altered sensorium and proceed with further assessment only if the child is stable. If the child is unstable, "the initial management priorities are to stabilize and support the airway, breathing, and circulation, irrespective of the etiology".

Every patient of altered sensorium/coma should be treated as having increased intracranial pressure (ICP) until proved otherwise: an unstable airway leads to hypoxia → cerebral vasodilation → increase in cerebral blood flow → increase in ICP.

Open with "jawthrust" or "chin lift" method if the spine is deemed unaffected.

Indications for intubation with full and proper sedation and muscle relaxant with premedication with lidocaine is illustrated in Box 1.

Focus on

- Oxygenation: partial pressure of oxygen (PaO_2) less than 60 mmHg (> 95% SpO_2)
- Ventilation: partial pressure of carbon dioxide ($PaCO_2$) → mid-30s

Box 1: Indications for intubation

- Glasgow Coma Scale ≤12 or AVPU [A (alert) V (responds to voice) P (responds to pain) U (unresponsive)]
- Features of herniation
- Abnormal respiration
- Asymmetric or dilated pupils
- Inability to handle secretions (absent gag, gurgling sounds)

Overzealous hyperventilation → CO_2 too low → danger of hypoperfusion and drop in cerebral perfusion.

Cerebral perfusion pressure = Mean arterial pressure – Intracranial pressure

- Target mean arterial pressures (MAP) to 70 mmHg minimum considering a target CPP of 50 mmHg
- Isotonic fluids, inotropes [maintain blood pressure (BP) = 95th centile
- When monitoring of ICP/MAP unavailable, avoid hypo-osmolar/hyperosmolar fluids—no role of fluid restriction
- High BP at presentation → effect/cause—reduce slowly after ICP ruled out
- Glycemic control less than 180 mg/dL.

BEWARE HYPOGLYCEMIA

Worsening Glasgow Coma Scale despite correction of Airway, Breathing, and Circulation (Box 2)

Box 2: Signs of raised intracranial pressure in coma

- Abnormal posturing
- Abnormal breathing pattern
- Abnormal oculocephalic (doll's eye) or oculovestibular reflex
- Abnormal pupillary response
- Cushing's triad

Chasing the cause: the list is exhaustive; a meticulous, "obvious causes" can be remembered by the "mnemonic COMA":

C: Convulsions (status epilepticus)

O; O_2 depriving events—resuscitation following episodes like drowning, electrocution, foreign body

M: Major illnesses, e.g., diabetes, hypertension (secondary), viral hepatitis, etc.

A: Accidents (trauma).

TABLE 1: Quick guide to causes of coma

Febrile	Afebrile
Bacterial meningitis	Well child: poisoning
Tuberculous meningitis	Metabolic
Herpes meningoencephalitis	Child abuse
Malaria	Sick child: tumor
Dengue	Hypertension
Immune mediated (ADEM)	Diabetic ketoacidosis
Onset in hours—drugs, poisoning	–
Onset in days—CNS infections	–
Onset in weeks—tumor, DKA, HTN	–

ADEM, acute disseminated encephalomyelitis; DKA, diabetic ketoacidosis; CNS, central nervous system; HTN, hypertension.

When the cause is not very clear, consider the following (Table 1):

INVESTIGATIONS

- Complete blood count, peripheral smear for malarial parasites (MP), cultures, blood sugar, blood urea nitrogen, electrolytes, liver function test, ammonia, lactate, arterial blood gas: keep extra samples for further tests
- Prioritize as per working diagnosis
- Imaging: if signs of raised ICP, no lumbar puncture—magnetic resonance imaging preferable. If not, computed tomography to check edema and impending herniation.

IMMEDIATE TREATMENT

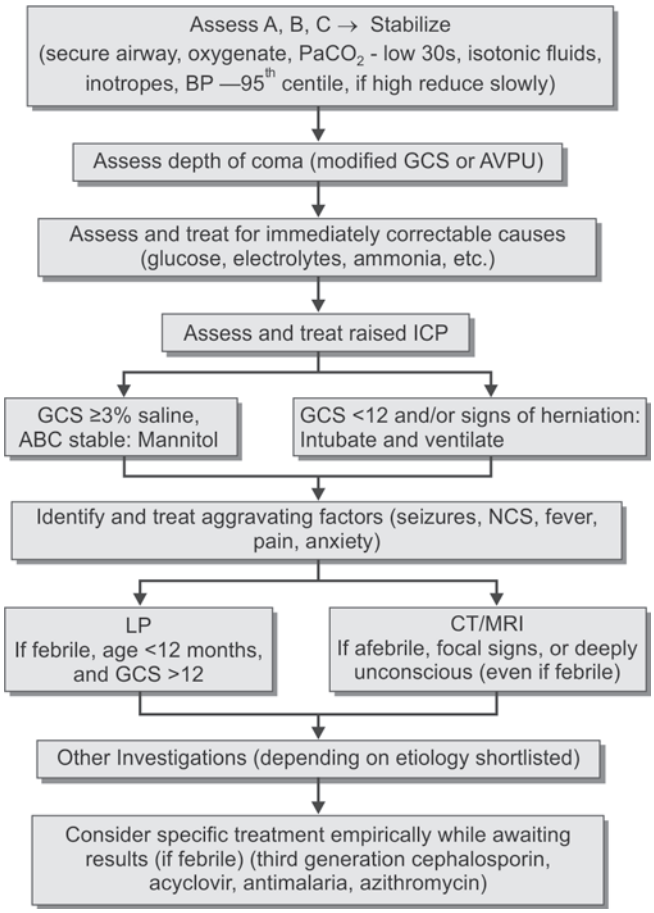
- Treatment for raised ICP: mannitol 1.25–2 mL/kg. Hypertonic saline to osmolarity of 310–360 mmol/L. Controlled ventilation and supportive nursing management.
- Specific treatment, if cause is known
- More broad based treatment covering meningitis, herpes, malaria, and other treatable infections, if cause is not known or till results are available.

Clinical Pearls

- Every patient of altered sensorium/coma should be treated as having increased intracranial pressure (ICP) until proved otherwise
- Raised ICP should be presumed until proven otherwise
- Overzealous hyperventilation → CO_2 too low → danger of hypoperfusion and drop in cerebral perfusion
- Hypertonic saline replaces mannitol as the osmolar agent of choice
- No role of fluid restriction.

ALGORITHM 1

Simplified approach to Coma



$PaCO_2$, partial carbon dioxide pressure: BP, bllod pressure; GCS, glasgow coma scale; AVPU, alert, voice, pain, unresponsive; ICP, intracranial pressure; NCS, nonconvulsive seizures; LP, lumbar puncture; CT, computed tomography; MRI, magnetic resonance

KEY POINTS

- ☞ Neuroprotective strategies should be employed from the time of first contact
- ☞ Supportive care is as important as specific treatment
- ☞ Repeated assessment is important
- ☞ Prevention and rapid treatment of aggravating causes
- ☞ Institute early rapid empirical treatment of probable causes
- ☞ Eye on good outcome, not only on survival.

SUGGESTED READINGS

1. Kirkham FJ. Non-traumatic coma in children. Arch Dis Child. 2001;85(4):303-12.
2. Udani S. Advances in neurocritical care. Indian J Pediatr. 2015;82(3):272-6.
3. Udani S. The comatose child. In: Udani S, Chugh K, Ugra D, Khilnani P (Eds). IAP Specialty Series Textbook on Pediatric Intensive Care, 2nd edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd;2013. pp. 341-451.

CHAPTER 49

Fever without Focus in Infants Less than 3 Months of Age

Balasubramanian Sundaram

INTRODUCTION

The differential diagnosis involving fever in neonates and young infants 29–60 days of age includes both infectious and non-infectious causes. Although self-limited viral infections are the most common cause of fever, the incidence of serious bacterial infections (SBIs) may be higher in this population compared to older children; neonates have been shown to be at particularly high risk. SBIs include bacteremia (e.g., sepsis), cellulitis, osteomyelitis, septic arthritis, meningitis, pneumonia, and urinary tract infection (UTI).

Among these, UTI is the most common type of SBI. Among bacterial pathogens causing SBI in infants less than 90 days of age, Gram-negative bacteria such as *E. coli* and *Klebsiella* are most frequently identified. Other common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *S. aureus* and less commonly Group B streptococcus and *Listeria monocytogenes*. Neonatal herpes simplex virus (HSV) is an important consideration in infants 0–28 days of age. Neonates with cutaneous vesicles, seizures, and/or elevated transaminases present a high index of suspicion for HSV infection; however, it is rare for a neonate with HSV to present with fever of uncertain source (FUS).

Because the clinical examination alone is unable to reliably predict serious illness in infants less than 60 days of age with FUS and culture results are not immediately available, clinicians must often approach management of patients with fever by relying on a combination of history, physical examination findings, and diagnostic screening tests.

DEFINITION

The term fever without focus or fever without localizing Signs or FUS is defined as an acute febrile illness in which the etiology of the fever is not apparent after a thorough history and physical examination. A rectal temperature higher than 38°C (100.4°F) has been defined as fever in literature.

EPIDEMIOLOGY

Risk of SBI varies with age. Risk is greatest during the immediate neonatal period and through the first month (and is heightened in the infant born prematurely). Even among neonates, only 7% of those who have fever without focus have an SBI.

LABORATORY DIAGNOSIS

Various diagnostic tests to quantify the risk of bacteremia and its complications have been assessed including the white blood cells count and differential, microscopic examination of buffy coat of blood, erythrocyte sedimentation rate, C-reactive protein, procalcitonin serum levels, morphologic changes in peripheral blood neutrophils, and quantitative cultures of blood. In addition, clinical scales have been developed to help identify the febrile child with a serious illness.

The outcome of primary concern is not occult bacteremia but meningitis. An ideal diagnostic test would specifically identify febrile children at risk of a serious complication, because many focal infections after bacteremia (e.g., most cases of either pneumonia or cellulitis) can be treated when they become apparent and are not usually associated with serious sequelae. Unfortunately, there is no such test. Lowering the risk of serious complications by preventing infections through use of conjugate vaccines has proven to be the most effective strategy.

MANAGEMENT

There is general agreement that febrile children who are "very young" (variably considered to be younger than 3, 2, or 1 month of age) should be managed differently from the way in which older children are managed (Algorithm 1). Some clinicians adhere to a protocol of treating all young infants with fever and no apparent focus of infection with broad-spectrum antimicrobial agents administered intravenously

in the hospital until the results of cultures of the blood, urine and cerebrospinal fluid (CSF) are known. Although sometimes perceived as the "safe" approach, such management incurs considerable financial cost and risk of iatrogenic complications and of diagnostic misadventures associated with hospitalization.

These risks include errors in the type and dosage of drugs, complications of venous cannulation (such as phlebitis and sloughing of the skin), and nosocomial infections. many experts believe that febrile infants from 2 to 3 months of age with no apparent focus of infection who appear well and/or who have a laboratory-documented viral infection can be managed without either additional laboratory tests or hospitalization, provided that careful follow-up is ensured.

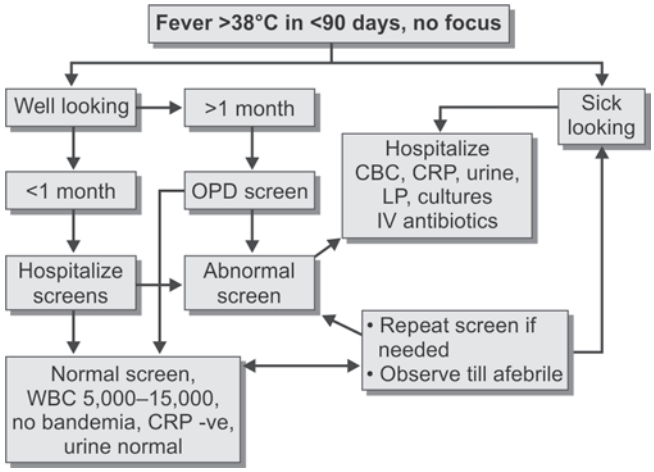
If an antimicrobial agent is to be administered, cultures of the blood, urine and CSF should be obtained first. Rapid tests for specific viral pathogens, which now are widely available, may aid decisions about managing patients and may reduce the need for and/or the duration of hospitalization.

Febrile infants at low risk of SBI for whom adequate home observation and follow-up cannot be ensured should be hospitalized and can be observed without antimicrobial treatment. Doing so (if the child appears well) is reasonable and avoids the adverse side effects of antimicrobial agents and intravenous cannulation, shortens the duration of hospitalization, and saves money without placing the child at significant risk of complications.

Most febrile infants with no apparent focus of infection who are younger than 1 month should be hospitalized and treated with antimicrobial therapy. The choice of antibiotic would depend on local epidemiological data and antibiotic susceptibility patterns in the area of practice. A third generation cephalosporin with an aminoglycoside would be generally sufficient for initial empiric therapy in most infants with community acquired infection.

ALGORITHM 1

Management algorithm



OPD, outpatient department; CBC, complete blood count; CRP, c-reactive protein; IV, intravenous; LP, lumbar puncture; WBC, white blood cell.

PITFALLS AND PEARLS IN ASSESSMENT AND DIAGNOSIS

1. Parental report of fever via palpation is unreliable as a sole method of determining fever.
2. Practice guidelines recommend that if a neonate has had a fever recorded at home by a reliable parent, the patient should be treated as a febrile neonate.
3. If excessive clothing and blankets encasing the infant are suspected of falsely elevating the body temperature, then the excessive coverings should be removed and the temperature retaken in 15–30 minutes. If body temperature is normal after the covers are removed, then the infant is considered afebrile.
4. A response to antipyretic medication does not change the likelihood of an infant having an SBI.
5. Clinical assessment include a thorough history and physical examination (include questions about recent symptoms, vaccinations, exposure to sick contacts, and the child's birth history in the patient history).
6. The large majority of children with fever without localizing signs in the 1–3 months age group likely have a viral syndrome.
7. Ill-appearing (toxic) febrile infants less than or equal to 3 months of age require prompt hospitalization and immediate parenteral antimicrobial therapy after cultures of blood, urine, and CSF are obtained. It is recommended that the following laboratory studies be performed in neonates with FUS, complete blood count, differential, blood culture urinalysis and urine culture. cerebrospinal fluid studies:
   i. Tube 1: protein and glucose
   ii. Tube 2: culture, sensitivity, Gram stain
   iii. Tube 3: cell count and differential
   iv. Tube 4: hold for additional studies. Stool culture if diarrhea is present.
8. Well-appearing infants 1–3 months of age can be managed safely using low-risk laboratory and clinical criteria if reliable parents are involved and close follow-up is assured (Table 1).
9. Among SBIs, pyelonephritis is the most common and may be seen in well-appearing infants who have fever without a focus or in those who appear ill. Urinalysis may be negative in infants less than 2 months of age with pyelonephritis.
10. Analysis of CSF for HSV using polymerase chain reaction (PCR) may be considered in neonates with CSF pleocytosis and a negative Gram stain.
11. Delaying or omitting a lumbar puncture for CSF analyses may be considered in young infants 29–60 days of age with FUS who meet all applicable low-risk clinical and laboratory criteria (Box 1).

Box 1: Low-risk criteria for infants with fever 1–3 months of age

Low-risk clinical criteria

- Well-appearing
- Previously healthy
- No focal source of infection

Low-risk laboratory criteria

- Urinalysis
  - ≤10 WBC/hpf
  - No bacteria on Gram's stain
- Complete blood count
  - WBC 5,000 to 15,000/mm^3
  - ≤1,500 band cells/mm^3
- Chest radiograph (if obtained)
  - No evidence of discrete infiltrate
- Stool smear (when diarrhea is present)
  - Negative for blood
  - ≤5 WBC/hpf

WBC, white blood cell

12. If antimicrobial therapy will be initiated in infants who meet low-risk criteria, CSF specimens need to be collected prior to treatment.
13. A chest X-ray may be performed in neonates and young infants 29–60 days of age who manifest one or more of the following clinical findings: tachypnea more than 60 breaths/min, crackles in the chest, retractions, nasal flaring, cyanosis or oxygen saturation less than 95%.
14. In patients who are not responding to antimicrobial therapy, the clinician should consider additional evaluation and treatment options, including: alternative antimicrobial therapy for resistant organisms (in neonates only) CSF HSV PCR (if not completed previously) and empiric treatment with acyclovir.

KEY POINTS

- ☞ Although controversy remains as how to best manage acutely febrile infants and children, there are several areas of near consensus
- ☞ Infants aged less than or equal to 60 days continue to have the highest rates of serious bacterial infections (SBIs) and pose a challenge to practitioners attempting to determine how extensive an evaluation to perform in a non-toxic appearing child
- ☞ Urinary tract infections (UTIs) are the most common SBIs in all age groups
- ☞ Assessment for UTI should be part of any evaluation for all but the lowest-risk patients (i.e., circumcised boys)
- ☞ New technologies can more rapidly diagnose common viral and bacterial infections and recommendations to simplify the management of these febrile infants and children are needed.

SUGGESTED READINGS

1. Huppler AR, Eickhoff JC, Wald ER. Performance of low-risk criteria in the evaluation of young infants with fever: review of the literature. Pediatrics. 2010;125(2):228-33.
2. Jhaveri R, Byington CL, Klein JO, Shapiro ED. Management of the non-toxic-appearing acutely febrile child: a 21st century approach. The Journal of Pediatrics, 2011;159(2):181-5.
3. Kramer, Michael S, Steven G. Rothrock, Andy Jagoda."The young febrile child: evidence-based diagnostic and therapeutic strategies" An Evidence-Based Approach to Infectious Disease.(2015.
4. Olaciregui I, Hernández U, Muñoz JA, Emparanza JI, Landa JJ. Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. Arch Dis Child. 2009;94(7):501-5.

CHAPTER 50

Acute Viral Encephalitis

Jaydeep Choudhury

INTRODUCTION

Acute viral encephalitis is an important cause of mortality and morbidity in children. Most of the times acute viral encephalitis is a clinical diagnosis and laboratory confirmation is not possible due to lack of availability of diagnostic testing for most of the agents. A period of up to 14 days is considered to define "acute". Acute encephalitis syndrome (AES) including Japanese B encephalitis (JE) is a group of clinically similar neurologic manifestation caused by several different viruses, bacteria, fungus, parasites, spirochetes, chemical/toxins, etc. There is seasonal and geographical variation in the causative organism. It may be sporadic like herpes simplex encephalitis (HSE) or epidemic such as JE. The outbreak of JE usually coincides with the monsoon and post-monsoon period when the density of mosquitoes increases while encephalitis due to other viruses especially enteroviruses occurs throughout the year as it is water borne disease. For surveillance purposes, all the acute encephalitis cases to be reported under the heading of acute encephalitis.

The case fatality rate of AES is very high and those who survive may suffer with various neurological sequelae. Children are at risk of highest attack rates because of lack of cumulative immunity due to natural infection. Encephalitis, usually caused by a virus, cannot be treated with antibiotics. A good clinical management is important to reduce the risk of disability or death from the disease.

Clinically, a case of AES is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, come, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness.

It is important to note that in an epidemic situation fever with altered sensorium persisting for more than 2 hours with a focal seizure or paralysis of any part of body is encephalitis. Presence of rash on body excludes Japanese encephalitis. AES with symmetrical signs and fever is likely to be cerebral malaria.

A suspected case that meets the clinical case definition for AES may be classified in one of the following four ways as shown in algorithm 1.

- Laboratory-confirmed JE: a suspected case that has been laboratory-confirmed as JE
- Probable JE: a suspected case that occurs in close geographic and temporal relationship to laboratory-confirmed case of JE, in the context of an outbreak
- Acute encephalitis syndrome (due to agent other than JE): a suspected case in which diagnostic testing is performed and an etiological agent other than JE virus is identified
- Acute encephalitis syndrome (due to unknown agent): a suspected case in which no diagnostic testing is performed or in which testing was performed but no etiological agent was identified or in which the test results were indeterminate.

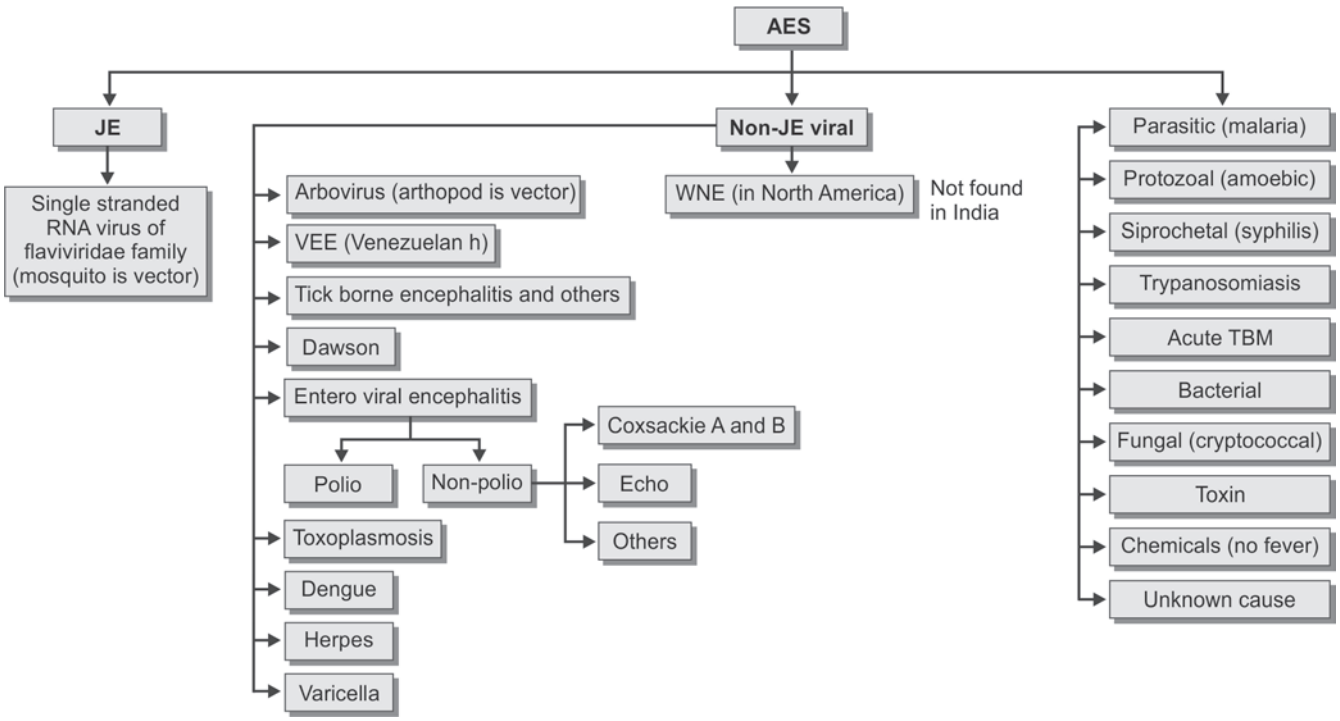
CLINICAL MANIFESTATIONS

A case of viral encephalitis including JE presents with a prodrome of fever, headache, nausea, diarrhea, vomiting, and myalgia lasting for 1–5 days. It is followed by irritability, altered behavior, convulsions, and coma. The progression of disease is rapid. Features of raised intracranial tension are commonly present in acute stage of illness. The patient may develop difficulty of speech and other neurological deficits like ocular palsies, hemiplegia, quadriplegia and may have extrapyramidal signs in the form of dystonia, choreoathetosis, and coarse tremors.

All the cases of AES should be reported as they have similar clinical manifestations. Their case management usually follows a common protocol along with situation specific treatment.

ALGORITHM 1

Causes of acute encephalitis syndrome



VEE, venezuelan equine encephalitis; JE, japanese B encephalitis; WNE, west nile encephalitis; TBM, tuberculous meningitis; RNA, ribonucleic acid.

MANAGEMENT

Acute encephalitis syndrome is a medical emergency and it requires immediate consideration of vital functions including life support, identification of cause and institution of specific therapy if available. Management of AES including Japanese encephalitis is essentially symptomatic. To reduce severe morbidity and mortality, it is important to identify early warning signs and refer patients to health facility.

The step-wise management of AES is as follows.

Step I: Rapid Assessment and Stabilization

- Establish and maintain airway: The child has to be intubated if glasgow coma scale (GCS) less than 8, there is impaired airway reflexes, abnormal respiratory pattern, signs of raised intracranial pressure (ICP), oxygen saturation less than 92% despite high flow oxygen and fluid refractory shock
- Ventilation, adequate oxygenation
- Circulation: intravenous (IV) access has to be established, samples to be collected for investigation (complete blood count, blood sugar, liver function test, renal function test, electrolytes, blood gas, lactate, peripheral smear and rapid diagnostic test for malarial parasite, serology for viruses). Fluid bolus to be given if in circulatory failure (20 mL/kg 0.9% NaCl), inotropes if required
- Signs of cerebral herniation or raised ICP should be identified
- Temperature: fever and hypothermia should be treated
- Ongoing seizures: benzodiazepine, followed by phenytoin loading if required.

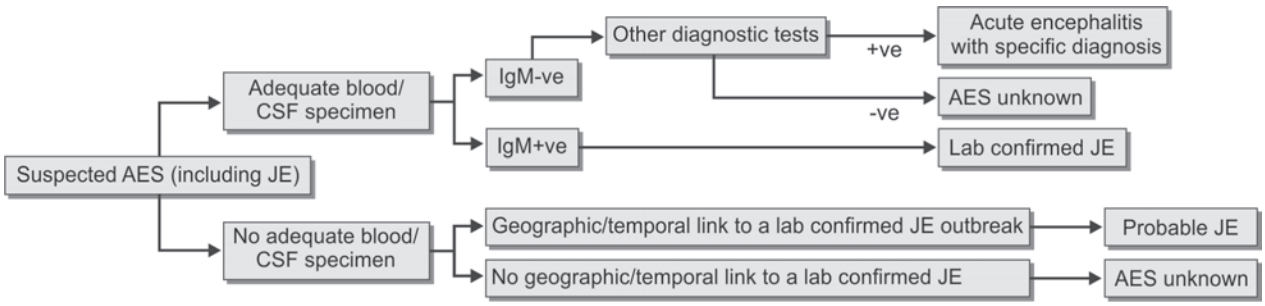
Step II: Clinical Evaluation: History and Examination

The following are the important aspects in history and examination. The approach to a suspected case of AES is shown in algorithm 2.

- Fever, headache, vomiting, seizures, abnormal posturing
- Altered behavior, cognition, personality changes, altered consciousness
- Prodromal symptoms, flu-like illness, diarrhea
- Rash, vesicles, past history of chicken pox
- Residence: rural/urban, endemic for cerebral malaria, any epidemic of AES in neighborhood
- History of animal contact, insect bite, dog bite
- Drug or toxin exposure
- Recent history of travel
- History of trauma
- Personal or family history of seizure disorder
- Recent immunizations
- History of recurrent episodes of encephalopathy: These are characteristic of some inborn errors of metabolism (urea cycle defects, organic acidemias, and fatty acid oxidation defects). It may also be present in migraine, epilepsy and substance abuse

ALGORITHM 2

Approach to a child with acute encephalitis syndrome



CSE, cerebrospinal fluid; IgM, immunoglobulin M; JE, Japanese B encephalitis; AES, acute encephalitis syndrome.

- Other concurrent systemic illness, e.g., jaundice (hepatic failure), pneumonia (hypoxic encephalopathy), diarrhea (dyselectrolytemia), dysentery (shigella encephalopathy)
- Past medical illness: diabetes, congenital heart disease, chronic kidney or liver disease
- Family history of previous infant/child deaths
- Pre-morbid developmental/neurological status of the child
- Risk factors for immunodeficiency: HIV risk factors, cancer treatment and steroid/immunosuppressant treatment.

Step III: Investigation/ Samples to Be Collected

- Cerebrospinal fluid (CSF): in hemodynamically stable patients without any features of raised intracranial pressure, lumbar puncture should be performed. Cerebrospinal fluid should be examined for cytology, biochemistry, Gram stain, Ziehl–Neelsen stain for acid fast bacilli, bacterial culture, latex agglutination, polymerase chain reaction for herpes simplex virus 1 and 2, and immunoglobulin M antibodies for JE and for dengue virus depending on clinical suspicion. Usual CSF findings in viral encephalitis include lymphocytic pleocytosis, mild to moderately elevated protein, and normal CSF sugar. Similar findings may occur in tubercular meningitis and partially treated pyogenic meningitis; however, the CSF sugar is likely to be low in these situations
- Blood/serum, urine: complete blood count including platelet count, blood glucose, serum electrolytes, liver and kidney function tests, blood culture, arterial blood gas and lactate. Peripheral smear for malarial parasite and rapid diagnostic test for malaria should be obtained. Chest X-ray should also be obtained
- Neuroimaging: magnetic resonance imaging (MRI) or computed tomography scan may give valuable information such as presence of bleed, cerebral edema, temporal lobe hypodensities in HSE, thalamic abnormalities in JE, and basal exudates and hydrocephalus in tubercular meningitis. Computed tomography may also show brain herniation, effacement of cisterns, infective collections such as brain abscesses and subdural empyema. Neuroimaging is not needed if the etiology is clear by other investigations, e.g., cerebral malaria, pyogenic meningitis. Suggestive MRI findings are present in some conditions of viral encephalitis such as HSE, JE, and enterovirus encephalitis
- Throat swab, nasopharyngeal swab.

Step IV: Empirical Treatment

Empirical treatment must be started, pending the results of investigations.

- Ceftriaxone: a broad spectrum antibiotic, such as ceftriaxone must be given, which can be stopped if there is no evidence of bacterial meningitis
- Acyclovir (should be started in all suspected sporadic viral encephalitis). Dose of acyclovir 3 months to 12 years is 500 mg/m^2 8 hourly. In children above 12 years 10 mg/kg 8 hourly. Duration of treatment in confirmed cases should be 14–21 days intravenous treatment and minimum 21 days for those aged 3 months to 12 years
- Artemether combination therapy: in cerebral malaria.

Step V: Supportive Care and Treatment

- Euglycemia should be maintained, fever should be controlled and hydration maintained
- Raised ICP to be treated with mild head-end elevation by 15–30°. Mannitol 20% IV 5 mL/kg over 30 min as first dose then 2.5 mL/kg at 6 hourly intervals up to 48 hours. Injection furosemide IV 1 mg/kg up to 40 mg can be given
- Seizures: anticonvulsant to be given if history of seizures or if GCS less than 8, or child has features of raised ICP
- Steroids: pulse steroids (methylprednisolone or dexamethasone) to be given in children with suspected acute disseminated encephalomyelitis.

Step VI: Prevention/Treatment of Complications and Rehabilitation

- Physiotherapy, posture change, prevention of bed sores, and exposure keratitis
- Complications like aspiration pneumonia, nosocomial infections, and coagulation defects to be treated accordingly

- Nutrition: early feeding should be initiated
- Psychological support to patient and family.

PREVENTION OF ACUTE ENCEPHALITIS SYNDROME

Prevention and/or control of AES require a multipronged strategy. It consists of:

- Surveillance for cases of AES
- Vector control
- Reduction in man-vector contact
- Vaccination.

KEY POINTS

- ☞ Acute encephalitis syndrome (AES) may be due to different viruses including Japanese B encephalitis, bacteria, fungus, parasites, spirochetes, chemical/toxins, etc.
- ☞ Clinically acute onset of fever (period of up to 14 days is considered acute)and a change in mental status and/or new onset of seizure
- ☞ Case fatality is high and survivors often have neurologic sequelae
- ☞ Acute encephalitis syndrome is a medical emergency, requires immediate consideration of vital functions, identification of cause, and institution of specific therapy, if available
- ☞ All AES cases should be reported.

SUGGESTED READINGS

1. Guidelines: Clinical Management of Acute Encephalitis Syndrome including Japanese Encephalitis. Government of India. Directorate of National Vector Borne Disease Control Programme. Directorate General of Health Services, Ministry of Health & Family Welfare, 2009.
2. Japanese Encephalitis Clinical Care Guidelines. PATH, November, 2006. [online] Available from: www.path.org/vaccineresources/filesJE_clinical_care_guidelines_PATH. pdf. [Accessed November, 2013].
3. John TJ. Outbreak of killer brain disease in children: mystery or missed diagnosis? Indian Pediatr. 2003;40:863-9.
4. Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, et al. Management of suspected viral encephalitis in children—Association of British Neurologists and British Pediatric Allergy Immunology and Infection Group National Guidelines. J Infect. 2012;64:449-77.
5. Kumar R, Tripathi P, Singh S, Bannerji G. Clinical features in children hospitalized during the 2005 epidemic of Japanese encephalitis in Uttar Pradesh, India. Clin Infect Dis. 2006;43:123-31.
6. Ministry of Health and Family Welfare, Government of India. Facility-based IMNCI (F-IMNCI) Participants Manual. Government of India, New Delhi, 2009. [online] Available from: www.unicef.org/india/FBC_Participants_Manual.pdf. [Accessed November, 2013].
7. Sharma S, Mishra D, Aneja S, Kumar R, Jain A, Vashishtha VM. Consensus Guidelines on Evaluation and management of Suspected Acute Viral Encephalitis in Children in India. Indian Pediatr. 2012;49:897-910.
8. World Health Oraganization. Acute Encephalitis Syndrome. Japanese encephalitis surveillance standards. January 2006. From WHO-recommended standards for surveillance of selected vaccine-preventable diseases. WHO/V&B/03.01. [online] Available from: http://www.who.int/vaccines-documents/DocsPDF06/843.pdf. [Accessed November, 2013].

CHAPTER 51

Acute Osteomyelitis

Baldev S Prajapati, Rajal B Prajapati

INTRODUCTION

Acute osteomyelitis in children is an important condition because of its potential to cause permanent disability. It is common in infants and toddlers than in older children. Early recognition of acute osteomyelitis in young patients before extensive infection develops and prompt institution of appropriate medical and surgical therapy minimize permanent damage. Acute osteomyelitis in neonates and infants is commonly associated with septic arthritis due to peculiar vascularity of the physis and epiphysis. The risk is greatest if the physis (the growth plate of bone) is damaged. Once the growth plate forms, it acts as a barrier and in toddlers and children the infection is usually confined to the metaphysis.

PATHOGENESIS

The unique anatomy and circulation of the ends of long bones result in the predilection for localization of blood borne bacteria. In the metaphysis, nutrient arteries branch into non-anastomosing capillaries under the physis, which make a sharp loop before entering venous sinusoids draining into the marrow (Fig. 1). Blood flow in this area is sluggish and provides an ideal environment for bacteria seeding. Once a bacterial focus is established, phagocytes migrate to the site and produce inflammatory exudates (metaphyseal abscess). The generation of proteolytic enzymes, toxic oxygen radicals, and cytokines result in decreased oxygen tension, decreased pH, osteolysis, and tissue destruction. As the inflammatory exudate progresses, pressure increases spread through the porous metaphyseal space via the Haversian system and Volkmann canals into the subperiosteal space. Purulence beneath the periosteum may lift the periosteal membrane of the bony surface, further impairing blood supply to the cortex and metaphysis.

In the newborns and young infants, transphyseal blood vessels connect the metaphysis and epiphysis (Fig. 2). So it is common for pus from the metaphysis to enter the joint space. This extension through the physis (growth plate) has the potential to result in abnormal growth and bone or joint

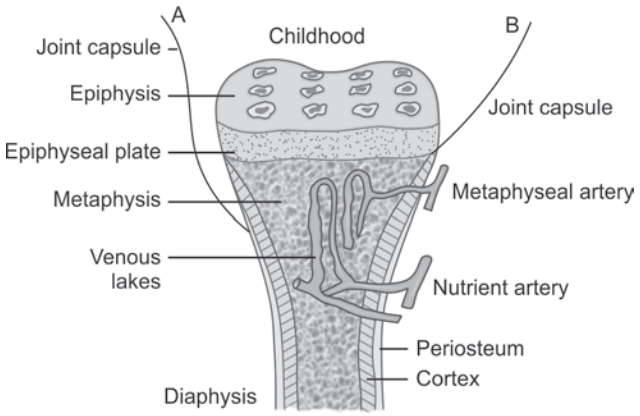


Fig. 1: Anatomy and circulation of the ends of long bones—the hair-pin bend (sharp loop) of the blood vessels resulting in sluggish blood flow and stasis of bacteria

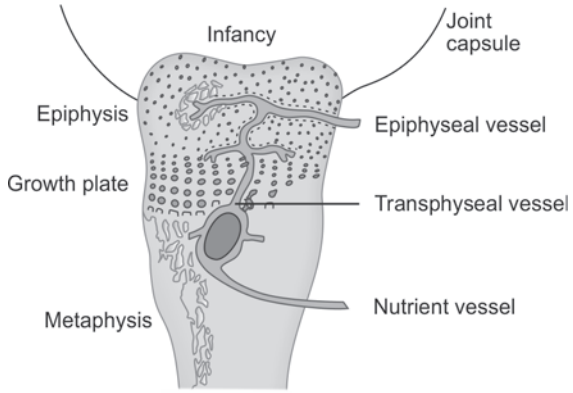


Fig. 2: In the new born and young infant, transphyseal blood vessels connect the metaphysic and epiphysis resulting in osteomyelitis with septic arthritis.

deformity. During the later part of infancy, the physis forms, obliterating the transphyseal blood vessels. Joint involvement once the physis forms may occur in joint where the metaphysis is intraarticular (hip, ankle, shoulder, and elbow) and subperiosteal pus ruptures into the joint space.

In the later childhood, the periosteum becomes more adherent, favoring pus to decompress through the periosteum. Once the growth plate closes in the late adolescence, hematogenous osteomyelitis more often begins in diaphysis and can spread to the entire intramedullary canal. With trivial trauma, the hematoma which forms in the metaphysis acts as a perfect soil for bacteria to seed.

ETIOLOGY

Bacteria are the most common pathogens in acute osteomyelitis. *Staphylococcus aureus* is the most common infecting organism in all age groups, including new borns. *Escherichia coli*, *Klebsiella,* and Group B streptococci are also prominent pathogens in neonates. Group A streptococci constitutes less than 10% of all cases. After the age of 6 years, most cases of acute osteomyelitis are caused by *S. aureus*, *streptococcus* or *Pseudomonas aeruginosa*. *Salmonella* species and *S. aureus* are the two most common causes of osteomyelitis in children with sickle cell anemia. *Pneumococcus* may also cause osteomyelitis in children with sickle cell anemia.

Infection with atypical mycobacteria, *S. aureus* or *Pseudomonas* can occur after penetrating injuries. Fungal infection usually occurs as part of multisystem disseminated disease. Candida osteomyelitis sometimes complicates fungemia in neonates with indwelling vascular catheters.

Overcrowded neonatal nursery, poor aseptic precautions while insertion of indwelling catheters and other procedures and their poor maintenance are common factors responsible for hematogenous spread acute osteomyelitis in neonates and young infants. It is very common scenario at our set up that a neonate presents with acute osteomyelitis after few days of discharge from nursery. Nosocomial infections are also very common in this group.

Community acquired Methicillin-resistant *Staphylococcus aureus* (MRSA) is also emerging as a potent cause of acute osteomyelitis in children in many parts of the world, including India.

Acute osteomyelitis following skin infection like pyoderma or pneumonia is also known in our patients (Table 1).

CLINICAL MANIFESTATIONS

The signs and symptoms of acute osteomyelitis are highly dependent on the age of the patient (Box 1).

- Abrupt onset of high grade fever. Fever is present in only 50% of neonates
- Signs of toxemia and irritability, like generalized manifestations, are more common in neonates
- Pain with movement of the affected extremity. Pseudoparalysis (restriction of movement) is very common in neonates and young infants due to pain

TABLE 1: Shows organisms causing acute osteomyelitis and their association with different conditions

Common clinical association	Microorganism
Frequent microorganism in any type of osteomyelitis	*Staphylococcus aureus* (MSSA or MRSA)
Sickle cell disease	*Salmonella* species, *S. aureus* and *S. pneumoniae*
Foreign body associated infections (catheters)	CONS (coagulase negative Staphylococcus)
Nosocomial infections	Enterobacteriaceae, *Pseudomonas, Canadida*
HIV	Bartonella
Immunocompromised	*Aspergillus* species, *Candida albicans*, *Mycobacteria* species

HIV, human immunodeficiency virus; MRSA, methicillin resistant *staphylococcus aureus*; MSSA, methicillin sensitive *staphylococcus aureus.*

Box 1: Common clinical manifestations

- Abrupt onset of high grade fever. Fever only in 50% of neonates
- Signs of toxemia, irritability more common in neonates
- Pain with movement of affected extremity
- Restriction of movement—pseudoparalysis
- Limp or refusal to walk
- Limb held in flexion of adjacent joints
- Local edema, erythema, tenderness, cellulitis

- Limp or refusal to walk in older children with involvement of lower extremities
- Affected limb held in position of flexion of adjacent joints
- Local edema, erythema and tenderness
- Focal tenderness over a long bone
- Local swelling and redness indicate infection has spread out of the metaphysis into the subperiosteal space. It represents secondary soft tissue inflammatory response (cellulitis)
- Long bones are commonly involved in acute osteomyelitis. Femur (27%), tibia (22%), and humerus (12%) are common bones involved in osteomyelitis. The femur and tibia together constitute almost half of the cases. Flat bones are less commonly affected
- Single site of bone or joint involvement is common. The exception is osteomyelitis in neonates, in whom two or more bones are affected in almost half of the cases
- Subacute symptoms and focal findings in metaphyseal area over tibia may be due to a Brodie abscess.

LABORATORY INVESTIGATIONS (BOX 2)

- No specific laboratory tests for osteomyelitis
- Complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are sensitive for bone infections but are non-specific and cannot distinguish between skeletal infections and other inflammatory conditions. Leukocytosis with increased polymorphs is

Box 2: Laboratory investigations

- No specific laboratory tests
- Leukocytosis with raised polymorphs
- Significantly raised erythrocyte sedimentation rate and C-reactive protein
- Blood culture
- Aspiration for Gram stain and culture

very common. Acute phase reactants, like ESR, and CRP are significantly raised

- Blood culture should be routine in all cases of suspected osteomyelitis. It may be positive in 50% of cases with hemaotgenous osteomyelitis
- Aspiration for Gram stain and culture is the definitive diagnostic technique.

RADIO IMAGING STUDIES (BOX 3)

Radio imaging studies play a crucial role in evaluation of osteomyelitis. Conventional radiographs, ultrasonography, computed tomography, magnetic resonance imaging and radionuclide studies may all contribute to establishing the diagnosis. Plain radiographs are often used for initial evaluation to exclude other causes such as trauma and foreign bodies. Magnetic resonance imaging has emerged as a very sensitive and specific test and is widely used for diagnosis. The sequence of radionuclide studies or MRI is often determined by age, site and clinical presentation.

Plain Radiographs

- Overlying soft tissue edema after 3–5 days infection may be suggesting osteomyelitis
- Lytic bone changes are evident on radiographs after 7–14 days of onset of infection in tubular long bones. Flat and irregular bones can take longer time. Lytic bone changes are not visible on radiographs until 30–50% of bony matrix is destroyed.

Ultrasonography

- Simple and inexpensive
- Very sensitive, can diagnose subtle signs like subperiosteal edema soft tissue swelling within 2–3 days of infection
- USG guided aspiration can be attempted to determine presence of infection. Aspiration has found positive results in 70–80% of cases.

Box 3: Radio imaging studies

- Plain radiograph shows lytic bone changes after 7–14 days of onset of infection. It is very late. Do not wait for radiographical changes for diagnosis
- Ultrasonography (USG)—simple and inexpensive. Very sensitive. USG guided aspiration has found positive in 70–80% of cases
- Magnetic resonance imaging is best radiographic imaging, effective in early detection and surgical localization, sensitivity 90–100%

Computed Tomography Scan

- CT can demonstrate osseous and soft tissue abnormalities and is ideal for detecting gas in soft tissues
- Can depict abnormal calcification, ossification and intracortical abnormalities
- Most useful in the evaluation of spinal vertebral lesions, pelvis, sternum, etc.

Magnetic Resonance Imaging

- Best radiographic imaging technique for identification of abscess and differentiation between bone and soft tissue infection
- Effective in early detection and surgical localization of osteomyelitis
- Sensitivity ranges from 90% to 100%.

Radionuclide Bone Scanning

- Useful when osteomyelitis is suspected but difficult to ascertain clinically
- Can detect osteomyelitis within 24–48 hours after onset of symptoms
- Three phase imaging with 99 m Tc has 85–100% sensitivity and 75–95% specificity in hematogenous osteomyelitis
- Sensitivity in neonates is much lower due to poor bone mineralization.

Radio nuclide bone scanning is useful when osteomyelitis is suspected but difficult to ascertain clinically, can detect in 24–48 hours, less sensitive in neonates.

DIFFERENT DIAGNOSIS

- Trauma
- Leukemia
- Sickle cell disease
- Hemophilia
- Collagen disorders
- Neuroblastoma

TREATMENT

The treatment of osteomyelitis comprised of:

- Antibiotic therapy
- Surgical therapy
- Physiotherapy.

Antibiotic Therapy (Box 4)

The primary treatment for osteomyelitis is parenteral antibiotics that penetrate bone and joint covities and most effective to the likely organisms.

- Neonates:
  - Cefotaxime 200 mg/kg/day divided in three doses Intravenous (IV) + Injection cloxacillin 150–200 mg/kg/day divided in four doses IV
  - If MRSA is considered as likely organism → inj. vancomycin is substituted for cloxacillin

Box 4: Antibiotic therapy

Neonates

- Inj. cefotaxime 200 mg/kg/day divided in three doses IV + inj. cloxacillin 150–200 mg/kg/day divided in four doses IV
- If MRSA suspected → inj. vancomycin is substituted for inj. cloxacillin
- If preterm or central vascular catheter → consider antibiotics to cover CONS, pseudomonas and fungi

Older infants and children

- Injection cefazolin 100–150 mg/kg/day divided in three doses IV or inj. cloxacillin 150–200 mg/kg/day in four divided doses IV
- If MRSA suspected → vancomycin is substituted by cloxacillin
- Injection cefotaxime or inj. ceftriaxone for Hib and other organisms

Sickle cell

- Injection cefotaxime or inj. ceftriaxone or inj. clindamycin
- Immunocompromised children:
- Injection vanocmycin + inj. ceftizidime or Inj. piperacillin – tazobactam + Inj. amikacin
- Intravenous antibiotics 2–3 weeks → oral antibiotics. Total duration 4–6 weeks

Inj., injection; MRSA, methicillin-resistant staphylococcus aureus; Hib, haemophilus influenzae type B; CONS, coagulase negative staphylococcus.

  - If neonate is a preterm baby or has a central vascular catheter → Possibility of nosocomial bacteria like pseudomonas or coagulase negative staphylococcus or fungi should be considered
- In older infants and children:
  - Common organisms are *S. aureus* and streptococcus → inj. cefazolin 100–150 mg/kg/day divided in three doses or inj. cloxacillin 150–200 mg/kg/day in divided four doses
  - If MRSA is suspected → vancomycin is substituted for cloxacillin
  - Injection cefotaxime 200 mg/kg/day in three divided doses or inj. ceftrixone 100 mg/kg/day in two divided doses may be used to cover haemophilus influenzae type B (Hib) and other organisms
- Patients of sickle cell disease with osteomyelitis, *Salmonella* and *S. aureus* should be covered → inj. cefotaxime 200 mg/kg/day divided in three doses IV or inj. ceftraixone 100 mg/kg/day divided in two doses IV → inj. clindamycin 40 mg/kg/day divided in four doses IV is useful alternative for sensitive to beta lactam drugs. In addition to good anti-staphylococcus activity, clindamycin has broad activity against anaerobes and is useful for the treatment of infection secondary to penetrating injuries or compound fractures
- Injection vancomycin and injection clindamycin are alternatives for MRSA
- Immunocompromised patients with osteomyelitis:
  - Injection vancomycin + inj. ceftzidime or inj. piperacillin – tazobactam + inj. amikacin
- Changes of antibiotics should be considered, once pathogens are identified
- Sequential antibiotics therapy:
  - Intravenous antibiotics duration varies from 10 days to 3 weeks. Appropriate antibiotic respond includes clinical and laboratory improvement. A decreasing CRP and white blood cell count with absence of local signs and symptoms should initiate to oral antibiotics.
- Duration of antibiotic therapy:
  - For *S. aureus* or Gram-negative bacillary infections, the minimal duration of antibiotics is 28 days, but 6 weeks therapy is desirable.
  - For Group A streptococcus and *S. pneumoniae* or Hib, the minimal duration is 14 days.

Surgical Therapy

Indications for surgical therapy should be defined (Box 5).

- Interventions:
  - Drainage of subperiosteal abscess
  - Decompression of intra-medullary cavity
- Complete removal of all necrotic tissues
- Splint application to prevent muscle spasm and pathological fractures.

Physiotherapy for Prevention of Contractures and Early Mobility

Prognosis

- When the pus is drained and appropriate antibiotic therapy is given, improvement in signs and symptoms is rapid
- Failure to improve or worsening by 72 hours, requires review of the appropriateness of antibiotic therapy, need for surgical intervention or correctness or diagnosis
- Acute phase reactants (ESR and CRP) may be helpful for monitoring the response to therapy. Long-term follow-up is necessary for sequelae like contractures and bone length
- Meticulous following to algorithm 1 is quite rewarding in most cases.

Complications

- Septicemia
- Chronic osteomyelitis
- Septic arthritis
- Pathological fracture
- Growth plate disturbances.

CONCLUSION

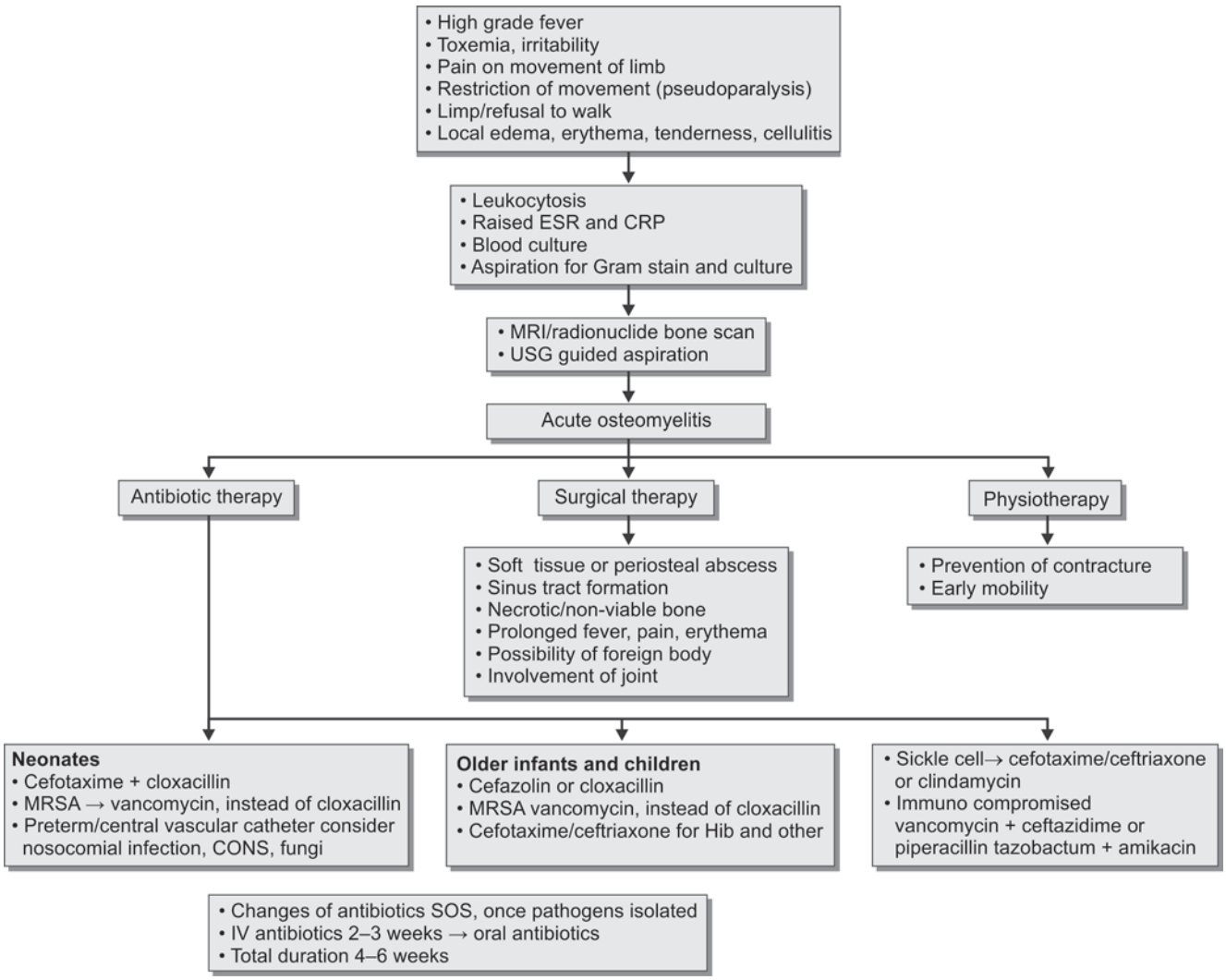
Acute osteomyelitis in children is an important condition because of its potential to cause permanent disability.

Box 5: Indications for surgical therapy

- Soft tissue or periosteal abscess
- Sinus tract formation
- Presence of necrotic or non-viable bone
- Prolonged fever, swelling, pain and erythema
- Possibility of foreign body
- Involvement of joint

ALGORITHM 1

Management of acute osteomyelitis



ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; USG, ultrasonography; MRI, magnetic resonance imaging; IV, intravenous; CONS, coagulase negative staphylococcus; MRSA, methicillin-resistant *staphylococcus aureus.*

Long bones are commonly involved in acute osteomyelitis in children. The unique anatomy and circulation of the ends of long bones (hair-pin bend of blood vessels) result in sluggish circulation and localization of blood borne bacteria. Acute osteomyelitis in neonates and infants is commonly associated with septic arthritis due to peculiar vascularity of physis and epiphysis. Bacteria are the most common pathogens in acute osteomyelitis in children. *Staphylococcus aureus* is the most common infecting organism in all age groups, including newborns. Sickle cell anemia, penetrating injuries, nosocomial infections, certain skin infections, and immunocompromised like conditions are known to have association with very specific organisms responsible for acute osteomyelitis.

The clinical manifestations of acute osteomyelitis in children are highly dependent on the age of the patient. Fever, signs of toxemia, and irritability are more common in neonates. Pain, pseudoparalysis, limp, refusal to walk, local edema, erythema, tenderness, and cellulitis are other manifestations. There are no specific laboratory tests for osteomyelitis. Leukocytosis with polymorphonuclear reactions, significantly raised ESR and CRP are very common. Blood culture should be routine in all cases of suspected osteomyelitis. Aspiration for Gram stain and culture is the definite diagnostic technique.

Radio imaging studies play a crucial role in evaluation of osteomyelitis. Plain radiograph shows lytic bone changes after 7–14 days of onset infection. Do not wait for plain radiographical changes for diagnosis of acute osteomyelitis, it is very late. Soft tissue edema may be evident after 5 days of infection. Ultrasonography is simple, inexpensive and very sensitive for subtle signs like subperiosteal edema and soft tissue swelling. Ultrasonography guided aspiration is rewarding, positive in 70–80% of cases. Magnetic resonance imaging is considered as best radio imaging technique for effective early detection and surgical localization of osteomyelitis. Sensitivity ranges

from 90 to 100% Radionuclide bone scanning is useful when osteomyelitis is suspected but difficult to ascertain clinically. It is less sensitive in neonates.

The treatment of acute osteomyelitis is comprised of proper antibiotics in optimum doses by specific route of administration, for defined duration, usually 4–6 weeks, surgical intervention if required and physiotherapy. Early diagnosis and prompt, efficient management favor good prognosis.

Clinical Pearls

- Acute osteomyelitis is an important condition because of its potential to cause permanent disability
- Long bones are commonly involved in acute osteomyelitis in children. In neonates and infants, it is commonly associated with septic arthritis due to peculiar vascularity of physis and epiphysis
- Bacteria are the most common pathogens in acute osteomyelitis in children. *Staphylococcus aureus* is the most common organism. Association of different organisms with very specific condition is known
- Fever, toxemia, and irritability are common clinical manifestations in neonates. Pain, pseudoparalysis, limp, refusal to walk, local edema, erythema, tenderness, and cellulitis are other manifestations
- Leukocytosis with raised polymorphonuclear cells and raised erythrocyte sedimentation rate and C-reactive protein are very common. Blood culture should be routinely done in all cases
- Radioimaging studies play a crucial role in evaluation of osteomyelitis. Plain radiograph shows lytic bone changes after 7–14 days of onset of infection. Do not wait for radiological changes for diagnosis, it is very late. Ultrasonography is simple, inexpensive, and very sensitive for subtle signs. Ultrasonography guided aspiration is rewarding, positive in 70–80% of cases. Magnetic resonance imaging is considered as the best radioimaging technique. Radionuclide bone scanning is useful when osteomyelitis is suspected but difficult to ascertain
- The treatment of acute osteomyelitis is comprised of appropriate antibiotics in optimum doses by specific route of administration, for 4–6 weeks duration, surgical intervention if required, and physiotherapy
- Early diagnosis along with prompt and efficient management favor the good prognosis.

KEY POINTS

- ☞ Acute osteomyelitis in children is an important condition because of its potential to cause permanent disability
- ☞ Long bones are commonly involved in acute osteomyelitis in children
- ☞ *Staphylococcus aureus* is the most common infecting organism in all age groups, including newborns
- ☞ Fever, signs of toxemia, and irritability are more common in neonates. Pain, pseudoparalysis, limp, refusal to walk, local edema, erythema, tenderness, and cellulitis are other manifestations
- ☞ Blood culture should be routine in all cases of suspected osteomyelitis. Aspiration for Gram stain and culture is the definite diagnostic technique
- ☞ Plain radiograph shows lytic bone changes after 7–14 days of onset infection. Magnetic resonance imaging is considered as the best radio imaging technique
- ☞ The drug of choice for treating osteomyelitis is cefazolin/cloxacillin for 4–6 weeks. Intravenous antibiotics can be switched to oral once acute signs of inflammation have subsided.

SUGGESTED READINGS

1. Bhaskar A. Acute osteomyelitis in children. In: Shah MA, Vekariya PM, Chowdhary J (Eds). Challenges in the Management of Pediatric Bone & Joint Infections. pp. 81-3.
2. Gutierrez KM. Osteomyelitis In: Long SS, Pickering LK, Prober C. (Eds). Principles & Practice of Pediatric Infectios Diseases, 3rd ed. 2008. pp. 474-82.
3. Kaplan S. Osteomyelitis. In: Kliegman RM, Stanton BF, Geme III JWS, et al. (Ed.). Nelson Textbook of Pediatrics. 19th ed. India. Elsevier Saunders. 2012. pp. 2394-98.
4. Mitra M. Skeletal infections. In: Ghosh TK, Yewale V, Parathasarathy A, Shah NK (Eds). IAP Speciality Series on Pediatric Infectious Diseases (Under IAP Action Plan, 2006), 1st ed. 2006. pp. 111-22.

CHAPTER 52

Algorithmic Approach to Short Duration Fever without Focus in Older Infants and Children

Suhas V Prabhu

INTRODUCTION

Fever in an older infant and child (>3 months of age) is one of the most common cases presenting to the pediatrician (up to half of out-patient visits). The causes may vary from something as innocuous as a non-specific viral infection needing only symptomatic treatment to more dangerous ones like dengue, malaria, or bacteremic infections requiring correct diagnosis and prompt intervention.

CAUSES

Bacteremia will be seen in between 3 and 5% of children with fever without focus in this age group especially if the fever is more than 39°C. While bacteremia due to organisms like *Streptococcus pneumoniae, Staphylococcus* and *Haemophilus influenzae* is more common in children younger than 2 years, in older children, typhoid and paratyphoid fevers account for the majority of bacterial causes. Parasitic infestations like malaria also account for a large percentage of fevers in this age group in certain parts of the country in certain seasons.

APPROACH

The clinician's approaches to these patients need to be one of a cautious balance between over investigation and/or unnecessary usage of antibiotics versus the other extreme of missing the child with serious infection who will suffer because of delayed diagnosis and intervention. While the majority of cases will need only symptomatic treatment and observation for the first 2 or 3 days, the clinician needs to be alert to pick up those who are more likely to have serious illnesses bacterial or otherwise that need to be investigated promptly.

The first step therefore is to assess for toxicity (degree of severity of illness). Signs of severe infection/sepsis or danger signs requiring immediate workup and possible hospitalization can be easily remembered by the mnemonic ABCD:

- **A**ctivity and **A**lertness (reduction of or **A**ltered sensorium)
- **B**reathing (difficult or fast)
- **C**olor (cyanosis, pallor, decreased capillary fill time) and **C**ry (weak or high pitched)
- **D**ehydration (poor intake, oliguria).

Additional factors may exist that need to be considered such as an immune-compromised patient (human immunodeficiency virus, asplenia, etc.), child with an indwelling foreign body (port, shunt, prosthesis, etc.), condition predisposing to subacute bacterial endocarditis (bicuspid aortic valve, small ventricular septal defect, etc.), compromised due to chronic cardiovascular disease or severe protein energy malnutrition, latent cortisol deficiency congenital adrenal hyperplasia, and so on. This sub-set of patients should be investigated and treated more aggressively than the general population.

The second step is to ensure that it is truly a fever without focus. Make an extra effort to look for a focus although in the history or on cursory examination there is no apparent one. In particular, look for otitis media, joint involvement, local skin infections, rash, urinary symptoms, etc., if found appropriate investigation and treatment should be done.

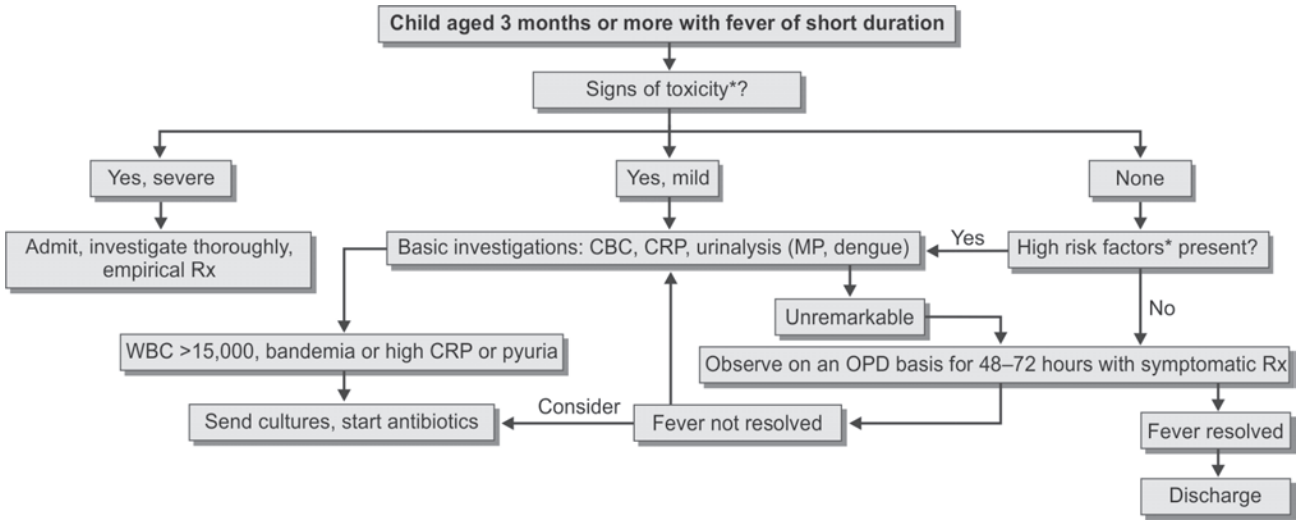
If no focus is found after a thorough history and physical examination, and the child is not toxic, there are no risk factors, and the temperature is less than 39°C, it is safe to observe the child with antipyretics alone and reassess after 48–72 hours. Parents must be informed about danger signs (ABCD listed above) that should prompt them to return for medical re-evaluation earlier. However, if the child is already suffering with fever for the past 2–3 days and there is no focus found on the day of presentation, then the child should be investigated straightaway.

If otherwise, initial investigation should consist of the following: complete blood count, acute phase reactant marker like C-reactive protein (CRP), urinalysis and, where feasible, blood and urine cultures. Tests for malaria (smear for malarial parasite and/or rapid malarial antigen test) or dengue (NS1 antigen ± dengue immunoglobulin G and immunoglobulin M) should be added if the epidemiology warrants.

However, additionally, if the child is severely toxic or dehydrated or has signs of early sepsis, hospitalization

ALGORITHM 1

Approach to short duration fever without focus in older infants and children



WBC, white blood cell; CRP, C-reactive protein; CBC, complete blood count. *See text for details.

TABLE 1: Clues to the diagnosis from the humble complete blood count

Parameter	Enteric fever	Malaria	Dengue fever	Other viral fevers
hemoglobin/hematocrit	Normal	Low	Normal/High	Normal
Total white blood cell	Normal/Low	Normal/Low	Low/Very low	Normal/Low
Differential white blood cell	Polys predominant, Eosinopenia	Monocytosis	Lymphocytosis	Lymphocytosis, activated lymphocytes
Platelets	Normal/Low	Low	Low	Normal/Low

is mandatory for observation, stabilization, and prompt empirical administration of antibiotics. Ceftriaxone at 100 mg/kg/day is usually an appropriate initial choice. On the other hand, in situations where availability or affordability is a problem and the child is not too sick, the initial step may be only a complete blood count with (where appropriate) smear for malarial parasite and a routine urinalysis. If the white cell count is more than 15,000/mm^3 or bandemia or toxic granulation is present, a blood culture would be advisable. Similarly, if the urinalysis shows pyuria, urine culture should be asked for before the first dose of antibiotic is administered. If there is leukopenia [White blood cell (WBC) count below 4,000] then possibilities of enteric fever, malaria, dengue, and viral infection should be considered and appropriate investigations asked for. If the WBC count is normal and low with absolute eosinopenia and there is a very high CRP enteric fever should be considered and blood cultures sent before starting antibiotics.

The CBC needs to be evaluated in detail rather than only looking for leukocytosis. Table 1 indicates possible clues to the diagnosis from the humble CBC.

The CRP (if done) can help to distinguish bacterial from viral fevers even on the 2nd or 3rd day of illness. But a mildly elevated CRP can be seen in some viral infections like adenovirus or viral infections with secondary bacterial complications. However, a very high CRP (> 40 mg/L) is more likely to be due to a bacterial infection and a clue to further investigation or empirical antibiotic therapy.

Clinical Pearls

- Examine thoroughly to rule out an occult focus
- In all sick children or in those with no focus even after 2–3 days of fever, perform investigations including complete blood count (CBC), smear for malarial parasite, C-reactive protein (CRP), and urine routine
- Other investigations that may be asked for depending on findings on initial investigations or clinical setting include urine and blood cultures and dengue serology
- Careful interpretation of the CBC is important, often repeat testing is required
- Mildly elevated CRP can be seen in viral infections
- Widal test is of no value in the first 7 days. Blood culture is the most reliable method to diagnose enteric fever.

In certain circumstances, the first CBC may be unremarkable but repeat CBCs might yield the diagnosis, e.g., in dengue, serial CBC shows decline in the WBC and platelet count and rising hematocrit. The widal test is of no utility in evaluation of fever of less than 7 days duration.

SUGGESTED READINGS

1. Baker MD. Evaluation and management of infants with fever. Pediatr Clinics North Am. 1999;46:1061-72.
2. Lorin MI. Fever: Pathogenesis and treatment. In: Feigin RD, Cherry J, (eds). Textbook of Pediatric Infectious Diseases, 4th ed. Philadelphia, WB Saunders; 1998. pp. 89-94.

CHAPTER 53

Fever with Rash

Ritabrata Kundu

INTRODUCTION

Skin is the mirror of many internal ailments which may manifest as rashes. At the outset one should determine the types of rashes which are as follows.

Macules are flat lesions of altered color in the skin. Papules are raised flat topped lesions with diameter of less than 5 mm, whereas nodules are more than 5 mm in diameter with raised rounded configuration. Vesicles are fluid filled lesions less than 5 mm in diameter and are known as bullae when they are more than 5 mm in diameter. Pustules are raised pus filled lesions. Purpuras are bleeding into the skin which are nonblanchable. When they are less than 5 mm in diameter they are known as petechiae and if more than 5 mm in diameter ecchymoses.

A good history in all cases must include site of onset of rash, rate and direction of its spread. Inquire about medications taken in recent months, history of travel, exposure to insects and animals, immune status and immunization history. It should also include history of any cardiac abnormality including prosthesis, exposure to ill individual, and sexually transmitted diseases.

Next one should determine the type of rash, i.e., its morphology, distribution, and arrangement of the lesions. At times, the morphology might change with passage of time for instance in dengue the initial diffuse flushing may give away to maculopapular rash. Also the spread of lesions should be taken into account as maculopapular rash of dengue which starts in the trunk spreads centrifugally to extremities and face.

CLASSIFICATION OF RASH WITH FEVER

It is broadly classified as follows:

- Centrally distributed maculopapular rash
- Peripheral rash
- Confluent desquamative rash
- Vesiculobullous rash
- Urticarial rash
- Nodular rash
- Purpuric rash
- Rashes with ulcer.

Centrally Distributed Maculopapular Rash

They are most common type of rash which is mainly truncal. Most common viral infections seen in children belong to this group are discussed in table 1.

TABLE 1: Centrally distributed maculopapular rash

Diseases	Common recognizing features
Measles	Respiratory prodrome; Koplik's spot in buccal mucosa which gradually wanes after onset of rash, maculopapular rash starting from hairline and behind the ears, spread down the trunk and limbs. Rash fades in the order in which it appeared with brownish discoloration and desquamation.
Rubella	Prodrome of fever and malaise, followed by posterior auricular, cervical and suboccipital lymphadenopathy; fever and rash. Rash, maculopapular begins on face and spreads downward.
Erythema infectiosum	Common in children between 3–12 years; bright (fifth disease) red "slapped cheek" appearance following a minor febrile prodrome.
Exanthem subitum	Common in children below 3 years; diffuse (ro seola) truncal maculopapular rash sparing face following resolution of fever.
Infectious	• Common in older children and adolescents Fever, mononucleosis sore throat, and lymphadenopathy is most common • Morbiliform or papular rash develops usually on trunk and arms

Continued

Continued

Diseases	Common recognizing features
Drug rash	• Usually maculopapular common in trunk and symmetrical • Intensely pruritic, absence of respiratory catarrh and enanthems helps to distinguish from a viral eruption
Dengue	• Initially diffuse red flushing with pruritus followed by maculopapular rash on trunk which spreads centrifugally to extremities and face • Petechiae may be seen in some cases on extremities
Systemic lupus erythematosus	• Photosensitive butterfly rash on check and nose • Discoid, urticarial, or bullous lesion may also be seen
Juvenile rheumatoid arthritis	Evanescent erythematous papules on trunk appearing at the height of fever

Peripheral Rash (Table 2)

These rashes start at the periphery (acral) and then spread centripetally.

TABLE 2: Peripheral rash

Diseases	Common recognizing features
Erythema multiforme (infection, drugs)	• Target lesions symmetrical on palms, soles, knee, and elbow • The center of the lesion dusky violet color or petechiae • In erythema multiforme major there is usually involvement of ocular, nasal oral, or genital mucous membrane
Hand-foot and mouth disease (Coxsackie virus and enterovirus)	• Tender maculopapular lesion on hand, fingers, feet, buttocks associated and groin • Vesicular lesions are also seen • Involvement of buccal mucosa, pharynx, gingiva, and palate
Secondary syphilis	• Maculopapular rash frequently involving palms and soles • They are dark colored, nonpruritic, and discrete • Constitutional symptoms other than fever include malaise, sore throat, weight loss, and headache • There is also involvement of mucous membrane
Bacterial endocarditis	• Erythematous or hemorrhagic macules on palms and soles are painless (Janeway lesions) • Petechiae on skin and mucosa; tender red nodules on finger and toe pads (Osler's node) • Associated heart murmur

Confluent Desquamative Rash (Table 3)

They start with diffuse erythema often followed by desquamation.

TABLE 3: Confluent desquamative rash

Disease	Common recognizing features
Scarlet fever	• Blanchable erythema over face and upper trunk to start • Minute papules which give the skin a sand paper feel • Associated feature include strawberry tongue • Subsidence of rash is followed by desquamation
Streptococcal toxic shock syndrome	• Generalized erythematous macular rash which desquamate • May develop other features which usually include hypotension, renal impairment, respiratory distress syndrome, coagulopathy, or soft tissue infection
Staphyloccocal scalded skin syndrome	• Seen in infants and children below 5 years • Scarlatiniform erythema develops followed by sterile flaccid blisters • Nikolsky sign is positive with skin peeling off leaving moist, glistening denuded areas • Patient may appear well despite marked skin tenderness
Staphylococcal toxic shock syndrome	• Acute onset with high fever, erythematous macular rash which desquamates later and associated with hypotension • Multisystems involvement with thrombocytopenia, renal failure, liver and central nervous system abnormality are seen
Kawasaki disease rashes	• Maculopapular, scarlatiniform or erythema multiforme with accentuation in the groin area • Associated feature includes fissuring of the lips, conjunctivitis, strawberry tongue, edema of hands and feet with periungual desquamation of finger and toes • Illness predominantly in young children with majority under 5 years
Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)	• SJS start as erythematous macule which develops central necrosis to form vesicles, bullae, and skin denudation • Extend of involvement is less than 10% of body surface area • Skin lesions are accompanied by two or more mucous membrane involvement like conjunctivitis, oral ulceration, or anogenital inflammation • TEN has involvement more than 30% of body surface area with more systemic symptoms like pulmonary or gastrointestinal involvement • In SJS/TEN involvement is between 10 and 30%

Vesiculobullous Rash (Table 4)

They are mostly due to virus or bacterial infections.

TABLE 4: Vesiculobullous rash

Disease	Common recognizing feature
Varicella	• Macules appears on trunk and face that rapidly spreads to other areas of the body • Lesions have an erythematous base which quickly evolves to vesicles, pustules and then crust formation • Lesions appear in crops with different stages of development • In healthy children it is usually associated with mild fever and malaise
Herpes simplex virus (HSV) infection	• Cutaneous lesions usually involve face, lips, gingiva, tongue and palate • Erythema followed by grouped vesicles, which progress to pustules and crust formation • There is regional lymphadenopathy but systemic symptoms are usually absent
Herpes Zoster	• Clustered vesicular lesions confined to one or two dermatomes • Pain, hyperesthesia and fever are mild as compared to adults • Lesions completely resolve within 1 or 2 weeks

Urticarial Rash

Classic urticaria (hives) is not associated with fever. They do not last at a Particular location for more than 24 hours, does not have purpuric or pigmented component and itch rather than burn.

TABLE 5: Urticarial rash

Disease	Common recognizing feature
Urticarial vasculitis	• Raised erythematous lesions with flat top • They are indurated, painful and sometimes lesions are purpuric • May have burning sensation and individual lesion lasts up to 5 days.

Purpuric Rash (Table 6)

Nonpalpable purpura is flat lesion due to bleeding in the skin. If less than 3 mm in diameter then it is known as petechiae whereas more than 3 mm in diameter then called ecchymoses. Palpable purpura is due to inflammation of the vessel wall (vasculitis) with subsequent hemorrhage causes raised lesions.

TABLE 6: Purpuric rash

Disease	Common recognizing feature
Acute meningococcemia	• Initial maculopapular lesion involving trunk and lower extremities • Lesions quickly evolving to petechiae

Continued

Disease	Common recognizing feature
	• and purpura may spread to involve upper extremities and face • Large ecchymoses with hemorrhagic bullae (purpura fulminans) indicate DIC • Associated features of meningitis and shock may be evident
Dengue hemorrhagic fever	• After a relatively benign first stage with fever, malaise and headache patient suddenly collapses with cold extremities and irritability • Petechiae and purpura may be seen in extremities and face followed by ecchymoses
Rickettsial infections	• Indian spotted fever is associated with an initial maculopapular and then petechial/ purpuric rash with peripheral distribution and involvement of palms and soles • In scrub typhus a necrotic rash is seen at the bite site and a centrally distributed rash

DIC, disseminated intravascular coagulation.

Nodular Rash

The most common nodular rash with fever is erythema nodosum. They are violaceous, tender, and large subcutaneous nodules seen particularly on lower legs above the shin bone. It may be due to drugs (penicillin, sulfonamide) infection (streptococcal, mycobacterial, fungal) or idiopathic. Common associated feature include arthralgias.

KEY POINTS

- ☞ Fever with rash is a common and vexing problem
- ☞ It may signify a serious disorder such as meningococcemia or dengue hemorrhagic fever or may be associated with a minor drug allergy
- ☞ The most important factor that helps to determine the etiology of an exanthematous febrile illness is the nature of rash
- ☞ All efforts should be made to diagnose the serious entities first and institute immediate treatment
- ☞ For stable children, a specific diagnosis may not be always be possible. In this situation symptomatic therapy, close observation, explanation of danger signs to parents, and staying away from school until the rash resolves are recommended.

SUGGESTED READING

1. Cherry JD. Cutaneous manifestations of systemic infections. In: Feigen RD, Cherry JD (Eds). Textbook of Pediatric Infectious Diseases, 4th ed. Philadelphia: WB Saunders; 1998. pp. 713-37.

CHAPTER 54

Approach to Managing New Onset Fever in the Intensive Care Unit

Tanu Singhal

INTRODUCTION

New onset fever defined as fever occurring after 48 hours of admission to the intensive care unit (ICU) in a patient who was previously afebrile is generally considered as a sign of a hospital acquired/health care associated or nosocomial infection. However, an infection may occur without fever and not all fever is due to infection. In certain circumstances, a new onset fever may also be a continuum or a complication of a community acquired infection. Approach to diagnosis and management of this clinical entity is discussed in this chapter.

GENERAL PRINCIPLES IN DIAGNOSIS

Distinguishing Infectious from Noninfectious Causes of Fever

It must be remembered that fever can often be the result of noninfectious causes. Noninfectious causes of fever in the hospitalized patient include postoperative atelectasis, drug fever, thrombophlebitis, transfusions, deep venous thrombosis, central fever, etc. Similarly, leukocytosis may not always be due to an infection; noninfectious causes include stress, bleeding, atelectasis, and steroids.

Determining the Site of Infection

Once, major noninfectious causes are excluded a thorough clinical assessment should be made for determining the site of infection. Common sites if infections in the ICU are blood stream infections especially in patients who have central lines, sinusitis/tracheobronchitis/pneumonia in patients on invasive ventilation, urinary tract infections in those who have indwelling catheters, surgical site infections in postsurgical patients and sometimes enteric infections. *Clostridium difficile* is less common in children as compared to adults. Central nervous system (CNS) infections and intra-abdominal sepsis should be also considered in children with predisposing procedures/interventions at these sites. Occult sites of infection include sinusitis, osteomyelitis, and septic arthritis. Eliciting symptoms referable to a particular system is often difficult in very sick children but should be done whenever possible. A head to toe assessment should be done with careful inspection of the central line, exit site of central venous, respiratory system, nature of tracheal secretions, abdomen, bones, joints, examination of neck stiffness and surgical sites and the skin. It is important to disrobe and examine the entire skin as these might show areas of cellulitis, eschars, and pustules which often indicate bacteremia/fungemia.

Distinguishing Infection from Colonization in the Nosocomial Setting

An important issue in managing nosocomial infections is to differentiate infection from colonization. In several ICUs, surveillance cultures are sent from nonsterile sites like endotracheal tubes, central line ports, urinary catheters, and EVD drains. These will always grow microbes as these sites are inevitably colonized. It is important that these colonizations are not treated with antibiotics as treating colonization will not prevent infection and only contributes to selection of resistant organisms. Unless an infection is suspected, no surveillance cultures should be sent. More difficult is to differentiate infection from colonization, in the setting when fever is associated with positive cultures from nonsterile sites. Here careful interpretation is needed to ascertain whether the positive culture is colonization or true infection.

INVESTIGATIVE APPROACH

The initial investigations include a complete blood count and peripheral smear evaluation with acute phase reactants such as C-reactive protein (CRP)/procalcitonin. Signs of sepsis include neutrophilia/neutropenia, thrombocytopenia, shift to left/bandemia and toxic granules in the neutrophils. While CRP has limited sensitivity/specificity for diagnosing sepsis,

a serum procalcitonin level of more than 2 ng/mL is highly specific for serious bacterial infection in a previously stable patient. Procalcitonin can also be high due to previous surgery/trauma/burns, etc.

At least two aerobic/one aerobic and one anaerobic culture should be sent. If there is a central catheter then one culture should be sent from the catheter lumen and the other from peripheral venipuncture. Increasing the volume of blood cultured by sending two sets of culture (four bottles) increases the sensitivity. Confirmation of the diagnosis of a catheter-related bloodstream infections (CRBSI) involves isolation of the identical organism with the same antibiogram from simultaneous cultures; one obtained through peripheral venipuncture and the other either catheter lumen blood culture or culture of the catheter tip. A positive lumen culture alone has poor positive predictive value for CRBSI as it may just indicate colonization; but high negative predictive value (90%).

In all children and especially those with suspected urinary tract infection, a routine urine analysis and culture should be sent. Results of these investigations should be interpreted carefully as some degree of pyuria and significant bacteriuria (colony count of more than 10^5/mL may be seen in any catheterized patient with no urinary tract infection).

For suspected hospital acquired pneumonia, cultures of the respiratory secretions should be sent. Several methods like quantitative endotracheal aspirates, bronchoalveolar lavage, protected specimen brush have been recommended for diagnosis of pneumonia. Generally speaking, quantitative cultures of endotracheal secretions are easily done and of almost comparable yield as those of the bronchoscopic methods. Hence, in suspected ventilator associated pneumonia (combination of fever/leukocytosis/purulent secretions/new infiltrates) quantitative endotracheal cultures should be sent and empirical antibiotic therapy initiated.

Cultures should also be sent from other suspected sites of infection such surgical sites, cerebrospinal fluid (CSF), abscesses, etc. Care should be taken to send deep samples; skin swabs and cultures from drains may just indicate colonization.

Imaging also assists in diagnosing site of infections. Basic imaging includes chest X-ray and ultrasonography abdomen. Presence of a new infiltrate on chest imaging is also not specific enough for a pneumonia as it may be due to atelectasis, progression of underlying lung disease, or due to thoracic surgery. In some patients, computerized scans of the thorax and abdomen may be needed to detect site of infection.

TREATMENT

The most important component of treatment of a nosocomial infection is appropriate antimicrobial therapy administered as soon as possible once sepsis is considered. However, source control such as removal of an infected central line and drainage of pus and supportive therapy are also crucial.

Factors Determining Choice of Antimicrobial Therapy

Various factors determine the empiric choice of antibiotics and include:

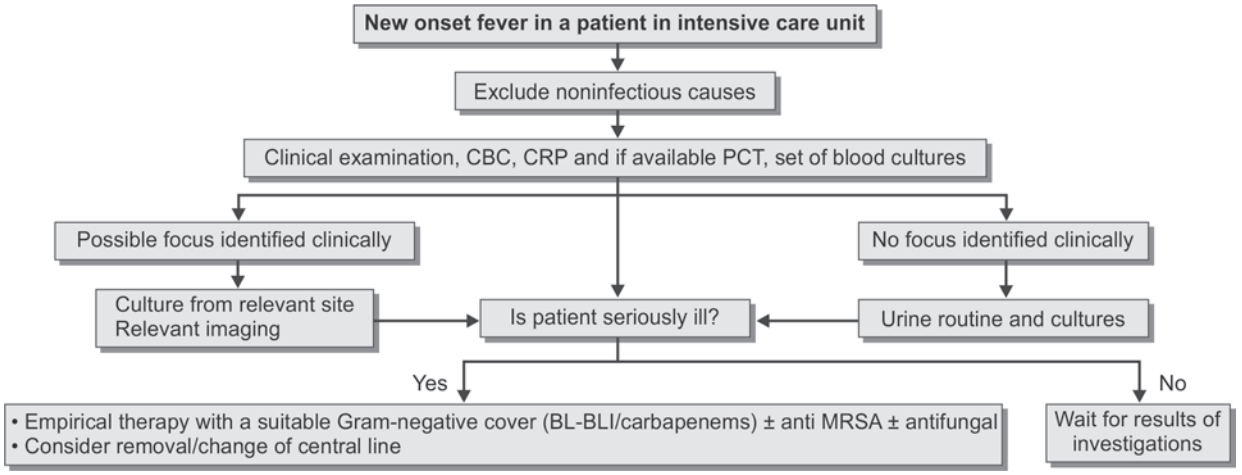
- Local epidemiologic data: knowledge of common microbial pathogens and their resistance profile in a particular intensive care unit helps in making empirical choice of antibiotics till cultures are available. The most common etiologic agents for nosocomial infections in India are Gram-negative pathogens including *Klebsiella*, *E. coli*, *Pseudomonas, Acinetobacter, Enterobacter*. These are followed by Gram-positive including *S. aureus*, *S. epidermidis* and enterococci There is an increase in infections due to fungi, mainly *Candida albicans* but also non-albicans candida such as *Candida tropicalis, Krusei, Glabrata,* and *Parapsilosis*. Most of the nosocomial pathogens are multidrug resistant. Foremost is drug resistance in Gram-negative pathogens with 80% of nosocomial *E. coli* and *Klebsiella* infections being resistant to third generation cephalosporins by virtue of production of extended spectrum beta lactamases (ESBL). The emergence of Amp C mediated resistance, traditionally found in *Pseudomonas, Enterobacter, Serratia, Citrobacter* but now even in other Gram-negative bacilli has made third generation cephalosporins and beta lactam-beta lactamase inhibitor (BL-BLI) combinations ineffectual. The fall out of ESBL and Amp C mediated resistance has been excessive use of carbapenems in ICU settings. Consequently, a significant proportion of *Pseudomonas* and *Acinetobacter* isolates in certain ICUs of tertiary care hospitals are now resistant to even carbapenems. This has led to colistin overuse and sporadic reports of colistin resistance. *S. aureus* are generally methicillin resistant, vancomycin resistant *S. aureus*/enterococci are not a problem as yet. Also seen over time with increasing use of fluconazole for therapy and prophylaxis, is rising incidence of non-albicans Candida infections some of which are fluconazole resistant
- Previous antibiotic usage: this again helps in predicting the likely resistance profile of the microbe till culture results are available. Additionally, it helps in guessing what pathogens have not been appropriately covered till now
- Severity of infection: for a patient who is critically sick or in septic shock, a carbapenem may be needed as there is high organism load and there is no leeway for making an error in choice of antibiotic nor is their time to upgrade. On the other hand, if there is doubt about the presence of infection or there is mild infection a BL-BLI combination may be used
- Associated comorbidities: these are important considerations. For instance if there is associated renal compromise, nephrotoxic drugs such as aminoglycosides, vancomycin, and colistin should be avoided or used with caution
- Site of the infection: in the presence of a CNS infection a drug with good CSF penetration must be used. Hence, BL-BLI combinations cannot be used as the BLI does not cross the blood brain barrier.

Initial Empirical Antimicrobial Regimes

Initial empirical therapy is necessary in seriously ill patients before culture reports are available. The choice of such

ALGORITHM 1

Algorithmic approach to new onset fever in intensive care unit



CBC, complete blood count; CRP, C-reactive protein; PCT, procalcitonin; BL-BLI, beta lactam-beta lactamase inhibitor; MRSA, methicillin-resistant *Staphylococcus aureus*.

antimicrobial therapy should be carefully thought of since studies demonstrate that inappropriate initial therapy is associated with higher mortality. Since most nosocomial infections in Indian ICUs are due to resistant Gram-negative pathogens, the initial empirical regime should comprise of an adequate Gram-negative cover such as BL-BLI combination or carbapenems. In units with high rates of carbapenem resistance, colistin may be required upfront in very sick patients. An anti methicillin-resistant *Staphylococcus aureus* (MRSA) cover should be added to the regime if there is a high incidence of MRSA in that unit, if there are Gram-positive cocci in the Gram stain of secretions or if there are other features suggesting a Gram-positive infection. If risk factors for fungal infections are present such as prolonged ICU stay, renal failure, prolonged antibiotic use, gut surgery, renal failure, use of corticosteroids, use of intralipids, immunocompromised stay, extreme prematurity and isolation of candida from multiple nonsterile sites then an antifungal should be added either upfront or of there is failure to respond in 48 hours. The choice of antifungal depends on previous azole exposure, the local patterns in the unit, the severity of infection and associated comorbidities but for most fluconazole suffices.

Dosing of Antibiotics

Adequate attention is needed toward administration of appropriate doses. Higher doses may be needed for serious infections. Time dependent antibiotics such as beta lactams and vancomycin should be dosed frequently to maintain serum levels continuously above the minimum inhibitory concentration. Recent data supports administration of beta lactams by continuous infusion. On the other hand, concentration dependent antibiotics, such as aminoglycosides, may be effectively dosed once a day.

De-escalation

This is extremely important to prevent or mitigate antibiotic resistance. Once culture reports are available and so indicate, the higher level antibiotic can be switched to a narrow spectrum one. This may mean switching from a carbapenem such as imipenem or meropenem to a cephalosporin/BL-BLI/quinolone or ertapenem. Even if cultures are negative, de-escalation may be practiced such as stopping the MRSA cover if no Gram-positive pathogen has been isolated.

Duration of Therapy

Newly emerging data supports the use of short-term antibiotic therapy (usually 7 days) for most nosocomial infections (exception *S. aureus*, fungal infections and necrotizing pneumonias). This helps in reducing the antibiotic pressure in the unit and chances of selection of resistant pathogens apart from reducing costs.

CONCLUSION

A new onset fever in the intensive care unit may be a harbinger of a serious possibly drug resistant infection. It is crucial to pay due attention to infection control strategies so that such an event can be prevented.

Clinical Pearls

- A robust infection control program is crucial in preventing health care associated infections
- Appropriate antimicrobial therapy is essential for improving outcomes and reducing the burden of antimicrobial resistance
- Knowledge of local microbial flora and susceptibility helps in designing empirical regimes.

KEY POINTS

- ☞ All new onset fever in intensive care units may not be infectious
- ☞ A careful examination is needed to identify the source of fever
- ☞ Relevant cultures should always be sent prior to starting antimicrobial therapy
- ☞ Results of investigations including cultures from nonsterile sites should be carefully interpreted
- ☞ The empirical antimicrobial therapy should be guided by local susceptibility patterns, severity of illness, and prior antibiotic use. It should be broad enough especially in sick patients
- ☞ Efforts should be made to de-escalate antimicrobials at the earliest
- ☞ Infection control strategies are paramount.

SUGGESTED READINGS

1. Alcon A, Fabregas N, Torres A. Hospital-acquired pneumonia: etiologic considerations. Infect Dis Clin N Am. 2003;17(4):679-95.
2. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. Am J Infect Control. 1988;16:128-40.
3. Huskins WC, Goldmann DA. Nosocomial infections. In: Feigin RD, Cherry JD (Eds). Textbook of Pediatric Infectious Diseases, 4th ed. Philadelphia: WB Saunders Company; 1998. pp. 2545-85.
4. Lodha R, Natchu UC, Nanda M, Kabra SK. Nosocomial infections in pediatric intensive care units. Indian J Pediatr. 2001;68:1063-70.
5. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, Harris JS, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis. 2001;32:1249-72.

CHAPTER 55

Infant Born to Human Immunodeficiency Virus Infected Mother

Ira Shah

INTRODUCTION

Human immunodeficiency virus (HIV) in children is predominantly acquired as a vertically transmitted disease. Without intervention the transmission rate from mother to child has varied from 20 to 40%. However, this risk can be reduced to less than 2% with effective prevention of parent to child transmission of HIV (PPTCT) programs.

Vertical transmission of HIV can occur *in utero* through placental transmission, intrapartum through contact with infected birth canal secretions or postpartum through breastfeeding. It is estimated that of the 30% of babies who get infected vertically, 2% get infected in early gestation, 3% get infected in late gestation, 15% get infected intrapartum and 10% get infected via breastfeeding.

Clinical Pearls

- Mother to child transmission of Infant Born to human immunodeficiency virus Infected Mother occurs in 20–40% children without intervention
- 2% get infected in early gestation, 3% get infected in late gestation, 15% get infected intrapartum, and 10% get infected via breast feeding

Prevention Modalities

Human immunodeficiency virus transmission from infected mother to child is mainly prevented by antiretroviral drug (ARV) prophylaxis to mother and baby, replacement feeding and elective caesarean section (ECS). Antiretroviral prophylaxis acts by reducing viral load in the mother and as post-exposure prophylaxis to the fetus and baby. Caesarean section before onset of labor or rupture of membranes has been used as an intervention for PPTCT to decrease risk of intrapartum transmission of HIV.

The goal of effective PPTCT is to ensure minimum risk of transmission of HIV from mother to child and ensuring a healthy mother and child at the end of intervention. The year 2009 was the turning point for the prevention of postnatal transmission of HIV where three randomized controlled trials found that antiretroviral prophylaxis in pregnant women and their infants coupled with breastfeeding could lead to a significant decrease in the vertical transmission of HIV.

Clinical Pearls

Prevention modalities include:

- Antiretroviral drugs to mother during pregnancy and while feeding
- Antiretroviral prophylaxis to baby post delivery
- Choice of feeding
- Mode of delivery

ELECTIVE CAESAREAN SECTION

Elective caesarean section has been found to decrease transplacental hemorrhage during labor, reduce the length of exposure of baby to vaginocervical secretions, and reduces chances of ascending infection of HIV transmission. Studies have found that among HIV-1 infected women not taking ARV during pregnancy, ECS was efficacious for prevention of mother to child transmission (MTCT) of HIV-1, and decreased transmission by approximately 50% as compared to other modes of delivery.

However, ECS is associated with postpartum morbidity in the form of fever, urinary tract infection, endometritis and thromboembolism. Also, it is more expensive and not universally available especially in resource limited settings. When ARV prophylaxis to mother and child are available and replacement feeding can be issued, the added advantage of ECS is not seen and vaginal delivery may be a safe and inexpensive option in this setting.

ANTIRETROVIRAL PROPHYLAXIS

Many trials have demonstrated gradual reduction of the *in utero* and intrapartum transmission rates with an increasing length and potency of drug combinations used during pregnancy and at delivery. In industrialized countries, highly active antiretroviral therapy (Triple drug therapy) is used in pregnant women as prophylaxis.

CHOICE OF FEEDING

Human immunodeficiency virus has been detected in breast milk in cell-free and cell-associated compartments and there is now evidence that both compartments are involved in transmission of HIV through breast milk. Even if intra-uterine and intrapartum transmission are significantly reduced, postnatal transmission through breastfeeding still is an additional risk for transmission of HIV (risk varies from 10 to 15%). This risk increases with high viral load in the breast milk, maternal nipple lesions, mastitis, and breastfeeding for longer than 15 months.

Replacement feeding clearly abolishes the risk of breast milk transmission. However, replacement feeding increases the risk of diarrheal diseases and malnutrition.

Exclusive breastfeeding for up to 6 months, however, is associated with a threefold to fourfold decreased risk of transmission of HIV compared to non-exclusive breastfeeding; mixed feeding, therefore, appears to be a clear risk factor for postnatal transmission. Various recent clinical trials have now clearly shown that when antiretrovirals are taken through the pregnancy and breastfeeding stage, there is a greatly reduced HIV infection rate of 2%. This approach offers new hope for mothers with HIV infection who cannot safely feed their babies with replacement. It will improve the chances of infants remaining healthy and free of HIV infection as breast milk provides optimal nutrition and protects against other fatal childhood diseases such as pneumonia and diarrhea.

WORLD HEALTH ORGANIZATION (WHO) 2013 GUIDELINES

The new World Health Organization (WHO) 2013 Guidelines have suggested a once-daily three drug fixed-dose combination of tenofovir and lamivudine (or emtricitabine) and efavirenz as first-line antiretroviral therapy in HIV infected pregnant and breastfeeding women which should be continued lifelong. Infants of these mothers should receive 6 weeks of infant prophylaxis with daily nevirapine (or twice-daily zidovudine). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (Table 1).

DIAGNOSIS OF HUMAN IMMUNODEFICIENCY VIRUS IN INFANTS BORN TO HUMAN IMMUNODEFICIENCY VIRUS INFECTED MOTHERS

All infants born to HIV-infected mothers carry maternal immunoglobulin G antibodies which cross the placenta freely.

TABLE 1: WHO Guidelines 2013 for Prevention of parent to child transmission of human immunodeficiency virus

Option B+	
For pregnant women	Triple ARV drugs starting from as early as 14 weeks of gestation and continued lifelong
Recommended regimen	Tenofovir + 3 lamivudine (or emtricitabine) + efavirenz
For infants	Daily administration of zidovudine or nevirapine from birth until 4–6 weeks of age
Type of delivery	Vaginal
Feeding	Breastfeeding

These maternal antibodies may remain detectable in the infant's serum for up to 12–15 months after birth. As a result, serological diagnosis of HIV infection is only reliable after 15–18 months of age. Infants infected with HIV must be diagnosed as rapidly as possible to ensure the early institution of therapy to limit HIV related morbidity and to prevent opportunistic infections. Tests that can be done for diagnosis of HIV infection in children below 18 months of age are HIV culture, detection of HIV proviral DNA by polymerase chain reaction (PCR). Human immunodeficiency virus culture is done from peripheral blood mononuclear cells (PBMCs) but is technically difficult and time consuming. It is expensive and done in research institutes. Positive results are available by 1–2 weeks but negative results are not reported till there is no evidence of HIV replication for 30 days. Thus, the test commonly used for diagnosis of HIV in infants is PCR.

TIMING OF TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS AND ROLE OF POLYMERASE CHAIN REACTION

Human immunodeficiency virus PCRs are of two types: (1) Qualitative and (2) Quantitative. The potential utility of DNA PCR for the diagnosis of vertical HIV infection soon became readily apparent in infants. Human immunodeficiency virus deoxyribonucleic acid (DNA) PCR has been found to be highly sensitive and specific for early diagnosis of pediatric HIV infection. Sensitivity of HIV PCR is less at birth and sensitivity increases rapidly to 95% at 4 weeks and to 99% at 6 months of age. Thus, in non-breast fed infants, HIV PCR can be done at 4–6 weeks after birth. In breastfeeding populations, HIV PCR should be done after 1 or 2 months after cessation of breastfeeding. HIV PCR can be done on dried blood sample transported to a laboratory on a filter paper or on whole blood.

False positive and false negative results with HIV DNA PCR may occur. The authors have reported a very high incidence of false positive HIV DNA PCR (75%) especially in younger infants in their study. Repeating the PCR on independent samples may be required to reduce the test errors. One of the reasons stated for the false positive results is contamination. Optimal PCR conditions, inclusion of control samples, strict rules on sample preparation, pre- and post-PCR handling, repetition of results, confirmation of specificity by hybridization, choice

of material from which HIV-1 is amplified, and the primers used for amplification will all predict the reliability of HIV DNA PCR. Thus, diagnosis of HIV should never be based on one result but should always be confirmed by a repeat test. Serological diagnosis at 18 months with HIV enzyme-linked immunosorbent assay would also be useful.

DIAGNOSIS OF HUMAN IMMUNODEFICIENCY VIRUS IN CHILDREN ABOVE 18 MONTHS OF AGE

Enzyme-linked immunosorbent assay is the time-tested reliable method for detection of anti HIV antibodies with a sensitivity of more than 99.5% and specificity of 99%.

Clinical Pearls

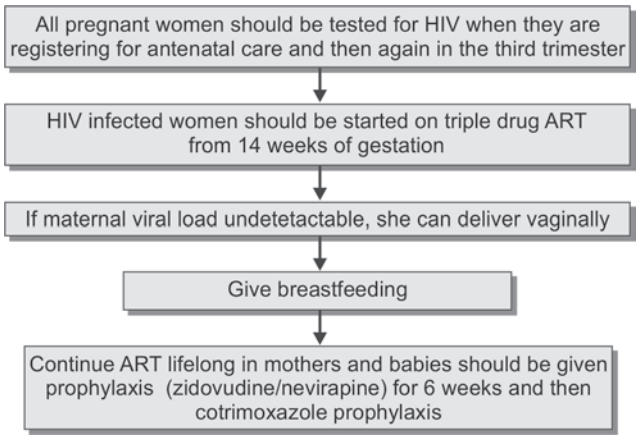
- Diagnosis in children less than 18 months—human immunodeficiency virus polymerase chain reaction
- Diagnosis in children above 18 months—human immunodeficiency virus enzyme-linked immunosorbent assay

COTRIMOXAZOLE PROPHYLAXIS

Cotrimoxazole prophylaxis is safe, inexpensive, and highly effective in reducing morbidity and mortality among HIV-infected infants and children, as well as in adolescents and adults. Ideally, all infants exposed to HIV should be started on cotrimoxazole prophylaxis during the first 4–6 weeks of life, as recommended by the WHO. This period is particularly critical for HIV-infected infants. Providing cotrimoxazole prophylaxis protects against serious, often fatal, opportunistic infections (OIs). It has also been recognized that cotrimoxazole prophylaxis provides benefits beyond the prevention of pneumocystis pneumonia.

ALGORITHM 1

Strategy for prevention of parent to child transmission of human immunodeficiency virus



HIV, human immunodeficiency virus; ART, antiretroviral therapy.

Children born to HIV-infected mothers should be administered prophylaxis with trimethoprim sulfamethoxazole beginning at age 4–6 weeks. Prophylaxis should be discontinued for children who are subsequently determined not to be infected with HIV. HIV-infected children and children whose infection status remains unknown should continue to receive prophylaxis for the first year of life.

Clinical Pearls

- Cotrimoxazole prophylaxis should be given to all children born to human immunodeficiency virus (HIV) infected mothers starting from 4 to 6 weeks of age
- Prophylaxis should be discontinued for children who are subsequently determined not to be infected with HIV
- Human immunodeficiency virus-infected children and children whose infection status remains unknown should continue to receive prophylaxis for the first year of life.

CONCLUSION

While interventions to prevent MTCT of HIV can dramatically reduce the risk of pediatric infections to less than 2% with continuation of breastfeeding.

KEY POINTS

- ☞ Human immunodeficiency virus (HIV) infected pregnant women should be started on triple antiretroviral therapy lifelong
- ☞ All babies should receive nevirapine or zidovudine after birth for 6 weeks
- ☞ Exclusive breast feeding recommended
- ☞ Early diagnosis consists of HIV deoxyribonucleic acid polymerase chain reaction in infants less than 18 months.

SUGGESTED READINGS

1. Mangano A, Pittis G, Galindoz C, Bologna R, Sen L. Reliability of laboratory markers of HIV-1 infection in Argentinean infants at risk of perinatal infection. AIDS Patient Care STDs. 1998;12:691-6.
2. Shah I. Efficacy of HIV PCR techniques to diagnose HIV in infants born to HIV infected mothers—an Indian perspective. JAPI. 2006;54:197-9.
3. Shah I. Management of Pediatric HIV, 2nd edition. Pediatric on Call, Mumbai. 2011.
4. Shah Ira, Dhabe H, Lala M. Prevention of maternal to child transmission of HIV: A profile in indian children. 42nd National Conference of IAP (PEDICON—2005), Kolkata, January 2005; JF/08(P).
5. The International perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1—a meta-analysis of 15 prospective cohort studies. N Engl J Med. 1999;340:977-87.
6. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. [online] Available from: http://www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html. [Accessed November 2015].
7. World Health Organization (WHO). Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. 2010. WHO.

CHAPTER 56

Fever of Unknown Origin

Raju C Shah, Tanu Singhal

DEFINITION

The definition of fever of unknown origin (FUO) is fever more than 101°F lasting for 3 weeks or more for which no cause is apparent after 1 week of outpatient investigation. A practical definition of FUO is simply fever more than 101°F measured on several occasions over a 7-day period.

CAUSES

The principal causes of FUO are listed in box 1. Infections account for most of the cases of FUO in children (60–70%). Most common among infectious causes are enteric fever, malaria, pulmonary or extrapulmonary tuberculosis, and urinary tract infections. Malignancies especially leukemia and autoimmune diseases chiefly juvenile rheumatoid arthritis (JRA) account for the remaining cases. Relatively rare causes include drug fever, temperature dysregulation, diabetes insipidus, sarcoidosis, ectodermal dysplasia, sensory autonomic neuropathies, etc. Even with extensive investigations the cause of FUO remains undiagnosed in 10–20% of the cases.

Box 1: Causes of fever of unknown origin

Infectious causes

- Enteric fever, Malaria, Urinary tract infections, Tuberculosis, Chronic hepatitis, HIV, Hidden abscesses (liver, pelvic), Mastoiditis, Sinusitis, Osteomyelitis, Meningitis, Infectious mononucleosis, Infective endocarditis, Brucellosis, CMV, Toxoplasmosis, Kala azar

Autoimmune causes

- Systemic onset Juvenile Rheumatoid Arthritis, Kawasaki disease, Systemic lupus erythematosus, Inflammatory bowel disease, Polyarteritis nodosa

Malignant causes

- Leukemia, Lymphoma, Langer Han Cell histiocytosis

APPROACH TO FEVER OF UNKNOWN ORIGIN

The first step is to identify sick patients who need stabilization and urgent referral to a tertiary care center. Subsequently, all attempts should be made to reach an etiologic diagnosis. A detailed history is of paramount importance. History should include:

- Whether and how fever was documented (it is not uncommon to find children with history of prolonged fever not to have fever documented by a thermometer)
- Duration and pattern of fever (distinguish from recurrent fever)
- Symptoms referable to all organ systems, weight loss
- History of recurrent infections, oral thrush [human immunodeficiency virus (HIV) infection]
- History of joint pain, rash, photosensitivity (autoimmune disease)
- History of contact with tuberculosis and animals (brucellosis)
- Travel to endemic zones (kala azar)
- Drug history particularly anticholinergics (drug fever).

History is followed by a complete physical examination. Documentation of fever is necessary, followed by assessment of general activity, nutritional status, and vitals. A head to toe examination, after removing all clothes, is vital. The physical examination should be repeated on daily basis as new findings may emerge that provide a clue to the etiology. One must keep Kawasaki disease (though a relatively uncommon illness) in mind as here diagnosis before the 10th day of fever is crucial to prevent coronary complications.

INVESTIGATIONS AND MANAGEMENT

Preliminary investigations, which should be repeated in all patients with FUO (even if done earlier) include complete blood counts (CBC), peripheral smear (PS), malarial parasite, ESR, blood cultures, Widal test, chest X-ray, tuberculin test, urinalysis and culture, hepatic transaminases, and abdominal

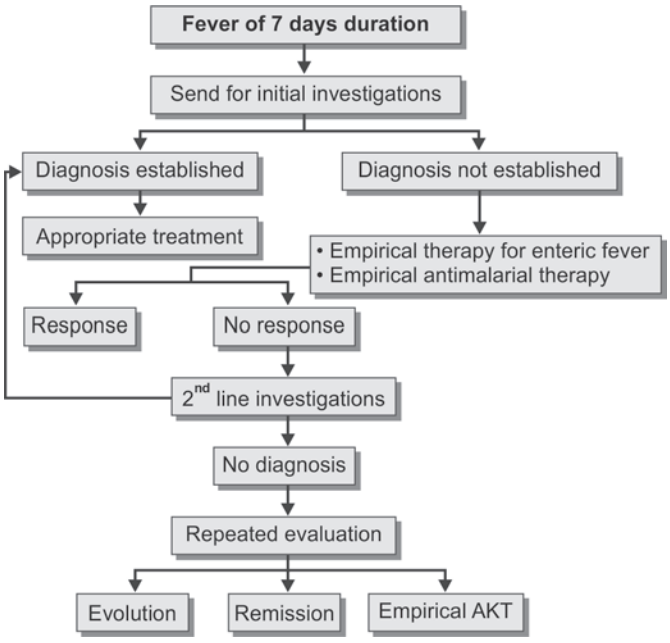
ultrasound. The CBC and PS will help in the differential diagnosis. If the counts are low or normal, enteric fever, malaria and viral infections are a possibility. A high white blood cell (WBC) count with neutrophilia indicates a bacterial infection/pus collection, possible Kawasaki's disease, systemic onset JRA or even tuberculosis. A high WBC count with lymphocytosis suggests a mononucleosis syndrome or a hematologic malignancy. Absolute eosinopenia is indicative of an acute bacterial/viral infection particularly enteric fever. A low platelet count points toward malaria, enteric fever or a malignancy whereas a very high platelet count is present in Kawasaki's disease or systemic onset JRA. The usefulness of an erythrocyte sedimentation rate (ESR) as an investigative modality in prolonged fever is often debated. It is not a sensitive or specific investigation. Studies show that one-third of pulmonary tuberculosis had a normal ESR. Exceptionally, a very high ESR is indicative of an autoimmune process such as Kawasaki disease or JRA. The C-reactive protein (CRP) parallels ESR and may not help to differentiate a viral from bacterial etiology. However, a very high CRP points to a bacterial infection or autoimmune disease. Evaluation for malarial parasite is a must. Repeated thick smears are gold standard for diagnosis and may be sent irrespective of the fever spike. However, in a setting where reliable microscopy is not available, the malarial antigen tests may be used; the parasite lactate dehydrogenase tests score over the histidine rich protein 2 based tests. The blood culture is a crucial investigation in this setting as enteric fever is the most common differential. Though, it should be sent prior to starting antibiotics, the yield is fair for *Salmonella* even if the patient is on antibiotics. If infective endocarditis is suspected then three blood cultures at 30 minutes interval should be sent and if brucellosis is being considered as a differential then the lab should be informed so that the cultures are incubated for longer and not discarded within 5 days. Widal may be sent as it is the 7th day of fever, but the results should be carefully interpreted. It may be considered positive if both TO and TH/TA titers are 1: 120/ 1: 160 or more. Either TO/TH being positive or titers of 1: 40/80 should be considered as false positive. Similarly a negative Widal does not rule out enteric especially if the patient has been on antibiotics. Typhidot M or Tubex tests do not offer any advantage over the Widal and are not routinely recommended. Liver enzymes both aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) should be assayed as these are often elevated in malaria, enteric, infectious mononucleosis, and brucellosis; SGOT being higher than SGPT. Urinary tract infection is a diagnostic possibility and hence urine routine is mandatory. Features of urinary tract infection include presence of one or more of the following: more than 10 pus cells/hpf of centrifuged urine, positive leukocyte esterase, positive nitrite tests, and presence of bacteria on the Gram stain. If the urine routine is suggestive of a urinary tract infection (UTI) then urine culture should be sent before starting antibiotics. This is to confirm the diagnosis and also to know the antibiotic susceptibility of the isolate. A chest X-ray should also be done to pick up pneumonia or features of pulmonary tuberculosis. An ultrasonography abdomen with pelvis is recommended as an initial investigation as it helps in detecting a liver abscess, gall bladder wall thickening and sludge (often seen in enteric fever), pyelonephritis, and retroperitoneal adenopathy. Non-specific mesenteric lymphadenopathy is a common finding and usually merits no consideration. The author does not recommend doing a tuberculin test at this point if there is no clinical or radiologic suspicion of tuberculosis and unless more common causes such as enteric are ruled out. This is because a positive tuberculin test at this juncture may be indicative of latent tuberculosis infection and may not be causally associated with the fever.

If a diagnosis is established on the basis of the above approach, appropriate treatment should be instituted. If no diagnosis is made, clinical reassessment and further investigations are merited. While second line investigations are being planned and executed, treatment with intravenous ceftriaxone may be considered as enteric fever is an important cause of FUO in our country, especially in those cases with negative clinical/preliminary investigations (Algorithm 1).

Second-line investigations include HIV enzyme-linked immunosorbent assay, contrast enhanced computed tomography of chest and abdomen, bone marrow histology and cultures, 2D echocardiogram, complement level, antinuclear and rheumatoid factors, tissue biopsies if indicated. Other serologic tests that may be done include brucella serology, hepatitis B surface antigen, Paul Bunnel/Monospot test/immunoglobulin M viral capsid antigen (VCA) for infectious mononucleosis. Tests which are of no clinical value include serology and polymerase chain reaction in blood for *Mycobacterium tuberculosis* or other organisms.

ALGORITHM 1

Approach to a child with prolonged fever



AKT, empirical antitubercular therapy?

Clinical Pearls

- Infections particularly tuberculosis is the commonest cause for fever of unknown origin in India
- A high index of suspicion should be kept for diagnosis of Kawasaki disease
- Empirical therapy should be avoided as far as possible
- The diagnosis often evolves with time and patience is the key.

KEY POINTS

- ☞ A practical definition of fever of unknown origin (FUO) is fever for which a cause cannot be established despite 1 week of investigations
- ☞ A detailed history and physical examination is most crucial. This should include travel history, contact with tuberculosis and animals
- ☞ The primary objective is to identify sick children and prompt referral to an appropriate center
- ☞ Kawasaki disease should always be considered as a possibility in young children
- ☞ Investigative approach should be stepwise starting with basic investigations and proceeding to more complex ones.
- ☞ Tuberculosis serology has no place in the diagnosis of FUO
- ☞ With patience and application of methods, it should be possible to make a diagnosis of the etiology of FUO in most cases
- ☞ In a small number of cases, it may not be possible to arrive at the etiologic diagnosis. In such cases, periodic reassessments should be done as the disease may finally surface (e.g., lymphoma, systemic onset juvenile eheumatoid artheits). Some cases of FUO may self-resolve over time
- ☞ Empirical use of steroids should be avoided.

SUGGESTED READINGS

1. Campbell J. Fever of unknown origin in a previously healthy child. Semin Pediatr Infect Dis. 2002;13:64-6.
2. Edwards K. Fever: From FUO to PFAPA to recurrent or persistent. Program and abstracts from the American Academy of Pediatrics National Conference and Exhibition; October 9-13, 2004; San Francisco, California. Session S375.
3. Miller L, Sisson B, Tucker L, Schaller J. Prolonged fevers of unknown origin in children: patterns of presentation and outcome. J Pediatr. 1996;12:419-23.
4. Miller ML, Szer I, Yogev R, Bernstein B. Fever of unknown origin. Pediatr Clin North Am. 1995;42:999-1015.
5. Steele R. Fever of unknown origin. A time for patience with your patients. Clin Pediatr. 2000;39:719-20.

CHAPTER 57

A Mass in the Abdomen: The Way to Diagnosis

Gauri Kapoor

INTRODUCTION

The identification of an abdominal mass in a neonate or child is a cause for concern because of the possibility of malignant disease. In addition, even benign conditions can be serious and warrant prompt evaluation and treatment. Hence, the pediatrician needs to be wary of these masses and give them urgent attention.

Although abdominal masses could be any one of the following:

- Fluid
- Fat
- Flatus
- Solid mass.

For the purpose of this chapter we will focus on solid abdominal masses.

PRESENTATION

Children with abdominal masses may be asymptomatic or symptomatic at diagnosis as shown in box 1. The asymptomatic cases may be incidentally picked up on a routine prenatal ultrasound or detected by a family member or alert pediatrician during an immunization visit. The general presentation varies depending on the underlying pathology of the abdominal mass. Patients can present with difficulty with urination or defecation if the mass physically obstructs the gastrointestinal (GI) or genitourinary (GU) tract. Patients presenting with constitutional symptoms such as fever and weight loss with an abdominal mass are more likely to be suffering from a malignant condition. Neuroblastoma and Wilms' tumor are two conditions pediatricians must be vigilant about as they are the two malignant tumors in children where abdominal mass is commonly the initial presentation.

Although it is imperative that a child be referred quickly to the appropriate specialist (e.g., pediatric oncologist, pediatric surgeon, nephrologist, gastroenterologist, gynecologist), evaluation by the pediatrician is of great value in deciding on initial management and in making the most appropriate referral. The evaluation of a child with an abdominal mass involves a number of possibilities and depends to some extent on the age and sex of the patient, the location of the mass, and the presence or absence of other potentially related signs and symptoms, as well as features of the physical examination. Determination of the organ or tissue of origin of the mass can narrow down the diagnostic possibilities considerably. Thus, a completion of a careful history and physical examination, baseline laboratory studies, and limited diagnostic imaging studies can provide sufficient information to determine the diagnosis or to choose the appropriate subspecialist and counsel the family.

Box 1: Presentation of abdominal mass

Asymptomatic

- Incidentally detected
- Prenatal ultrasound
- Immunization visit—alert pediatrician

Symptomatic

- Abdominal distension (right upper quadrant, epigastric mass)
- Respiratory distress
- Weight loss, fever, and anorexia
- Anemia, thrombocytosis, and leukocytosis
- Congestive heart failure, hydramnios, fetal hydrops
- Bowel obstruction, urinary retention

Clues to diagnosis based on:

- Age and sex
- Location of the mass
- Organ of origin
- Signs and symptoms
- Examination findings
- Investigative workup (limited).

Some of the common conditions that might produce an abdominal mass in a child are listed in table 1 and are categorized by the organ of origin. Abdominal masses in the

TABLE 1: Differential diagnosis based on organ of origin in the non-neonatal age group

Organ	Malignant disease	Nonmalignant disease
Adrenal	• Adrenal carcinoma • Neuroblastoma • Pheochromocytoma	• Adrenal adenoma • Adrenal hemorrhage
Gallbladder	• Leiomyosarcoma	• Choledochal cyst • Gallbladder obstruction • Hydrops (e.g., leptospirosis)
Gastrointestinal tract	• Leiomyosarcoma • Non-Hodgkin lymphoma	• Appendiceal abscess • Intestinal duplication • Fecal impaction • Meckel's diverticulum
Kidney	• Lymphomatous nephromegaly • Renal cell carcinoma • Renal neuroblastoma • Wilms' tumor	• Hydronephrosis • Multicystic kidney • Polycystic kidney • Mesoblastic nephroma • Renal vein thrombosis • Hamartoma
Liver	• Hepatoblastoma • Hepatocellular carcinoma • Embryonal sarcoma • Liver metastases • Mesenchymoma	• Focal nodular hyperplasia • Hepatitis • Liver abscess • Storage disease
Lower genitourinary tract	• Ovarian germ cell tumor • Rhabdomyosarcoma of bladder • Rhabdomyosarcoma of prostate	• Bladder obstruction • Ovarian cyst • Hydrocolpos
Spleen	• Acute or chronic leukemia • Histiocytosis • Hodgkin lymphoma • Non-Hodgkin lymphoma	• Congestive splenomegaly • Histiocytosis • Mononucleosis • Portal hypertension • Storage disease
Miscellaneous	• Hodgkin lymphoma • Non-Hodgkin lymphoma • Pelvic neuroblastoma • Retroperitoneal neuroblastoma • Retroperitoneal rhabdomyosarcoma • Retroperitoneal germ cell tumor	• Teratoma • Abdominal hernia • Pyloric stenosis • Omental or mesenteric cyst

neonatal age group are often benign as shown in table 2, and will be further discussed in the section on age. Not all of these possibilities need be considered in every patient; many can be eliminated on the basis of the age and sex of the patient, the location and type of mass, and features of the history or physical examination.

TABLE 2: Common abdominal masses in the newborn

Masses	Frequency
Retroperitoneal masses • Polycystic kidneys, hydronephrosis, dysplastic kidneys, neoplasms, other	65%
Gastrointestinal masses • Things that cause obstruction, hepatic masses, other	25%
Genitosacral masses • Teratomas, congenital genital anomalies, ovarian cysts, other	10%

The differential for an abdominal mass can be extensive and quite daunting, as it incorporates many systems including the GI, GU, and endocrine system. An organized approach to abdominal masses includes thinking about possible etiologies based on the location of the mass with regards to the underlining abdominal anatomy as well as discerning likely pathologies based on the age of the patient and associated symptoms or signs.

Clinical Pearl

- Most abdominal masses in neonates are benign unless they are solid.

HISTORY

When attempting to diagnose an abdominal mass, a proper history with a focused physical exam is necessary to direct you to the proper diagnostic tests to order, or the right specialist to refer too (i.e., pediatric oncologist, surgeon, gastroenterologist, nephrologists, or gynecologist).

Age

The age of the patient is very important when approaching abdominal masses in the pediatric population and should be the first question asked. Malignant tumors are uncommon in the newborn period. These conditions are often related to the kidney. Posterior urethral valves are manifested during the newborn period by a very large urinary bladder. Hydronephrosis secondary to distal obstruction may result in a unilateral or bilateral flank mass. A multicystic kidney also may be found at this time. Other considerations include developmental abnormalities, such as duplications or cysts of abdominal organs. Amongst the malignant conditions, neuroblastoma and extragonadal germ cell tumors are most common, followed by hepatoblastoma and Wilms' tumor. Moreover, of the malignant conditions, children younger than 2 years are more likely to suffer from neuroblastoma and hepatoblastoma, whereas older children more frequently have Wilms' tumor, hepatocellular carcinoma, GU tract tumors, and germ line tumors.

Other important points to be noted in history are detailed in table 3.

TABLE 3: History: special points

History	Clue
Age of the child	Neonates (benign), children (malignant)
How long has it been there	Months to years (benign)
How fast is it growing	Faster growing (malignant)
Pressure symptoms	Constipation, urine retention
Constitutional symptoms	Fever, weight loss, pallor, bruising (infection vs. marrow infiltrative)
Watery diarrhea	Neuroblastoma secreting vasoactive intestinal peptide
Hematuria	Renal pathology (Wilms' tumor)
Opsomyoclonus	Neuroblastoma
Periorbital ecchymosis, ptosis	Neuroblastoma (Raccoon eye)
Acute abdomen	Intussusception (benign or ileocecal lymphoma)
Cushing's syndrome	Adrenal adenoma, adrenocortical carcinoma
Genetic syndrome or inherited predisposition	Familial adenomatosis polyposis, Gardner's, Beckwith-Weidemann (Wilms', hepatoblastoma, adrenocortical carcinoma), aniridia (Wilms'), hemihypertrophy (Wilms')

Clinical Pearl

- Abdominal masses in older children are usually malignant and need prompt evaluation.

EXAMINATION

The importance of a thorough physical examination with vitals (including temperature and blood pressure) cannot be overemphasized. Table 4 highlights the salient features to look for in a child with abdominal mass. One must be patient as physical examination in young children can be a difficult proposition. Table 5 lists some of the important clinical findings to look for during examination.

TABLE 4: Points to be considered during examination

System	Clinical features
General appearance	Well, ill, cachexic, anxious, in pain
Weight and height	Plot on growth chart
Vitals	Include blood pressure, temperature
Skin	Jaundice, café au lait, nevi, freckles, skin nodules, petechiae, purpura
Head, neck, eyes, nose throat	Pallor, aniridia, periorbital ecchymosis, ptosis, lymphadenopathy
Abdomen	Details of mass, quadrant, consistency, tenderness, mobility, bruit, veins over it, possible organ of origin, bowel sounds
Cardiovascular	Murmurs
Respiratory	Wheeze, superior vena cava syndrome
Genitalia	Normal/abnormal
Others	Stigmata of congenital syndrome (e.g., hemihypertrophy)

TABLE 5: Laboratory investigations

Test	Indication/clues
Complete blood count with differential	• Anemia, neutropenia, or thrombocytopenia can indicate bone marrow infiltration
Bone marrow biopsy and/or aspiration	• Indicated if one or more bone marrow cell lines are compromised
Chemistry panel electrolytes uric acid, lactate dehydrogenase	• Electrolyte abnormality indicates pathology with the kidney or tumor lysis syndrome • Elevated uric acid or lactate dehydrogenase suggest a high grade malignancy
Urinalysis	• Hematuria or proteinuria suggest renal involvement
Urinary homovanillic acid and vanillylmandelic acid	• Elevated levels indicate neuroblastoma or pheochromocytoma
Tumor markers: serum B human chorionic gonadotropin, α-fetoprotein	• Elevated levels may occur in teratomas, liver tumors, and germ cell tumors

INVESTIGATIONS

All children with abdominal masses should have a complete blood count and peripheral smear examination as it may throw up important clues to diagnosis. Further investigations would include baseline chemistries and specific tumor markers on the basis of the clinical differential diagnoses (Table 5).

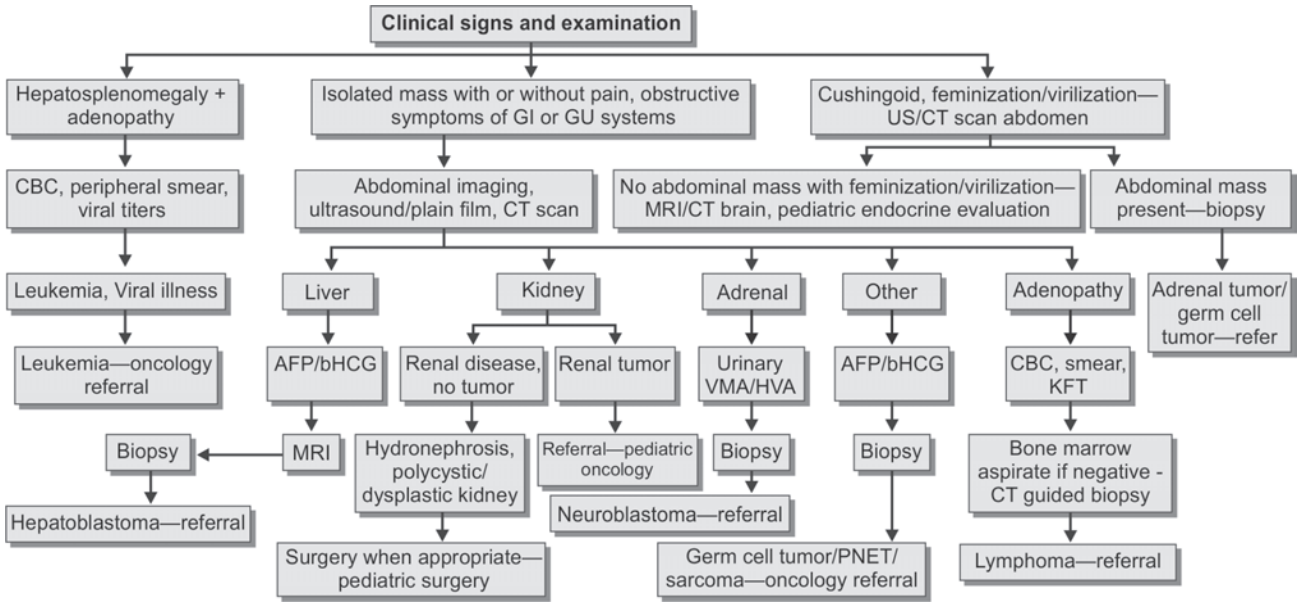
IMAGING

An abdominal mass in children is often first assessed by a plain abdominal radiograph to rule out GI obstruction. Next, an ultrasound study is helpful and can be done without sedation. It is noninvasive, easily available and fairly inexpensive and is sometimes the first investigation done for an abdominal mass. It can usually identify the organ of origin of the mass, such as the kidney, adrenal gland or liver, etc. and helps differentiate solid from cystic masses. Further information is provided in table 6.

An algorithmic approach to evaluation of a child with abdominal mass is depicted in algorithm 1. Once a malignancy is suspected it is recommended that the child be referred to a pediatric oncology unit, since early diagnosis of pediatric cancers are associated with very good cure rates. Delayed diagnosis not only reduces the chances of cure but is also associated with higher complication rate. Parents should, therefore, be appropriately counseled at this time and the pediatrician has a very important role to play in bridging the gap between the family and the oncology center.

ALGORITHM 1

Algorithmic approach to diagnosis of an abdominal mass in a child



GI, gastrointestinal; GU, genitourinary; US, ultrasound; CT, computed tomography; CBC, complete blood count; AFP, alpha-fetoprotein; β-HCG, β human chorionic gonadotropin; VMA, vanillylmandelic acid; HVA, homovanillic acid; KFT, kidney function test; PNET, primitive neuroectodermal tumor.

TABLE 6: Imaging studies

Test	Indication/clue
Plain abdominal X-ray	• First imaging study to be ordered • Helps determine the location and density of the abdominal mass. • Multiple air fluid levels or absence of air in the rectum—indicate obstruction • Calcification may indicate a neuroblastoma, teratomas, kidney stones, or biliary stones
Ultrasound	• Inexpensive and safe modality • Useful for discerning between solid versus cystic mass
Computed tomography scan	• Used to attain more specific anatomic information about the abdominal mass • CT scan can be used to determine invasion of the malignant lesion to adjacent structures
Magnetic resonance imaging	• Used for greater anatomic detai • Specially for imaging of brain and spine in patients presenting with neurologic deficits

KEY POINTS

- ☞ Abdominal masses in children are a cause for concern because of the possibility of malignant disease and need prompt evaluation
- ☞ Most abdominal masses in neonates are benign unless they are solid
- ☞ Age of the patient, along with history and examination findings provide important clues to the possible organ of origin and underlying pathology
- ☞ Neuroblastoma and Wilms' tumor are the two most common malignant conditions that present as abdominal masses in young children
- ☞ The pediatrician plays an important role in early diagnosis, prompt evaluation, and appropriate referral
- ☞ Most childhood cancers have good cure rates if diagnosed in time and treated properly.

SUGGESTED READINGS

1. Broecker B. Non-Wilms' renal tumors in children. Urol Clin North Am. 2000;27(3):463-9, ix.
2. Castleberry RP. Biology and treatment of neuroblastoma. Pediatr Clin North Am. 1997;44(4):919-37.
3. Golden CB, Feusner JH. Malignant abdominal masses in children: quick guide to evaluation and diagnosis. Pediatr Clin North Am. 2002,49(6);1369-92.
4. Graf N, Tournade MF, deKraker J. The role of preoperative chemotherapy in the management of Wilms tumor: The SIOP Studies. Urol Clin North Am. 2000;27(3):443-54.
5. Groff DB. Pelvic neoplasms in children. J Surg Oncol. 2000;77(1):65-71.
6. Grossman H. Evaluating common intra-abdominal masses in children - a systematic roentgenographic approach. CA Cancer J Clin. 1976;26(4);219-35.
7. Neville HL, Ritchey ML. Wilms' tumor, overview of the National Wilms Tumor Study Group results. Urol Clin North Am. 2000;27(3):435-42.
8. Pappo AS, Shapiro DN, Crist WM. Rhabdomyosarcoma. Biology and treatment. Pediatr Clin North Am. 1997;44(4):953-72.
9. Pfeifer SM, Gosman GG. Evaluation of adnexal masses in adolescents. Pediatr Clin North Am. 1999;46(3):573-92.
10. Rahhal RM, Eddine AC, Bishop WP. A Child with an Abdominal Mass. Pediatric Rounds. 2006;37-42.
11. Schteingart DE. Management approaches to adrenal incidentalomas. Endocrinol Metab Clin North Am. 2000;29(1):127-39.
12. Stringer MD. Liver tumors. Semin Pediatr Surg. 2000;9(4):196-208.

CHAPTER 58

Approach to a Child with Persistent Anemia

Mamta V Manglani

INTRODUCTION

Anemia in children is the most common cause of referral to a pediatric hematology-oncology clinic in our country. It reflects the disturbance of the dynamic balance between production and destruction of erythrocytes and hemoglobin. In normal subjects, the average life span of red cell, i.e., time between the release of red cell from bone marrow and its disappearance from circulation is between 100 and 120 days. Approximately 1% of the red cells are destroyed each day and replaced by new cells released from marrow. Any disruption of this balance, such as reduced production or increased destruction, leads to anemia.

DEFINITION OF ANEMIA

Anemia is defined as a reduction in the red cell mass and/or reduction in hemoglobin or hematocrit. A child is said to be anemic when the hemoglobin and/or hematocrit is two standard deviations below mean for normal population. This results in 2.5% of normal population being classified as anemic. On the other hand, some of the anemic individuals would be classified as normal and these would only be recognized after a response to treatment.

Table 1 gives the normal values (normal mean, lower limit) of various hematological parameters at different age groups.

The initial diagnostic approach to the anemic patient should include detailed history, physical examination, and screening laboratory tests followed by specific laboratory tests as indicated to confirm the diagnosis.

HISTORY IN THE DIAGNOSIS OF ANEMIA

Age

Nutritional anemia is uncommon below the age of 6 months (especially in term breastfed infants), except in preterm infants. Iron deficiency anemia (IDA) is most common in the age group of 6 months to 3 years and 11–17 years (adolescent) age group. Dietary habits and food fads may be responsible for anemia in adolescent period. Development of anemia is almost always insidious in children and may go unnoticed till hemoglobin concentration drops to as low as 3–4 g/dL, particularly in nutritional anemia. Hemoglobinopathies (thalassemia major) commonly present during 6–18 months of age and rarely before that age.

Anemia manifesting in the neonatal period is generally as a result of blood loss, including fetomaternal hemorrhage,

TABLE 1: Normal blood values at different age groups

Age	Hb g/dL	RBC million/μL	HCT %	MCV (μ^3)	MCH (pg)	MCHC (%)	Reticulocyte (%)
1 day	18.0	5.14	61	119	36.0	31.6	3.2
4 weeks	14.2	4.0	43	106	35.5	33.5	0.6
1 year	11.6	4.6	35	77	25.0	33.0	0.9
10–12 years	13.0	4.8	39	80	27.0	33.0	1.0
Adult men	16.0	5.4	47	87	29.0	34.0	1.0
Adult women	14.0	4.8	42	87	29.0	34.0	1.0

Hb, hemoglobin; RBC, red blood cell; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

fetofetal hemorrhage and occult hemorrhage, or due to hemolysis as a result of isoimmunization, uncommonly glucose-6-phosphate dehydrogenase (G6PD) deficiency, spherocytosis or due to congenital infections.

Clinical Pearls

- A neonate with hemoglobin of 11 g/dL is severely anemic, whereas a 1-year-old infant with same hemoglobin is normal
- When interpreting presence or severity of anemia, age plays an important role.

Gender/Family History/Inheritance

Though nutritional anemia is more common among females during adulthood, the incidence is equal in both genders during childhood. Certain inherited anemias are transmitted as X-linked recessive and hence are commonly seen in male children. This includes G6PD deficiency; hence similar history of anemia should be enquired in other male siblings, maternal male cousins, maternal uncles, and maternal grandfather. Hereditary spherocytosis is an autosomal dominant disorder, whereas hemoglobinopathies like thalassemia, sickle cell anemia, etc. are inherited as autosomal recessive conditions. It is important to enquire about family history of anemia, jaundice, gallstones, splenectomy, etc. in the other members of the family. A history of consanguineous marriage is also helpful in recessive conditions. Hence a detail pedigree chart including the family members, who have expired, should be obtained.

Community

Certain types of anemias are known to occur in particular communities. G6PD deficiency is commonly seen in Parsees, Punjabis, and Sindhis, whereas thalassemia is common amongst Sindhis, Punjabis, Lohanas, Bhanushalis, Kathiawadis, Mahars, Agris, Bauddhas, Kolis, Lingayat, Reddys, and Gaud communities. Sickle cell anemia is more commonly seen in hilly and tribal communities especially around Nagpur, Vidharbha, Andhra Pradesh, Orissa, etc. hemoglobin E is seen more in Eastern India among Bengalis and hemoglobin D in Punjabis and North Indians.

Dietary History

Nutritional anemias are associated with poor dietary intake of iron, folic acid, proteins, and vitamin E in the diet. Breast milk contains lesser quantities of iron; however, it has a very high bioavailability. Hence, IDA is uncommon in exclusively breastfed infants before 4–6 months of age. Inadequate iron containing weaning foods and/or predominantly milk-based diet beyond 4–6 months of age contribute significantly to occurrence of IDA in late infancy. History of pica may be present as a cause or effect of IDA. Lead toxicity should be ruled out in such children if there is a history of exposure to lead directly or through parents' occupation. Megaloblastic anemia due to folate deficiency may be seen in children fed predominantly goat's milk. Nutritional anemias are commonly seen in adolescent females due to various food fads.

History of Drug Ingestion

Certain drugs cause hypoplasia of the bone marrow. Some of these are chloramphenicol, nonsteroidal anti-inflammatory drugs, anticonvulsants, antihistaminics, sulfonamides, heavy metals, etc. Oxidant-induced hemolytic anemia may occur in people having G6PD deficiency (sulfonamides, antimalarials such as primaquine, quinine and mefloquine, vitamin C and K, furazolidone, nalidixic acid, etc.). Penicillins and cephalosporins, α-methyldopa, stibophen, etc. are known to precipitate autoimmune hemolytic anemias. Certain drugs can cause megaloblastic anemias due to altered metabolism of folate and vitamin B12. These include phenytoin, folate antagonists, etc.

Infections and Infestations

History of intrauterine infections (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Simplex and Other Agents) should be elicited when dealing with neonatal anemia, especially when associated with hepatosplenomegaly, purpura, etc. Hepatitis-induced aplasia and infection-induced pure red cell aplasia or hemolytic anemia (malaria) need to be kept in mind. Anemia also may be associated with chronic infections like tuberculosis, tropical sprue, kala-azar, or with chronic inflammations like collagen disorders, malignancies, etc. Anemia due to worms, especially hookworms, is common in developing countries.

Diarrhea

Malabsorption syndromes due to varied causes could be a cause for nonresponding nutritional anemias.

EXAMINATION FINDINGS AS A CLUE TO THE DIAGNOSIS OF ANEMIA

Skin

Hyperpigmentation is common with Fanconi's anemia, dyskeratosis congenita, megaloblastic anemia, etc. (Fig. 1). Petechiae and purpura may be present in aplastic anemia, leukemias, hemolytic uremic syndrome, etc. Leg ulcers are seen in chronic congenital hemolytic anemias such as HbS and HbC disease and occasionally in homozygous thalassemia (Fig. 2). Cavernous hemangiomas may be associated with microangiopathic hemolytic anemia. Jaundice suggests hemolytic anemias, hepatitis-induced aplasia.

Facies

Presence of hemolytic facies is seen in congenital hemolytic anemias such as thalassemia major, sickle cell anemia and occasionally in severe chronic IDA (Fig. 3).

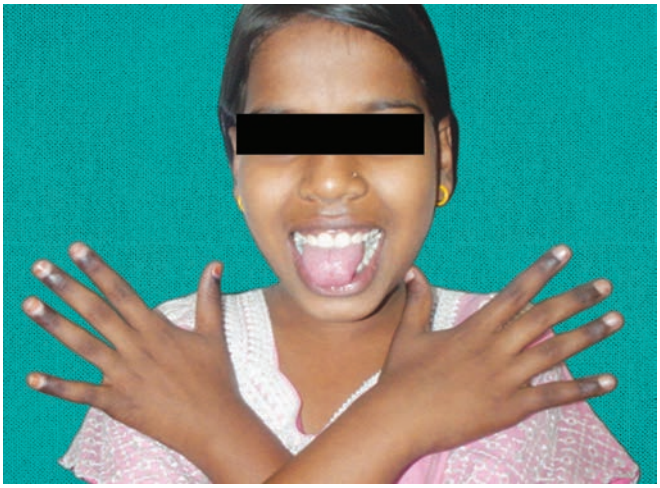


Fig. 1: Hyperpigmentation over distal phalanges in megaloblastic anemia

Eyes

Fanconi's anemia may have microphthalmia and microcornea, besides microcephaly (Fig. 4). Cataracts may suggest galactosemia with hemolytic anemia in the neonatal period. Vitreous hemorrhages are seen in sickle cell disease and retinal hemorrhages may occur in severe chronic anemias. Edema of the eyelids should make one suspect infectious mononucleosis, or exudative enteropathy with iron deficiency. Visual loss may be one of the features of osteopetrosis. Blue sclera is often a feature of IDA (Fig. 5).

Hands and Nails

Thumb anomalies suggest constitutional hypoplastic anemias (Diamond-Blackfan anemia, Fanconi's anemia) (Figs 6 and 7). If associated with radial anomalies, it is more likely to be Fanconi's anemia. Presence of platynychia and/or koilonychias (Fig. 8) are pathognomonic of IDA.

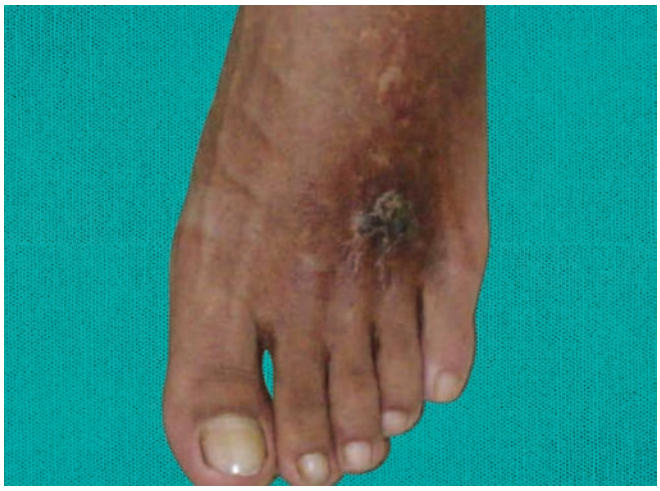


Fig. 2: Leg ulcer in an adolescent with thalassemia intermedia

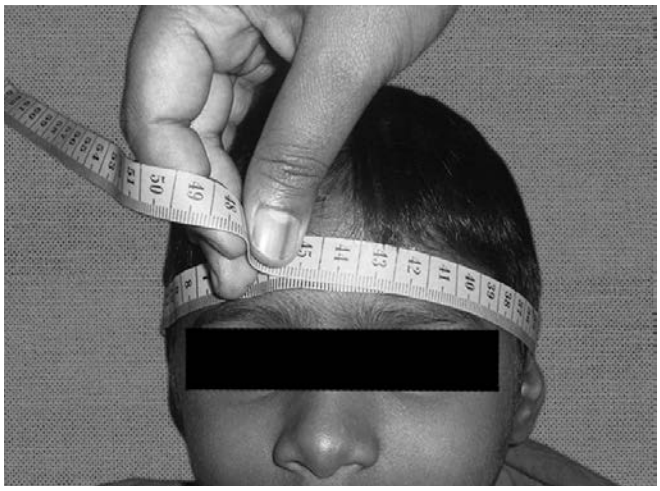


Fig. 4: Microcephaly in Fanconi's anemia

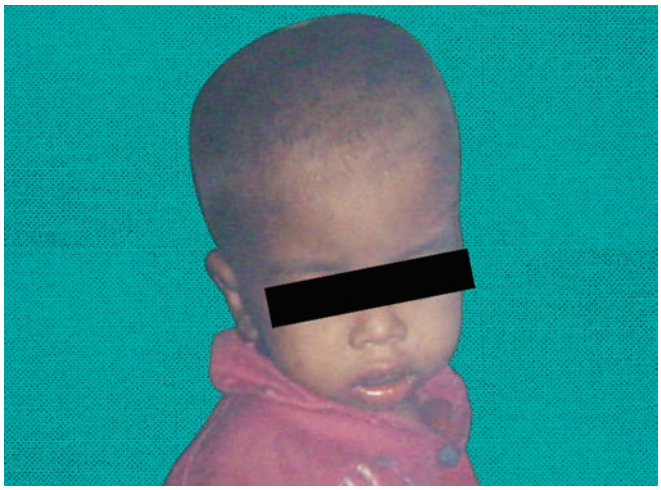


Fig. 3: Hemolytic facies in a thalassemic child

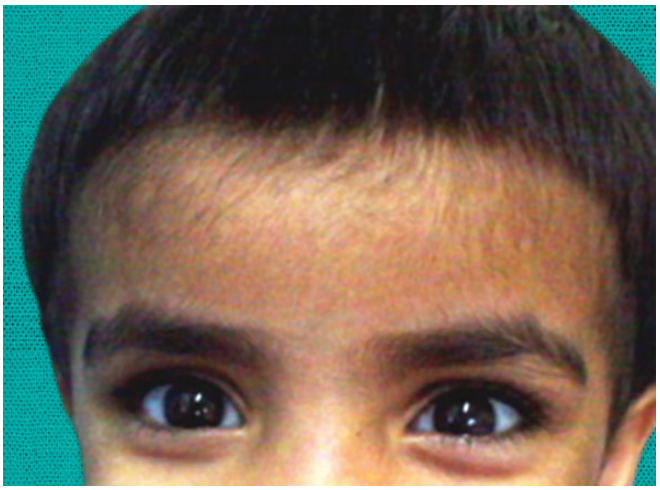


Fig. 5: Blue sclera in a child with iron deficiency anemia

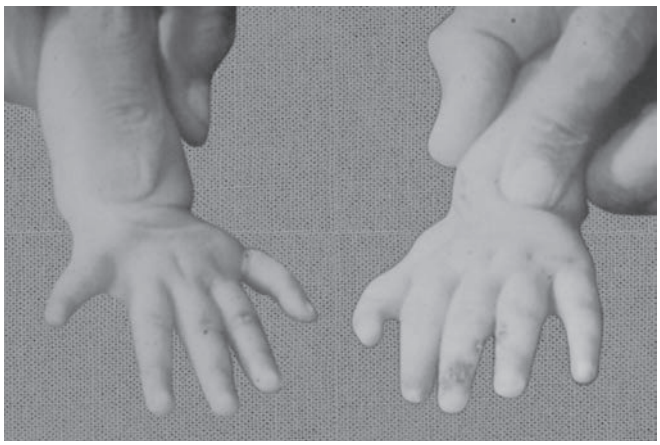


Fig. 6: Ape thumbs in a case of Diamond-Blackfan anemia

Clinical Pearls

- Presence of blue sclera, platonychia or koilonychias, and/or angular stomatitis suggests iron deficiency anaemia
- Iron deficiency anemia is a manifestation and not an etiological diagnosis.

Mouth

Glossitis is seen in vitamin B12, folate, and iron deficiency; angular stomatitis (Fig. 9) and bald tongue are seen in iron deficiency. Occasionally, gum hypertrophy (Fig. 10) may be seen in a patient with acute promyelocytic or acute myelomonocytic leukemia.

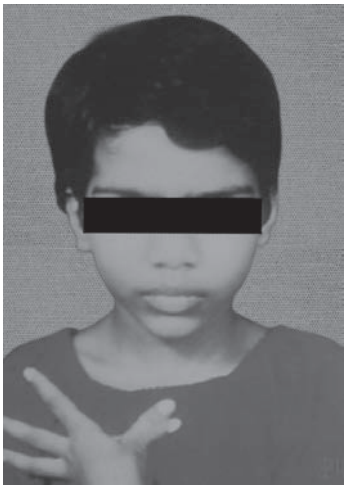


Fig. 7: Thumb anomaly in Fanconi's anemia

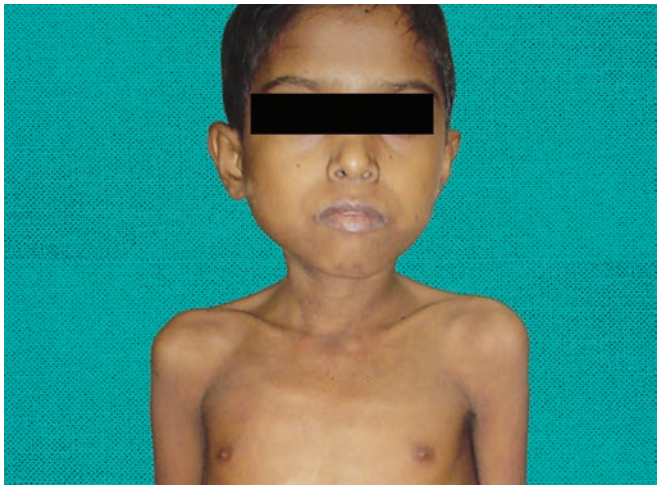


Fig. 9: Angular stomatitis in a case of malnutrition and iron deficiency anemia

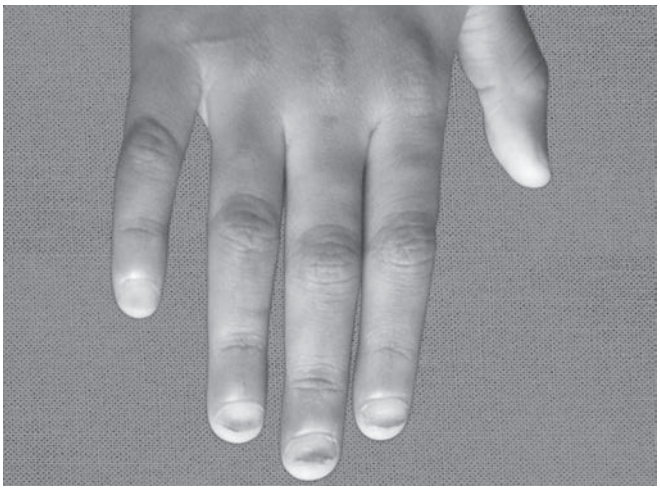


Fig. 8: Koilonychia in a child with iron deficiency anemia

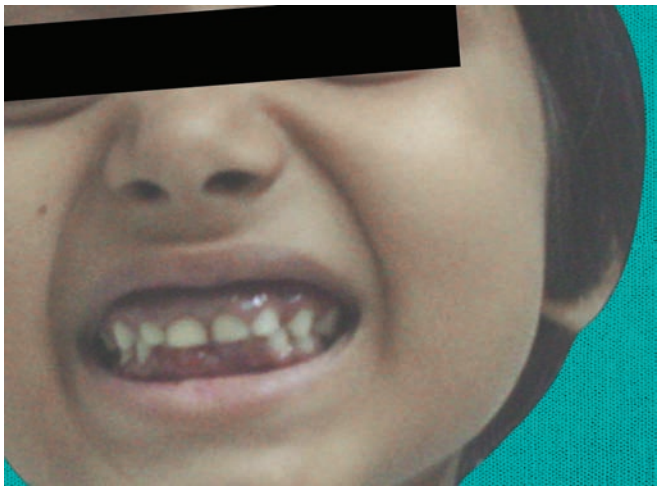


Fig. 10: Gum hypertrophy in a child with acute promyelocytic leukemia

Clinical Pearl

- Presence of lymphadenopathy, gum hypertrophy, and hepatosplenomegaly should prompt exclusion of malignancies especially in presence of affection of other cell lines, i.e., white cells and platelets.

Lymphadenopathy

Lymphadenopathy would prompt one to consider various malignant disorders, such as leukemias, lymphomas, metastatic malignancies such as neuroblastoma, infections such as tuberculosis, infectious mononucleosis, human immunodeficiency virus, cytomegalovirus (CMV), etc. (Fig. 11).

Hepatosplenomegaly

Presence of hepatosplenomegaly almost always rules out hypoplastic anemia except the infiltrative causes of marrow suppression. It suggests hemolytic anemias, the infiltrative causes such as leukemias, osteopetrosis, myelofibrosis, myelodysplasias, etc. (Fig. 12).

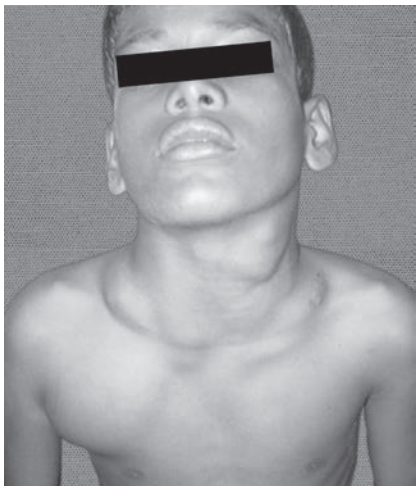


Fig. 11: Lymphadenopathy in a case of lymphoma

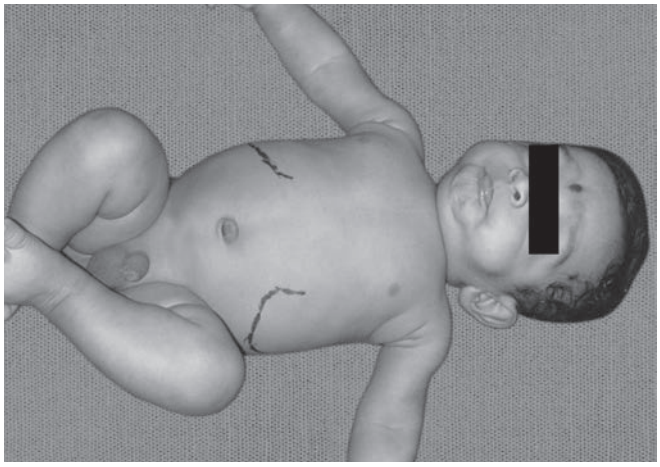


Fig. 12: Anemia and hepatosplenomegaly with malaria

LABORATORY APPROACH TO ANEMIA

The investigations in children with anemia should be done in a phased manner as expensive confirmatory tests may be useless and unnecessary in concluding the cause of anemia, unless done judiciously. Therefore, it is imperative to follow a stepwise testing to get a better yield without spending the patient's money unnecessarily.

Investigations should be done as follows:

- Screening tests
- Definitive diagnostic tests.

Screening Tests

Screening tests include:

- Complete blood count including hematocrit and blood indices
- Reticulocyte count
- Examination of the peripheral smear.

Complete Blood Counts

- Hemoglobin: the severity of anemia can be gauged with the value of hemoglobin
- Hematocrit: it is useful in neonates to diagnose polycythemia. In sickle cell disease, it is important to maintain the hematocrit at 30–35%
- Red cell indices: these include mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW). This helps in typing the anemia.

Based on MCV, MCH, and MCHC, anemias can be classified into three categories to give a morphologic classification. Besides, the RDW further elucidates the cause of anemia. Along with the findings of the peripheral smear findings, most anemias can be categorized completely with a few specific confirmatory tests.

- Microcytic, hypochromic anemia—MCV <80 μ^3, MCH <27 pg, and MCHC <32%
- Macrocytic anemia—MCV >95 μ^3
- Normocytic, normochromic anemia—MCV 80–95 μ^3, MCH 27–32 pg, and MCHC 32–36%.

Red cell distribution width: it is the measure of the degree of anisocytosis. This is calculated from the histogram of MCV and expressed as a coefficient of variation. The normal values are 11.5–14.5%. Along with MCV, it can help categorize anemias further. The relationship of MCV and RDW is given in table 2.

TABLE 2: Relationship of mean corpuscular volume and red cell distribution width

RDW	Low MCV	Normal MCV	High MCV
Normal	Thalassemia trait	Normal Lead poisoning	Aplastic anemia
High	Iron deficiency HbH disease HbS/thalassemia trait	Early IDA Liver disease Mixed nutritional deficiency	Newborns Vitamin B12/folate deficiency

MCV, mean corpuscular volume; RDW, red cell distribution width; IDA, iron deficiency anemia

Hemoglobin distribution width (HDW): it is obtained from the histogram of MCHC and depicts the hemoglobin distribution. Combining MCV, RDW, and HDW can offer better categorization of anemias. However, most automated cell counters presently used in our country do not have the feature of HDW.

Reticulocyte Count

As reticulocytes are the immediate precursors of mature red blood cells (RBCs), their presence in the peripheral blood reflects the marrow activity in response to anemia. Reticulocyte count is expected to be high in children with anemia if they have a responsive marrow. Therefore, one needs to consider whether the reticulocytes have increased proportionate to the degree of anemia. This is done by calculating the corrected reticulocyte count as:

$$\frac{\text{Reticulocyte count} \times \text{Observed HCT}}{\text{Desired HCT}}$$

Example: If the reticulocyte count of a child is 6% and the HCT is 15%, the corrected reticulocyte count would be as follows: $6 \times 15/45 = 2\%$, which is not as high as it seems.

Polychromasia and basophilic stippling on peripheral smear are indirect evidences of reticulocytosis.

Reticulocyte count is increased in hemolysis, hemorrhage, or after starting therapy for nutritional deficiencies. However, it is low or normal in nutritional anemias and it is below 1% in bone marrow suppression.

Clinical Pearls

- Reticulocyte count is a window to the bone marrow and if normal to increased suggests the pathology does not exist in the marrow
- Red blood cell indices along with red cell distribution width and reticulocyte count can help diagnose many of the causes of anemia.

Peripheral Smear Examination

This is the single most important, cost-effective test for anemia. It not only suggests the type of anemia but also gives the clue to the underlying cause and disease. The following morphologic information can be obtained by reviewing a peripheral blood smear:

Red blood cell morphology

- Size:
  - Microcytic: microcytic red cells are smaller than normal (Fig. 13)
  - Macrocytic: macrocytic red cells are larger than normal cells (Fig. 14)
- Shape (poikilocytosis):
  - Spherocytes: these are cells without a central pallor and are seen in hereditary spherocytosis where virtually all red cells are spherocytic, barring milder varieties, where about 30% of cells would be spherocytic. Spherocytes are also seen in autoimmune hemolytic anemias, ABO isoimmunization in the newborn, severe burns, *Clostridium welchii* sepsis, etc. (Fig. 15)
  - Ovalocytes: oval-shaped cells are seen in megaloblastic anemia (macro-ovalocytes), IDA, chronic hemolytic anemias like thalassemia, etc.
  - Elliptocytes: elliptical cells are seen in congenital elliptocytosis where more than 50% of cells will be elliptical and also there will be elongated rod-like cells in addition. Elliptocytes are also seen in thalassemia, myelophthisic anemia, megaloblastic anemia, etc.
  - Helmet cells/schistocytes: broken cells like helmets or caps are seen in microangiopathic hemolytic anemia, uremia, malignant hypertension, disseminated intravascular coagulation (DIC), etc. (Fig. 16)
  - Acanthocytes (spur cell): RBCs with several irregularly spaced large, coarse projections or

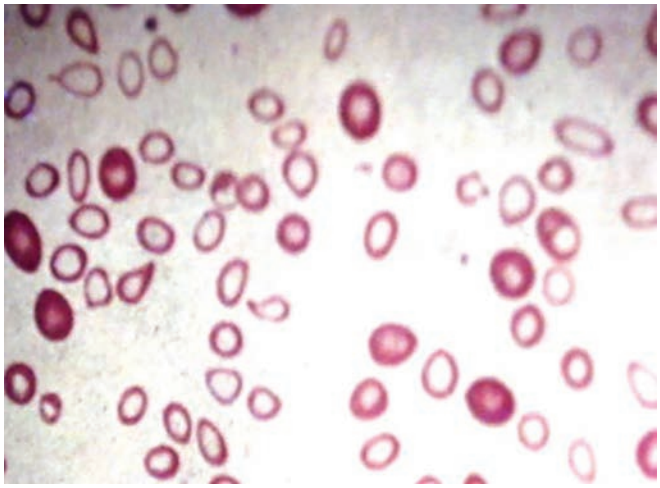


Fig. 13: Microcytic, hypochromic smear in iron deficiency anemia

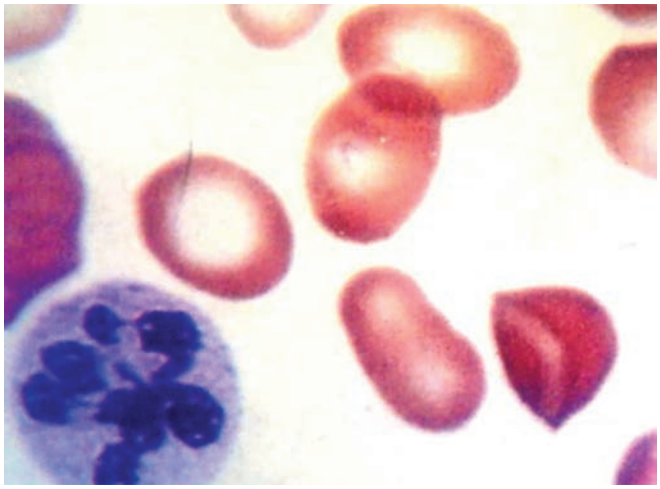


Fig. 14: Macrocytes with macro-ovalocytes and hypersegmented neutrophils in megaloblastic anemia

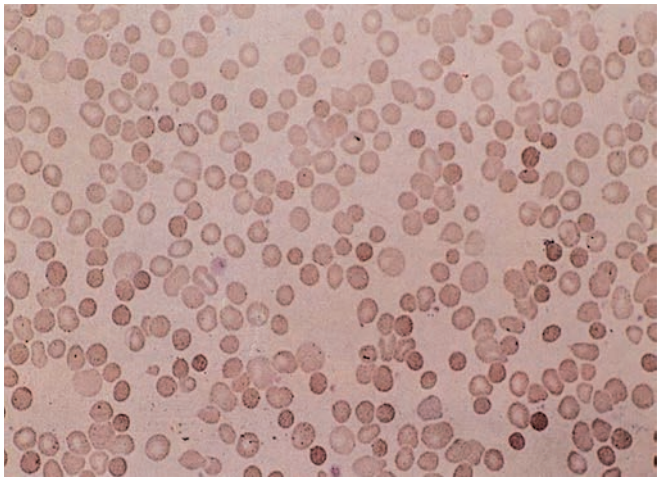


Fig. 15: Spherocytes in a peripheral smear of a child with hereditary spherocytosis

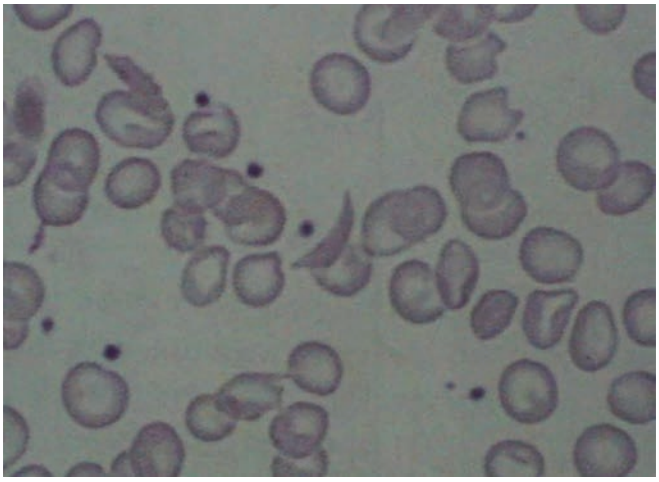


Fig. 17: Shows irreversibly sickled cells in a sickle cell disease

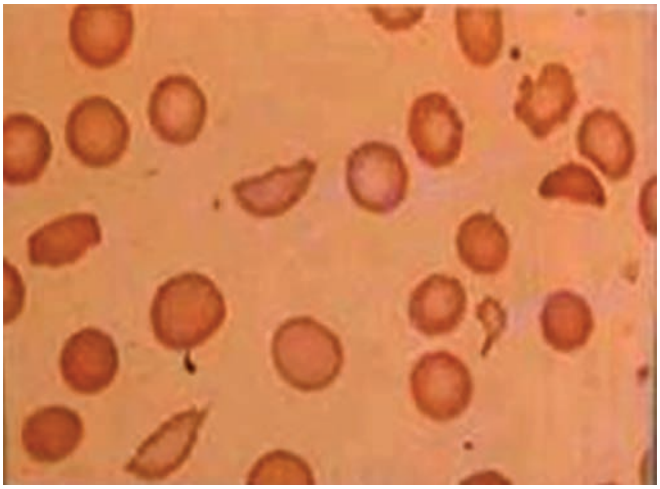


Fig. 16: Broken cells, helmet cells with thrombocytopenia in a case of hemolytic uremic syndrome

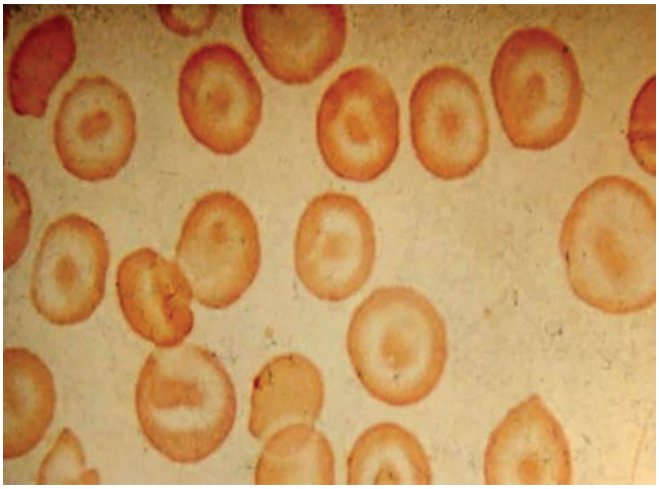


Fig. 18: Target cells in hemoglobinopathies

spicules of varying length and width are seen in abetalipoproteinemia, liver cirrhosis or metastasis, etc.

- Echinocytes: RBCs with regularly spaced, uniform in size, more numerous, and spicules are seen in uremia, PK or phosphoglycerate kinase deficiency, cardiac bypass, burns, etc.
- Tear drop cells: RBCs with a tear drop shape are seen in thalassemia, myelofibrosis, myelophthisic anemia, etc.
- Sickle cells are seen in sickle cell disease and double heterozygous states like HbSC, HbSD, HbS-thalassemia, etc. (Fig. 17)
- Xerocytes: dense, dehydrated, contracted cell seen in congenital xerocytosis
- Leptocytes: normal or large cells with thin membrane
- Target cells: in these cells, hemoglobin is concentrated in the center and in the periphery producing concentric dark light zones which gives a Bull's eye appearance. They are a kind of leptocytes or thin cells in which surface area to volume ratio is high and is out of proportion to its meager Hb content. They are seen in thalassemias, HbC, E, SS diseases, liver disorders, IDA, post-splenectomy, sideroblastic anemia, etc. (Fig. 18)
- Stomatocytes: these are RBCs with a central slit or stoma in place of central pallor. It is seen in hereditary stomatocytosis, elliptocytosis, alcoholism, etc.
- Cabot's ring: these are basophilic rings circular or twisted in figure of 8, staining reddish purple on Wright's stain. They represent the remnants of nuclear membrane or mitotic spindle apparatus and are seen in severe megaloblastic anemia, lead poisoning, thalassemias, etc.
- Heinz body: seen on a reticulocyte smear (supravital staining), as a deep purple, irregularly shaped small

body in the RBCs in G6PD deficiency, unstable hemoglobinopathy, thalassemia, chemical injury, etc.

- Howell-Jolly bodies: they are small, rounded, densely staining nuclear remnants occurring single, doubly or rarely more frequently. They are eccentrically placed and stain reddish blue or dark purple on Wright's stain. They are seen in megaloblastic anemia, postsplenectomy, functional asplenia, IDA, leukemia, congenital dyserythropoietic anemia, etc.
- Siderocytes: these are RBCs with non-Hb iron particles visible when stained with Prussian blue/safranin and are seen in sideroblastic anemia, aplastic anemia, hemolytic anemia, chronic infection and inflammation
- Pappenheimer bodies: single or double blue staining granules or dots on RBCs seen in hemolytic anemia, postsplenectomy and represent the remnants of ribosomes, mitochondria and ferric iron
- Normoblasts: these are seen when there is a shift of RBC maturation to the left as seen in cases of congenital hemolytic anemias such as thalassemias, sickle cell disease, congenital dyserythropoietic anemias, hemorrhage, etc. (Fig. 19)

Confirmatory Tests

These would be based on the screening test results. As per the algorithms given below and the suspected diagnosis, these confirmatory tests should be performed or ordered.

These include Coomb's test, G6PD estimation, osmotic fragility and flow cytometry for membrane defects, bone marrow aspiration and biopsy, high-performance liquid chromatography for hemoglobinopathies, serum iron studies, ferritin, vitamin B12 and folate levels as well as blood lead levels. Besides these, certain corroborative tests such as serum bilirubin, LDH, haptoglobins, etc. also assist in diagnosing the cause of anemia.

Occasionally, workup for α-thalassemia, unstable hemoglobins, rare hemoglobin variants, cytogenetics, and other RBC enzyme levels may be required.

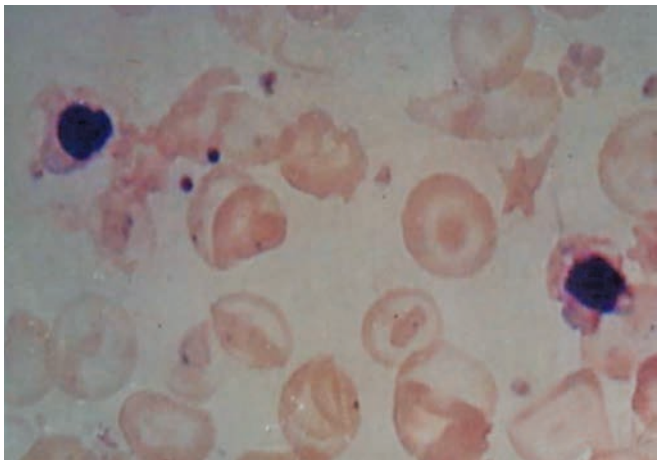
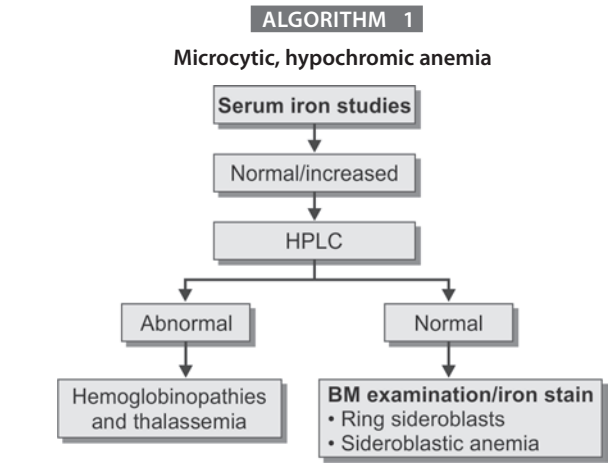


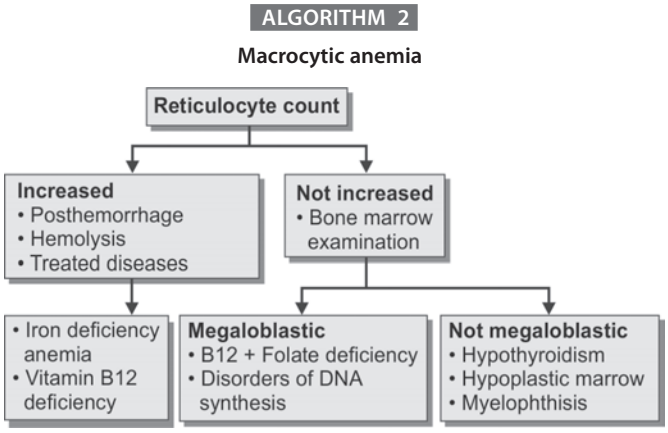
Fig. 19: Smear showing a bizarre picture with normoblasts and target cells in thalassemia major

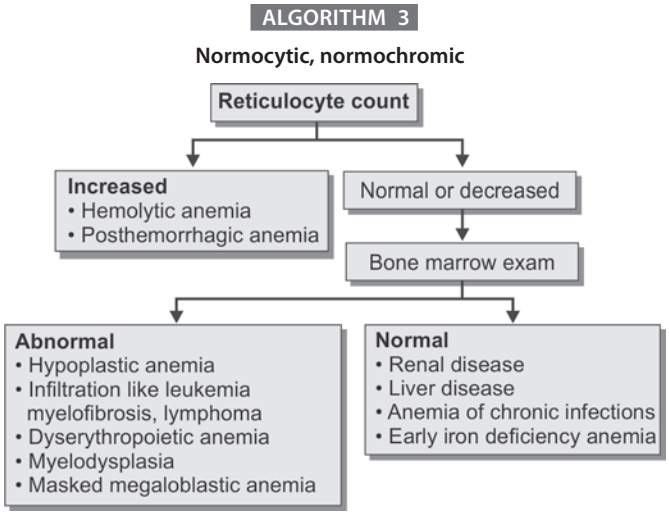
ALGORITHMS TO DIAGNOSE ANEMIA BASED ON VARIOUS INVESTIGATIONS

Methods to diagnose anemia based on various investigation are represented in algorithms 1–3.



HPLC, high performance liquid chromatography..





CONCLUSION

With detailed history taking and relevant clinical examination, basic screening tests, and minimum specific tests, it is possible to diagnose the type of anemia and institute appropriate treatment. This approach would definitely help in minimizing the need for useless and expensive tests in children with anemia.

KEY POINTS

- ☞ History and examination offers many important clues to the diagnosis of anemia
- ☞ A proper evaluation of the complete blood count especially red cell indices along with red cell distribution width, peripheral smear, and reticulocyte count would help in concluding the type of anemia in almost all patients
- ☞ A stepwise approach helps in limiting the investigations required to reach a diagnosis.

SUGGESTED READINGS

1. Bessman JD, Feinstein DI. Quantitative anisocytosis as a discriminant between iron deficiency and thalassemia minor. Blood. 1979;53:288-93.
2. Bessman JD, Gilmer PR, Gardner FH. Improved classification of anemia by MCV and RDW. Am J Clin Pathol. 1983;80:322-6.
3. Beuttler E. The red cell indices in the diagnosis of iron deficiency anemia. Ann Intern Med. 1959;50:313-22.
4. Buch AC, Karve PP, Panicker NK, Singru SA, Gupta SC. Role of red cell distribution width in classifying microcytic hypochromic anemia. J Indian Med Assoc. 2011;109:297-9.
5. de Benoist B, McLean E, Egli I, Cogswell M (Eds). Worldwide prevalence of anaemia 19932005: WHO global database on anaemia.
6. DeMaeyer EH, Adiels-Tegman M. The prevalence of anemia in the world. World Health Stat Q. 1985;38:302-16.
7. Hermiston ML, Mentzer WC. A practical approach to the evaluation of anemic child. Pediatr Clin North Am. 2002;49:877-91.
8. Irwin JJ, Kirchner JT. Anemia in children. Am Fam Physician. 2001;64:1379-86.
9. Janus J, Moerschel SK. Evaluation of anemia in children. Am Fam Physician. 2010;81:1462-71.
10. Lee GR. Iron deficiency and iron deficiency anemia. In: Lee GR, Bithel TC, Foester J, Athens JW, Lukens JN (Eds). Wintrobes Clinical Hematology. 9th ed. Philadelphia: Lea & Febiger; 1993. pp. 808-39.
11. Lokeshwar MR, Manglani M. Antenatal supplementation--effect on iron status of infants. Indian Pediatr. 1990;27:677-80.
12. Manglani M, Lokeshwar MR, Vani VG, Bhatia N, Mhaskar V. NESTROFT-an effective screening test for beta-thalassemia trait. Indian Pediatr. 1997;34:702-7.
13. Mehta BC. Approach to a patient with anemia. Indian J Med Sci. 2004; 58:26-9.
14. Orkin SH, Fisher DE, Look AT, Lux SE, Ginsburg D, Nathan DG (Eds). Nathan and Oskis Hematology of Infancy and Childhood, 7th ed. Saunders, an imprint of Elsevier Inc.; 2009.
15. Vasanta G, Pawashi AR, Susie H, Sujatha T, Raman L. Iron nutritional status of adolescent girls from rural area and urban slum. Indian Pediatr. 1994;31: 127-32.

CHAPTER 59

Algorithmic Approach to Thrombocytopenia in Children

ATK Rau, K Shreedhara Avabratha

INTRODUCTION

Platelets are discoid, non-nucleated cells of 2–3 mm in diameter and 5–9 fL in volume, produced in the bone marrow by fragmentation of megakaryocytes. Each megakaryocyte produces about 4,000 platelets. These platelets circulate in the blood for about 7–10 days and are subsequently culled by the spleen and bone marrow. The main function of the platelet is the formation of a platelet plug at the site of vascular injury (primary hemostasis). The normal range of platelet count is between 150,000/cumm and 450,000/cumm.

Thrombocytopenia is defined as platelet count of less than 150,000/cumm. However, clinically significant thrombocytopenia is defined as any count less than 100×10^9/L; furthermore, it is considered severe if the platelet count is below 30×10^9/L, moderate if it is between 30×10^9/L and 50×10^9/L, and mild (and usually asymptomatic) if above 50×10^9/L.

CLINICAL FEATURES

The clinical features of thrombocytopenia are due to the defect in primary hemostasis. It is clinically suspected when there is history of easy bruising or bleeding. Petechiae, purpura, epistaxis, gum bleeding, gastrointestinal (GI) bleeds, hematuria, and menorrhagia are some of the important presenting features. Intracranial bleeding, though rare, is one of the dreaded complications of low platelet counts. Deep and intramuscular bleeds are uncommon with thrombocytopenia and generally indicate a coagulation disorder, if encountered.

CAUSES

The causes of thrombocytopenia are many and broadly fall under three categories.

1. Decreased production of platelets—either congenital or acquired
2. Increased destruction of normally synthesized platelets—which could be due to immune or nonimmune causes
3. Sequestration of platelets in various organs.

Decreased Platelet Production

- Pancytopenia: leukemia, bone marrow infiltration, hypoplastic anemia, viral infections [e.g., human immunodeficiency virus (HIV)], drugs, and radiation
- Isolated thrombocytopenia: rare congenital defects—thrombocytopenia-absent radius syndrome, Wiskott-Aldrich syndrome, congenital amegakaryocytic thrombocytopenia, giant platelet disorder, e.g., Bernard-Soulier syndrome, viral infections like HIV, Epstein-Barr virus.

Increased Destruction

- Immune: immune thrombocytopenic purpura (ITP)—the most common cause of thrombocytopenia in children, neonatal thrombocytopenia (alloimmune or autoimmune), and autoimmune disease—systemic lupus erythematosus, drugs like heparin
- Nonimmune: malaria, dengue, disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), sepsis, thrombotic thrombocytopenic purpura (TTP), etc.

Platelet Sequestration

Mainly in the spleen as in hypersplenism due to infections, storage disorders, and portal hypertension.

CLINICAL APPROACH TO THE PATIENT WITH THROMBOCYTOPENIA

Detailed History

- Age at presentation
- Associated respiratory infection, diarrhea, or drug intake
- History suggestive of malaria and dengue
- Family history of bleeding disorder or immune disease
- History/risk for HIV or other immunodeficiency disorder
- History regarding the type and site of bleeding.

Physical Examination

Fever and toxic appearance may suggest infection, malignancy, DIC, TTP. The type and extent of bleeding is to be noted. An absent radius or upper limb deformity, chronic eczema, and recurrent infections are clues to various causes of congenital thrombocytopenia. Lymphadenopathy or splenomegaly may suggest malignancy, HIV, and infectious mononucleosis. Immune thrombocytopenic purpura is conspicuous by the nonoccurrence of splenomegaly. Arthritis, mouth ulcers, or a characteristic rash may suggest autoimmune or collagen vascular illness. Features of renal failure like edema, hypernatremia, and hypertension may be noted in HUS. Abnormal neurological examination should alert one to the possibility of an intracranial bleed or TTP.

Investigations

Causes for mucocutaneous bleeding are many and specialized testing for platelet disorders can be expensive and difficult to perform. However, before resorting to any of these tests, it is important to eliminate spurious "pseudo" thrombocytopenia by the direct finger prick peripheral smear examination.

Pseudo (or spurious) thrombocytopenia is an *in vitro* artifact where platelets clump together due to poor quality ethylenediaminetetraacetic acid used as an anticoagulant. As a result, the platelet counts appear to be decreased. A repeat count with another anticoagulant will resolve the problem.

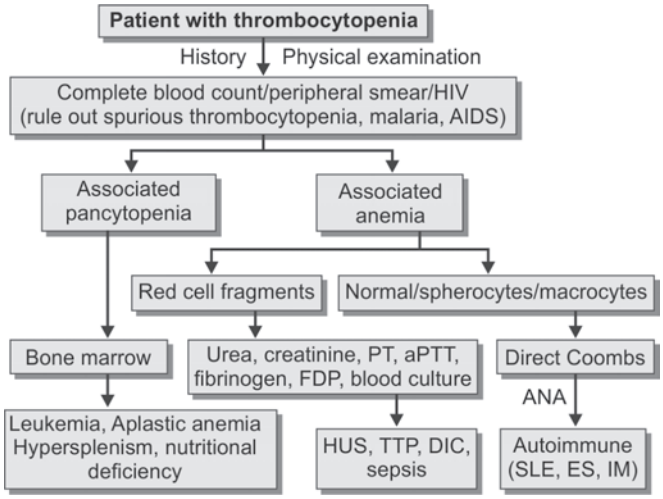
Further investigations will include:

- Complete blood count: will distinguish between pancytopenia and isolated thrombocytopenia
- An increase in mean platelet volume (MPV, normal 5–9 fL) will suggest increased turnover (e.g., in ITP where in the bone marrow attempts to replace peripherally destroyed platelets by younger larger platelets quickly) or hereditary giant platelet syndromes while small platelets (low MPV) suggest decreased platelet production and the Wiskott-Aldrich syndrome
- Bone marrow aspirate and biopsy is essential to differentiate ITP from leukemia and other infiltrative disorders when doubts arise clinically. Normal or increased megakaryocytes seen in the marrow in ITP will help resolve the issue
- Other clinically relevant investigations, e.g., specific serological titers for various infections and cytogenetic assessment for inherited disorders.

Algorithms 1 and 2 represent a simplified approach to thrombocytopenia.

ALGORITHM 1

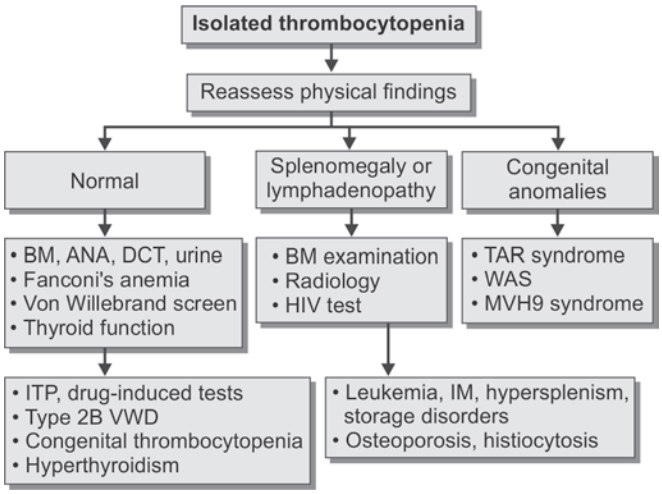
Approach to thrombocytopenia



HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; PT, prothrombin time; aPTT, activated partial thromboplastin time; FDP, fibrin degradation product; ANA, antinuclear antibody; HUS, hemolytic uremic syndrome; ITP, immune thrombocytopenic purpura; DIC, disseminated intravascular coagulation; ES, Evans syndrome; SLE, systemic lupus erythematosus; IM, infectious mononucleosis.

ALGORITHM 2

Approach to isolated thrombocytopenia



BM, bone marrow; ANA, antinuclear antibody; HIV, human immunodeficiency virus; TAR, thrombocytopenia-absent radius; WAS, Wiskott-Aldrich syndrome; ITP, immune thrombocytopenic purpura; VWD, von Willebrand disease; IM, infectious mononucleosis.

TREATMENT

Treatment involves management of the underlying cause. Platelet transfusions are often performed to tide over the crisis. Immune thrombocytopenic purpura is the most common cause of acute thrombocytopenia in a well child and the treatment involves observation, intravenous immunoglobulins, steroids, and others. In children without significant clinical bleeding, serial platelet counts will help decide the course of therapy to be adopted.

CONCLUSION

Thrombocytopenia is a common cause of bleeding in children. A knowledge of its causes, detailed history, and thorough clinical examination is necessary to narrow down the diagnostic possibilities. Relevant investigations need to be done to reach a correct diagnosis.

KEY POINTS

- ☞ Thrombocytopenia is defined as platelet count less than 150,000/cumm
- ☞ Thrombocytopenia can have multiple etiologies: either due to decreased production, or increased destruction or due to splenic sequestration
- ☞ Detailed history and thorough clinical examination and relevant investigations need to be done to reach a correct diagnosis
- ☞ Algorithmic approach to either isolated thrombocytopenia or with other cytopenias, along with a knowledge of causes will help at arriving the diagnosis.

SUGGESTED READINGS

1. Borkataky S, Jain R, Gupta R, Singh S, Krishan G, Gupta K, et al. Role of platelet volume indices in the differential diagnosis of thrombocytopenia: a simple and inexpensive method. Hematology. 2009;14:182-6.
2. Buchanan GR. Thrombocytopenia during childhood; what the paediatrician needs to know. Pediatr Rev. 2005;26:401-9.
3. Israels SJ, Kahr WH, Blanchette VS, Luban NL, Rivard GE, Rand ML. Platelet disorders in children: a diagnostic approach. Pediatr Blood Cancer. 2011;56:975-83.
4. Lombarts AJ, de Kieviet W. Recognition and prevention of pseudothrombocytopenia and concomitant pseudoleukocytosis. Am J Clin Pathol. 1988;89:634-9.
5. Panepinto JA. Thrombocytopenia. Berman's Pediatric Decision Making. Philadelphia: Mosby; 2011. pp. 612-5.
6. Scott JP, Montgomery RR. Platelet and blood vessel disorders. In: Kliegman RM, Stanton BM, St. Geme J, Schor NF, Behrman RE, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Saunders; 2011. pp. 1714-22.
7. Veneri D, Franchini M, Randon F, Nichele I, Pizzolo G, Ambrosetti A. Thrombocytopenias: a clinical point of view. Blood Transfus. 2009;7:75-85.

CHAPTER 60

Algorithmic Laboratory Approach to a Child with Anemia

Aarathi R Rau

INTRODUCTION

Anemia is a condition in which there is a reduction in the total circulating red cell mass below normal limits and consequent decreased oxygen carrying capacity that is insufficient to meet the body's physiologic needs. It is a common problem in India, and the National Family Health Survey III data showed the prevalence of anemia among children less than 5 years of age to be around 70% with nearly 73 million children below the age of 3 (79%) suffering from varying degrees of anemia.

Anemia is measured by reduction in the volume of packed red cells as measured by the hematocrit and reduction in the hemoglobin concentration below the normal for the age and gender of the individual. These values correlate with the red cell mass, except when there is change in the plasma volume caused by fluid retention or dehydration.

DIAGNOSIS OF ANEMIA

Basic investigations are done to document the presence of anemia and classify it according to morphology and function. Thereafter, based on the differential diagnosis and clinical features, specific diagnostic tests are indicated that help establish the etiology and pathophysiology of anemia. The initial laboratory studies should include a complete blood count with red cell indices, reticulocyte count, and study of a well-prepared peripheral blood smear.

CLASSIFICATION OF ANEMIA

Anemia is a manifestation of the underlying disease, which must then be determined and treated accordingly. The common mechanisms of anemia are decreased production, decreased lifespan of red cells, blood loss, and splenic pooling. However, if the cause is not readily apparent from clinical features, evaluation based on morphology and function is a well-established approach. Morphological classification of anemia is based on the red blood cell (RBC) indices that reflect the RBC volume [mean corpuscular volume (MCV)] and hemoglobin content [mean corpuscular hemoglobin concentration (MCHC)] and divided into microcytic hypochromic, normocytic, normochromic, and macrocytic anemia. As children (other than neonates) have smaller erythrocytes than adults the determination of MCV and subsequent classification of anemia must be determined by age-related ranges. Morphological classification is useful as the differential diagnoses of microcytic hypochromic anemia and macrocytic anemia are limited.

The functional classification is based on the number of reticulocytes produced as a response to anemia. Reticulocyte count can be corrected depending on the degree of anemia and the extent of stress/shift reticulocytosis to derive the reticulocyte production index (RPI), an index of bone marrow proliferation and its response to the degree of anemia. In hyperproliferative anemias seen in blood loss and hemolytic anemias, the RPI is greater than 2. In untreated thalassemia major, however, the reticulocyte count may be low. In hypoproliferative anemias and maturation defects seen in deficiency anemias, anemia of chronic disease, endocrine deficiencies, sideroblastic anemias, aplastic anemia, and myelodysplasia, the RPI is less than 2. The morphological classification combined with the functional classifications and the differential diagnoses thereof are applicable to the majority of anemias. Unusual patterns may occur while the anemia is not fully developed, when there is a combination of causes, the patient is under treatment or in an unusual cause of anemia.

USE OF AUTOMATED BLOOD COUNTING INSTRUMENTS IN ANEMIA

Automated counters are widely available and have improved accuracy, precision, and reliability compared to manual methods. Most modern automated blood-counting instruments give the complete blood count which includes hemoglobin, hematocrit, RBC indices, white blood cell (WBC), and platelet counts which are useful in the initial morphological diagnosis of anemia. Red cell distribution width (RDW) is a measure of anisocytosis and normally

Box 1: Red blood cell indices and their normal values

- MCV = hematocrit (%)/RBC count ($\times 10^{12}$/L) × 10
- Normal value: 70–84 fL at 1 year. Mean 80 fL by 5 years
- MCH = hemoglobin (g/dL)/RBC count ($\times 10^{12}$/L) × 10
- Normal value: 26–34 pg. Changes parallel to MCV in infancy and childhood
- MCHC = hemoglobin (g/dL)/hematocrit (%) × 100
- Normal value: 32–36 g/dL
- Increased MCHC seen in hereditary spherocytosis, dehydrated cells in sickle cell anemia, hereditary xerocytosis, and spuriously in immune hemolytic anemias

RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

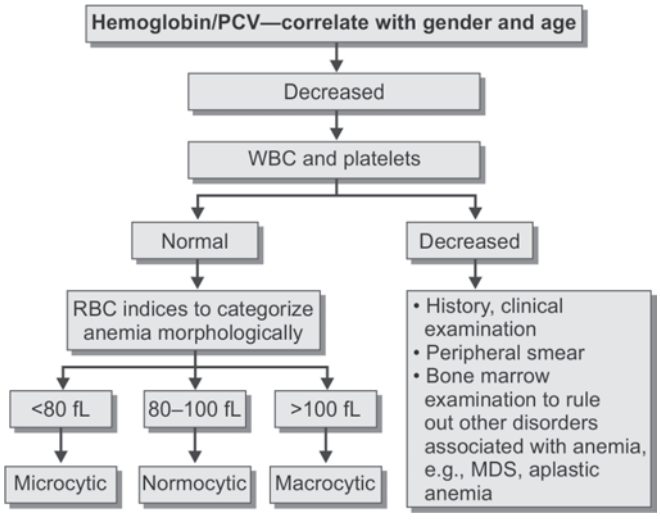
Box 2: Data that are useful in anemia from automated blood-counting instruments

- Complete blood counts hemoglobin, PCV, MCV, MCH, MCHC, RDW, WBC, and platelet counts
- Volume histograms: help to diagnose dimorphic patterns which can be present in combined nutritional anemias, sideroblastic anemia, MDS, post-transfusion, and during treatment
- Automated counters give data on the leukocytes and platelets which can be correlated with the RBC parameters
- Absolute reticulocyte count and immature reticulocyte fraction is an indication of the proliferation of the bone marrow and response to treatment

PCV, packed cell volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; WBC, white blood cell; MDS, myelodysplastic syndrome; RBC, red blood cell.

ALGORITHM 1

Approach to anemia



PCV, packed cell volume; RBC, red blood cell; MDS, myelodysplastic syndrome.

between 11.5 and 14.5%. A value of more than 14.5% indicates a heterogeneous population. Study of the volume histograms give a guide to the RBC morphology as well as distribution, which can be correlated with the peripheral smear. Absolute

TABLE 1: Hemoglobin and hematocrit cutoffs for a diagnosis of anemia in children

Age (years)/gender	Hemoglobin (g/dL)	Hematocrit (%)
Both sexes		
1–1.9	11.0	33
2–4.9	11.2	34
5–7.9	11.4	34.5
8–11.9	11.6	35
Females		
12–14.9	11.8	35.5
Males		
12–14.9	12.3	37

Box 3: Calculated indices which may be useful

- Mentzer's index = MCV/RBC count
- <13 suggests thalassemia trait
- >13 suggests iron deficiency
- It is a sensitive but less specific test, therefore, confirmatory tests must be carried out
- Reticulocyte production index = $\frac{\text{Patient hematocrit (\%)}}{\text{Normal hematocrit (\%)}} \times \frac{\text{Reticulotyte (\%)}}{\text{Maturation days}}$
- Maturation days depend on the hematocrit and are calculated as follows
  - Hematocrit 0.25–0.35, maturation days: 1.5
  - Hematocrit 0.15–0.25, maturation days: 2
  - Hematocrit <0.15, maturation days: 2.5
- <2 indicates hypoproliferative anemia
- >2 indicates hyperproliferative anemia

MCV, mean corpuscular volume; RBC, red blood cell.

reticulocyte count reflects the increased production of reticulocytes as a response of the erythropoietic elements of the bone marrow to anemia or treatment and is more useful than the manually counted reticulocyte percentage. In some automated counters, the immature reticulocyte fraction, which reflects the early reticulocyte fraction and the reticulocyte hemoglobin, which reflects the iron supply in the bone marrow, are also available.

Certain indices either numerical or computational can be calculated from data derived from automated counters, e.g., Mentzer's index, which is useful in the differentiation of thalassemia minor from iron deficiency anemia can be calculated.

EXAMINATION OF THE PERIPHERAL SMEAR

Examination of RBC morphology on a blood smear is important in diagnosing the type of anemia, assessing anisocytosis, and correlating it with the RDW. Smear examination can assess poikilocytes, the most specific being sickle erythrocytes. Erythrocyte inclusions when present are at times useful in determining the cause of anemia like Howell-Jolly bodies seen in some hemolytic anemias and Pappenheimer bodies in sideroblastic anemia. Evaluating the

morphology of the WBCs may be useful in diagnosing certain anemias like megaloblastic anemia and other hematological diseases where anemia is secondary to another cause, e.g., leukemia. Examination of a peripheral smear is also invaluable in the diagnosis of malaria, a common cause of anemia. Data from automated counters may be correlated with peripheral smear findings.

APPROACH TO MICROCYTIC HYPOCHROMIC ANEMIA

Microcytic RBCs are usually associated with decreased MCHC and are, therefore, microcytic hypochromic. Iron deficiency is the most common cause of microcytic hypochromic anemia but microcytic hypochromic anemia can also occur in thalassemia minor (both α and β), in the late stages of anemia of chronic disease, sideroblastic anemia, hemoglobin C and hemoglobin E, and other rare causes. Beta-thalassemia major and intermedia and hemoglobin H disease also cause microcytic hypochromic RBCs; however, their clinical features and peripheral smear findings are usually significant enough for them not to be included in the differential diagnosis of iron deficiency anemia. In iron deficiency anemia, the RBCs are microcytic hypochromic with moderate anisopoikilocytes. The platelet count is usually on the upper level of normal and reticulocyte response is usually identified 3 days after institution of iron therapy. Iron studies will show decreased serum iron and ferritin and increased total iron binding capacity. Serum transferrin receptor assay (sTFR) is useful in detecting and differentiating iron deficiency anemia from anemia of chronic disease; it is raised in patients with iron deficiency anemia in comparison to anemia of chronic disease, where levels are almost identical to normal individuals.

In α and β thalassemia trait, the peripheral smear will show microcytic hypochromic RBCs with minimal anisocytosis which is reflected as a decreased RDW. The RBCs are increased in number and both these are reflected in the Mentzer's index. While investigating for β thalassemia trait, estimation of HbA 2

TABLE 2: Differential diagnosis of iron deficiency anemia

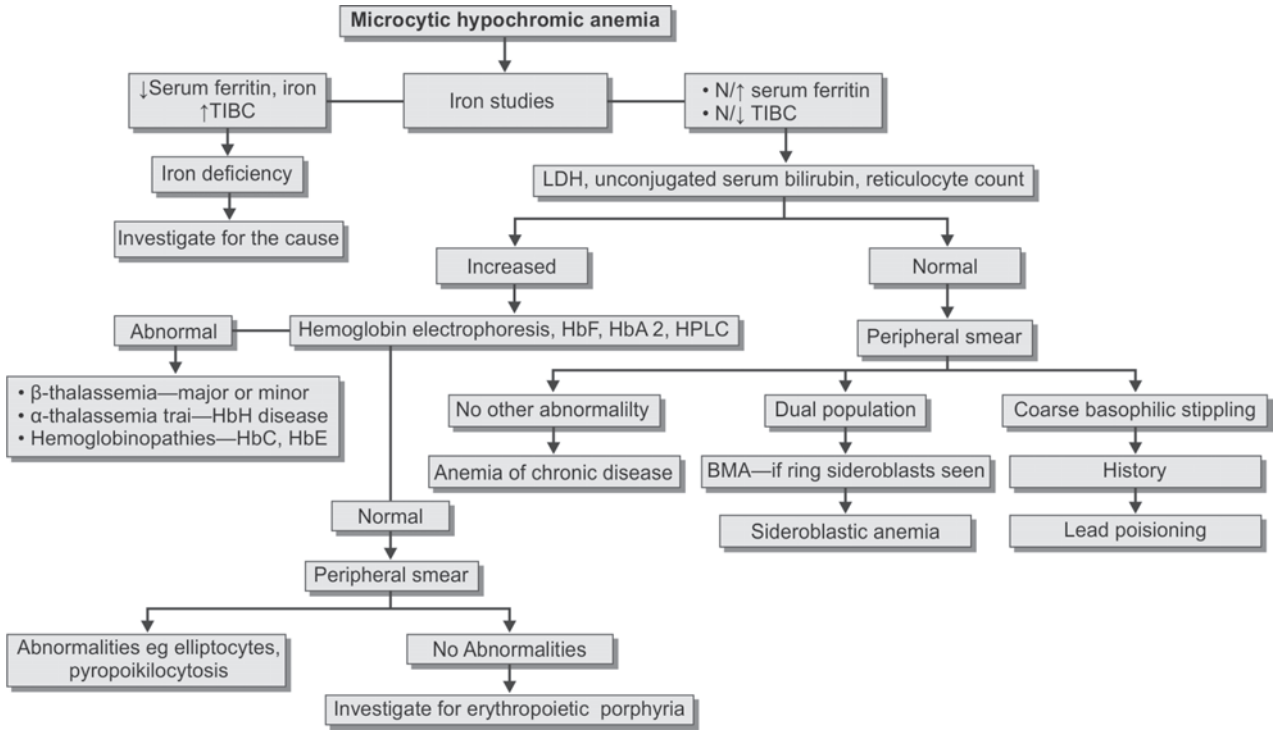
	Iron deficiency	Beta thalassemia minor	Anemia of chronic disease	Sidero-blastic anemia
Serum ferritin	↓*	Normal/↑	Normal/↑	↑
Serum iron	↓	Normal/↑	Normal/↓	Normal/↑
Total iron binding capacity	↑	Normal/↓	Normal/↓	Normal/↓
RDW/ anisocytosis	↑	Normal	Normal	↑/dimorphic population
Special tests for confirmation	Serum transferrin receptor assay—increased	HbA 2 estimation >4%	Serum transferrin receptor assay—normal	Ringed sideroblasts in bone marrow

RDW, red cell distribution width.

*Serum concentrations of ferritin are lower in children than in adults and ferritin <12 µg/L is considered appropriate for detecting iron deficiency.

ALGORITHM 2

Approach to microcytic hypochromic anemia



TIBC, total iron binding capacity; LDH, lactate dehydrogenase; BMA, bone marrow aspiration.

is important as an increase (usually a value of between 4 and 7%) is considered diagnostic of β-thalassemia trait. If, after evaluation of the common causes, a diagnosis has not been reached, unusual causes like lead toxicity may be considered.

APPROACH TO MACROCYTIC ANEMIA

Macrocytic anemias are those where the MCV is greater than 100 fL. Macrocytic anemias may be megaloblastic or non-megaloblastic.

In megaloblastic anemia, examination of the peripheral smear will show macro-ovalocytes and hypersegmented neutrophils. Increase in serum lactate dehydrogenase, unconjugated bilirubin, and decreased haptoglobin indicate ineffective erythropoiesis and hemolysis. The MCV is usually greater than 120 fL and there is likely to be decrease in the RBC, WBC, and platelet counts. The bone marrow in megaloblastic anemia shows nuclear: cytoplasmic asynchrony and giant metamyelocytes, however, bone marrow examination may not be essential for the diagnosis of megaloblastic anemia. Megaloblastic anemia may be due to folic acid, vitamin B12 deficiency which may be due to decreased absorption, inadequate nutrition, defects in metabolism, or increased requirements. Other causes include defects in purine and pyrimidine synthesis either inherited or acquired as in myelodysplastic syndrome (MDS), drug induced or associated with human immunodeficiency virus infection.

In nonmegaloblastic anemia, the MCV is usually mild and between 100 and 110 fL and the WBC and platelets are usually normal. Causes of nonmegaloblastic macrocytic anemia include hypothyroidism, liver disease, and rare conditions like pure red cell aplasia, and aplastic anemia. The smear shows round macrocytes and may show features of the underlying cause like target cells and stomatocytes in liver disease. Correlation with clinical and laboratory tests for the causative disease must be done to confirm the cause.

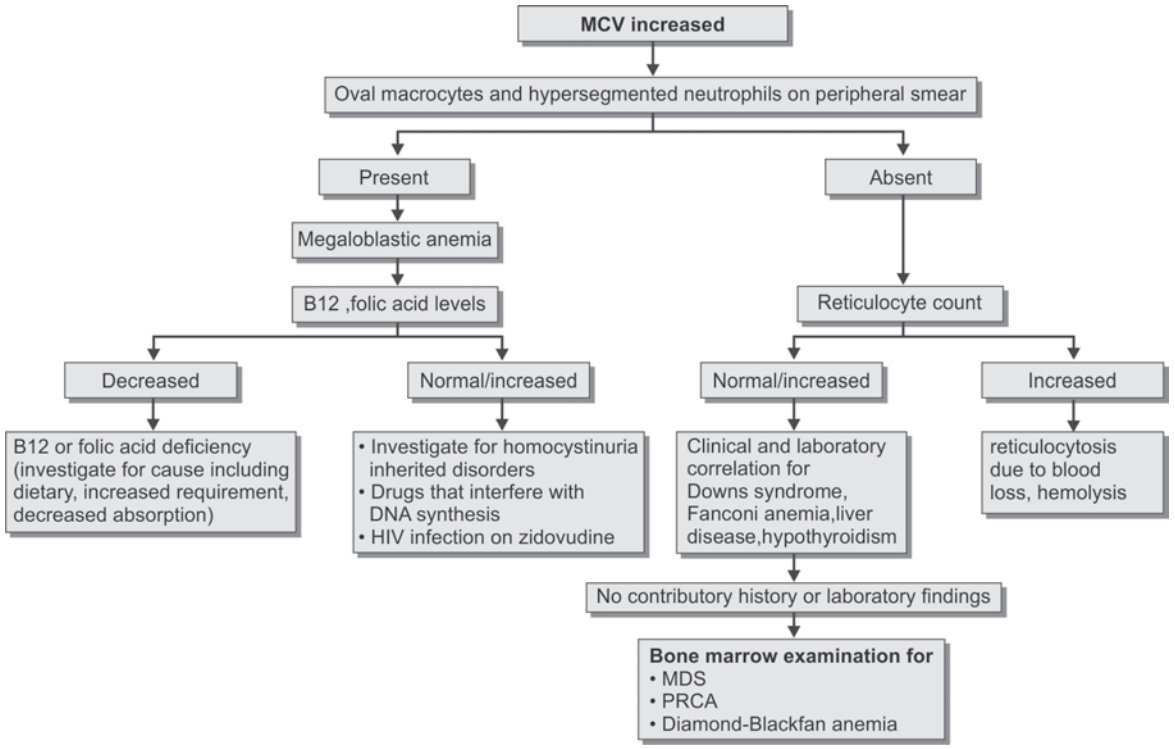
Hemolytic anemias and blood loss may also have raised MCV due to reticulocytosis which can be excluded by reticulocyte count and peripheral smear examination.

NORMOCYTIC NORMOCHROMIC ANEMIA

The causes of normocytic anemia are many. Depending on the RPI, they can be categorized into anemia with hyperproliferative or hypoproliferative marrow. Normocytic anemia with hyperplastic marrow (>2 RPI) present from birth are usually due to some nonthalassemic hemoglobinopathies, RBC enzyme, or membrane defects. In addition to peripheral smear examination and tests for increased turnover of cells, further tests like hemoglobin electrophoresis can characterize the disease. Rare causes of hemolysis including paroxysmal nocturnal hemoglobinuria and Wilson disease must be confirmed by specific tests. Normocytic anemia with hypoplastic marrow (<2 RPI) can be seen early in the course of iron deficiency, renal disease, liver disease, endocrine disorders, chronic inflammatory disease, and anemia secondary to medications. In these conditions, specific tests

ALGORITHM 3

Approach macrocytic anemia

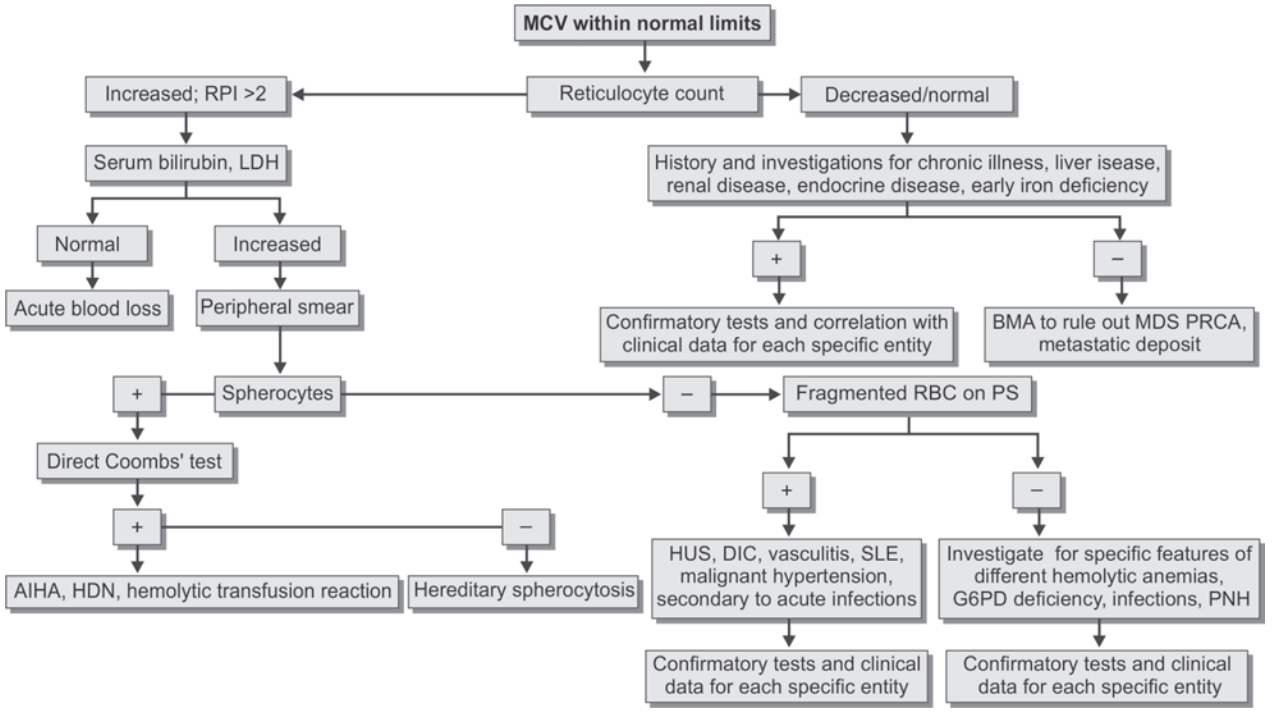


MCV, mean corpuscular volume; DNA, deoxyribonucleic acid; MDS, myelodysplastic syndrome; PRCA, pure red cell aplasia; HIV, human immunodeficiency virus.

Note: Autoagglutination can cause spurious increase in mean corpuscular volume in automated counters. This can be ruled out by examination of the peripheral smear and direct Coombs' test.

ALGORITHM 4

Approach to normocytic anemias



MCV, mean corpuscular volume; LDH, lactate dehydrogenase; AIHA, autoimmune hemolytic anemia; HDN, hemolytic disease of the newborn; HUS, hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; SLE, systemic lupus erythematosus; BMA, bone marrow aspiration; MDS, myelodysplastic syndrome; PRCA, pure red cell aplasia; PNH, paroxysmal nocturnal hemoglobinuria.

following clinical evaluation will confirm the diagnosis. Primary hematological conditions may also present with hypochromic anemia and these include MDS, aplastic anemia, pure red cell aplasia, and leukemia. Evaluation of the bone marrow will be useful in confirming these diagnoses

ANEMIA IN THE NEWBORN

Anemia in the newborn differs from those in children in that the level of hemoglobin is higher (16–22 g/dL at birth), the MCV is higher (average 107 fL at birth) and the reticulocyte count is higher (3–7%) in the newborn compared to children. The etiologies that are uncommon in older children that need to be considered in a newborn include congenital disorders, metabolic disorders, intrauterine infections, ABO/Rh incompatibility, and internal hemorrhage.

Clinical Pearls

- The final diagnosis in anemia must be done after correlating the laboratory test results with patient history, symptoms, and physical examination
- Results of laboratory tests should be interpreted with an understanding of the limitations of the test and the variations with respect to age, gender, sample collection, etc.
- All laboratory investigations should be interpreted in relation to the reference range established in that individual laboratory using blood samples from the local population.

KEY POINTS

- ☞ The morphological classification of anemia is based on red cell indices and correlated with the red blood cell morphology on peripheral smear examination
- ☞ The differential diagnosis of microcytic hypochromic anemia and macrocytic anemias are limited
- ☞ Based on the morphology and clinical features, further investigations can be done to help establish the etiology and pathophysiology of anemia; after which appropriate treatment can be given.

SUGGESTED READINGS

1. Bain BJ, Bates I, Laffan MA, Lewis SM. Dacie and Lewis practical hematology. 11th ed. Churchill Livingstone: Elsevier; 2012.
2. Brugnara C, Platt OS. The neonatal erythrocyte and its disorders. In: Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE, editors. Nathan and Oski's hematology of infancy and childhood. 7th ed. Philadelphia: Saunders Elsevier; 2009.
3. Centers for Disease Control (CDC). CDC criteria for anemia in children and childbearing aged women. MMWR Morb Mortal Wkly Rep. 1989;38(22):400-4.
4. Dallman PR, Simes MA. Percentile curves for hemoglobin and red cell volume in infancy and childhood. J Pediatr. 1979;94(1):26-31.
5. Khoury MJ, Rhodes M. How to approach chronic anemia. Hematology Am Soc Hematol Educ Program. 2012;2012:183-90.
6. Kotecha PV. Nutritional anemia in young children with focus on Asia and India. Indian J Community Med. 2011;36(1):8-16.
7. McKenzie SB, Williams JL. Clinical laboratory hematology. 3rd ed. New Jersey: Pearson Education Inc.; 2015.
8. Tkachuk DC, Hirschmann JV, editors. Wintrobe's atlas of clinical hematology. Philadelphia: Lippincott Williams and Wilkins; 2007.

CHAPTER 61

Recurrent Unusual Infections in a Child: The Way Forward

Tulika Seth

INTRODUCTION

Children are immunologically immature more prone to many infections compared to adults. More than six infections per year are suspicious of an immunodeficiency status, though some studies report 4 to 8 may be normal. So when is it warranted to do special and extra investigations in a child? Repeated infections with the same bacterial organism, serious infections of the lower respiratory tract, repeated diarrhea, recurrent urinary tract infection, and repeated pyogenic infections all warrant a detailed history and evaluation. Unusual organisms causing an infection should also get special attention. Before we discuss recurrent unusual infections, it is important to understand what are recurrent infections and unusual organisms.

DEFINITIONS

Recurrent or Repeated Infections: Common Causes

The child referred for repeated or recurrent infection needs a detailed history. Often a common mistake is to assume cases of repeated infections, when in fact it is a case of inadequate, improper, or incomplete treatment of a previous infection. Compliance, dosage of antibiotics, and all culture reports should be checked. Home environment, smoker at home, going to a crèche, etc. can predispose to recurrent infections in an otherwise normal child. The vaccination history and documentation of vaccines is important. Malnutrition is the most common cause of decreased immunity, hence nutritional parameters should be checked. Any anatomic malformation, gastroesophageal reflux, congenital masses, and foreign body aspiration may also be a cause of repeated infections. Atopic dermatitis may lead to skin infections due to scratching the pruritic rash. Other systemic disease, e.g., sickle cell, nephrotic syndrome, etc., needs to be evaluated, if previous illness, then medications should be checked as the child may be on steroids or other immune-suppressants. Occasionally, the recurrent infection can lead to the diagnosis of unsuspected condition like cystic fibrosis or a previously missed congenital heart disease, etc. Most common infections in children are viral, of short duration, and do not compromise growth. Children with inherited conditions like Down syndrome, DiGeorge syndrome, etc. are also more susceptible to infections. Family history of other family members prone to infections (siblings, parents), history of human immunodeficiency virus (HIV) needs to be taken. If none of the above then a primary immunodeficiency disorder may be the cause of the condition.

In neutropenic patients, there are frequent bacterial and fungal infections. Though they present with fever, the classic signs of infection are often less marked due to neutropenia, hence a high index of suspicion is needed.

Unusual Infections: Causes

An unusual infection may be either an uncommon setting, or a rare organism. These are warning flags to investigate a child for immunodeficiency disorders or undiagnosed systemic disease like malignancy. Certain signature infections can help pinpoint the type of immune defect (Box 1).

- If presented with an unusual organism, rule out contamination and obtain a detailed history of travel, exposure to pets, medication leading to immune-suppression, and previous courses of broad-spectrum antibiotics
- If a usual setting, rule out underlying undiagnosed disease such as malignancy, metabolic or systemic disease, HIV, malnutrition, or undisclosed use of steroids or other immune-suppressive medicines.

As seen by the above discussion, all children with recurrent infections do not have a primary immune deficiency disorder. It is important to rule out secondary immunodeficiency as these can be treated easily (Table 1) leaving the primary immunodeficiency child who needs a more detailed investigation.

Box 1: Clinical features of primary immunodeficiency disorders

Adaptive immunity

- B cell defects
  - Recurrent bacterial sinopulmonary infections, with polysaccharide encapsulated organisms (*Streptococcus pneumoniae, Haemophilus influenzae* type b) or bronchiectasis
  - Chronic or recurrent gastroenteritis (Giardia/enteroviruses)
  - Chronic enteroviral meningoencephalitis
  - Failure to thrive and/or autoimmune disease
- T cell defects
  - Lymphopenia as a neonate or infant
  - Repeated severe, or unusual viral infections (varicella-zoster, CMV, HSV)
  - Chronic candidiasis
  - Chronic diarrhea
  - Opportunistic infections like *Pneumocystis pneumonia*
  - Severe seborrheic rashes (skin rash, desquamating skin, abnormal liver function tests, and cytopenias)
  - Associated features: failure to thrive

Innate immunity

- Phagocytic defects
  - Delayed separation of the umbilical cord
  - Lymphadenitis or soft tissue abscesses
  - Repeated infections due to catalase-positive bacteria and/or fungi
  - Recurrent gastrointestinal or genitourinary tract obstruction
  - Poor wound healing, oral ulcers
- Complement defects
  - Angioedema of face, GI tract, etc.
  - Autoimmune disease
  - Pyogenic bacterial infections (e.g., *Neisseria meningitidis*), Herpes simplex meningoencephalitis in infancy
  - Papillomavirus infections of skin, including extensive warts
  - Autosomal dominant inheritance

CMV, cytomegalovirus; HSV, herpes simplex virus; GI, gastrointestinal.

Key Features of Unusual Recurrent Infections

- Not all children with recurrent infections have a primary immune deficiency disorder
- Immunodeficiency should be suspected if
  - Six or more new infections within 1 year
  - Two or more sinus infections or pneumonias in 1 year
  - Two or more episodes of sepsis or meningitis
  - Two or more months of oral antibiotics without resolution of problem.

WARNING SIGNS OF IMMUNE-DEFICIENCY

Presence of oral candidiasis, tissue or organ abscesses, and opportunistic infections all warrant investigation. A complication from a live vaccine, in the child or elder siblings and family history of siblings with history of early death or similar presentation are important.

The immunodeficiency may be secondary or primary. Secondary immune-deficiencies are due to contributing malnutrition, chronic disease, prematurity, cancer, HIV, etc. The type and pattern of recurring infections depend on which components of the immune system are affected (Box 1). History (Table 1) and examination (Box 2) give clues and signature infections help highlight disorders (Table 2). Initial steps with workup of the child is represented in algorithm 1.

GENERAL EXAMINATION

Physical examination in children with recurrent infections provides information as to their general health and may suggest the presence of allergy, chronic disease, or immunodeficiency. A dysmorphic appearance may signify an underlying genetic syndrome. Dark circles under the eyes, a transverse nasal crease, and congested nasal turbinates suggest allergy. Mouth ulcers, gingivitis, and mucosal candidiasis may be due to an immunodeficiency state. Diminished or absent tonsils and cervical lymphadenopathy with a history of recurrent respiratory infections suggest an antibody deficiency diagnosis. The presence of nasal polyps suggests cystic fibrosis, and confirmatory testing should be performed.

TABLE 1: Historical details useful in differentiating between cases of suspected primary or secondary immunodeficiency

Primary immunodeficiency	Secondary immunodeficiency
History	
• Feeding history, history of food intolerance • Delayed detachment of the umbilical cord should be noted since persistent attachment beyond 30 days is suggestive of a leukocyte adhesion defect	• Birth history: pregnancy history should be explored for maternal illness (e.g., HIV, CMV), birth history should include length of gestation, birth weight, and neonatal problems such as jaundice, respiratory distress, or need for intensive care. Transfusions in the neonatal period should be recorded
Growth	
• Weight, height, and head circumference should be plotted and followed over time. Children with chronic disease or immunodeficiency often have poor weight gain or even weight loss. Children with chronic lung, heart, or gastrointestinal disease are often small because of anorexia, high energy expenditure, or malabsorption caused by infection or bacterial overgrowth	
Development	
• Children with ataxia-telangiectasia and DiGeorge syndrome can have delayed developmental milestones • Progressive neurologic dysfunction is seen in Chédiak-Higashi syndrome	• Children with HIV, and TORCH may have delays in milestones; children with other chronic disease may also lag in development

Continued

Continued

Primary immunodeficiency	Secondary immunodeficiency
Immunization history	
• See for adverse effects from a vaccine, particularly live virus. The immunization record is valuable to see vaccine titers to evaluate antibody function	• The immunization record is valuable to see vaccine titers to evaluate antibody function
Medications	
• If immunoglobulin has been given, the route, dose, frequency, and adverse effects should be noted	• Current and past medications should be recorded, including duration, effectiveness, and adverse reactions. Use of any immunosuppressive medications, such as glucocorticoids, should be noted
Other illnesses	
• Other immune problems such as allergies, anaphylaxis, arthritis, or autoimmunity may give a clue to diagnosis	• Severity of prior chicken pox, roseola, and other febrile illnesses should be noted • Ask about surgery and hospitalizations
Family history	
• Consanguinity, family members with similar diseases, recurrent infections, unexplained death, or autoimmune disease • Autosomal recessive pattern in ataxia-telangiectasia • X-linked transmission (e.g., agammaglobulinemia, chronic granulomatous disease)	• HIV, TB • Other similar problems in siblings, or other family members, parental health, and occupation
Infection history	
• The infection history should include the age of onset, duration, frequency, sites, organisms, treatment, and response to therapy	
Age of onset	
• Birth to 6 months: ○ Several immune-deficiencies: congenital neutropenia, severe combined immunodeficiencies, and complete DiGeorge syndrome ○ Persistent diarrhea, chronic cough, or failure to thrive suggests cystic fibrosis or a primary immunodeficiency ○ Inherited antibody deficiencies present at 7 -9 months, as the maternal IgG decreases. Infants with TLR3 transduction may present with herpes simplex encephalitis.	• Birth to 6 months: ○ Infections shortly after birth may be due to prolonged rupture of membranes, congenital infection, or aspiration ○ Premature infants are at high risk for sepsis
• 2–6 years: ○ Less serious antibody deficiencies (e.g., immunoglobulin A deficiency and selective antibody deficiency) present at this age. Two or more episodes of bacterial meningitis or sepsis suggest a complement or other innate immune defect	• 2–6 years: ○ Secondary immune-deficiencies resulting from malignancy, nephrotic syndrome, or gastrointestinal problems, malabsorption often begin at this age ○ Daycare or school will result in frequent respiratory and gastrointestinal infections

HIV, human immunodeficiency virus; CMV, cytomegalovirus; TORCH, Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes infections; TB, tuberculosis.

Box 2: Examination findings to look for in a child with recurrent infections

Skin

- See breach of skin barriers due to prematurity, atopy, chronic eczema, burns, wounds, fistula and sinuses. Several immunodeficiency syndromes are also associated with eczema, including Wiskott-Aldrich, hyper immunoglobulin E, Omenn syndrome, and severe combined immunodeficiency disease (SCID)
- Cutaneous granulomas, impetigo, or nonhealing ulcers suggest the diagnosis of an antibody or phagocytic disorder. Pyogenic abscesses are common in chronic granulomatous disease, or leukocyte adhesion defects
- Oculocutaneous albinism is seen in Chédiak-Higashi disease
- Rashes: seborrheic dermatitis and alopecia can be seen in some forms of SCID, or may be found in other conditions like Langerhans cell histiocytosis. Lupus-like rash in the children with early complement component defects. A dermatomyositis-like rash is found in X-linked agammaglobulinemia (XLA)
- Extensive warts or molluscum contagiosum occurs in T cell disorders, innate immune defects, or a rare entity called Warts, Hypogammaglobulinemia, Infections and Myelokathexis syndrome

Lymphadenopathy, hepatosplenomegaly

- Immune deficiency disorders can be characterized by paucity or even overabundance of lymphoid tissue (e.g., tonsils, lymph nodes, adenoids, spleen). The absence of lymph tissue suggests XLA or SCID
- Lymphadenopathy and hepatosplenomegaly can be seen in B cell disorders (e.g., common variable immunodeficiency, IgA deficiency) and also in children with human immunodeficiency virus infection
- Suppurative adenitis is common in chronic granulomatous disease

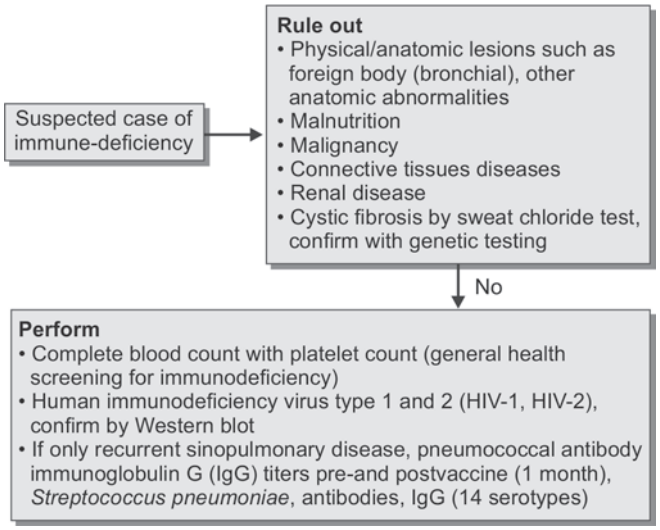
TABLE 2: Signature infections in certain immunodeficiencies

Infection	Immune defect
Recurrent sinopulmonary infections, pneumococcus, *Haemophilus influenzae* type b	B cell abnormalities
Enteroviral meningoencephalitis	X-linked agammaglobulinemia
Severe oral candidiasis	Abnormal T cell immunity
Staphylococcus aureus, coagulase-negative staphylococci, *Serratia marcescens*, *Aspergillus*	Chronic granulomatous disease
Neisseria species (*Neisseria meningitidis*, *Neisseria gonorrhoeae*)	Deficiencies of the late components of complement (C5–C9)
Infection with vaccine strains following live vaccines, e.g., oral polio, measles, varicella, or BCG	Primary immune deficiency
Some infections can occur in both primary and secondary immunodeficiency states	
Recurrent pneumococcal disease	Primary immunodeficiency such as agammaglobulinemia or complement defect or secondary immunodeficiency, due to sickle cell disease, asplenia, HIV/AIDS, or nephrotic syndrome, also results in recurrent pneumococcal disease
Pneumocystis jiroveci (*carinii*) pneumonia	Severe combined immune deficiency, primary or secondary T cell immunodeficiencies—HIV or immunosuppressive therapy
Pseudomonas infection	Cystic fibrosis, skin burns, trauma, or neutropenia

BCG, Bacillus Calmette-Guérin; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

ALGORITHM 1

Initial evaluation with workup of a child with unusual recurrent infections



LABORATORY EVALUATION

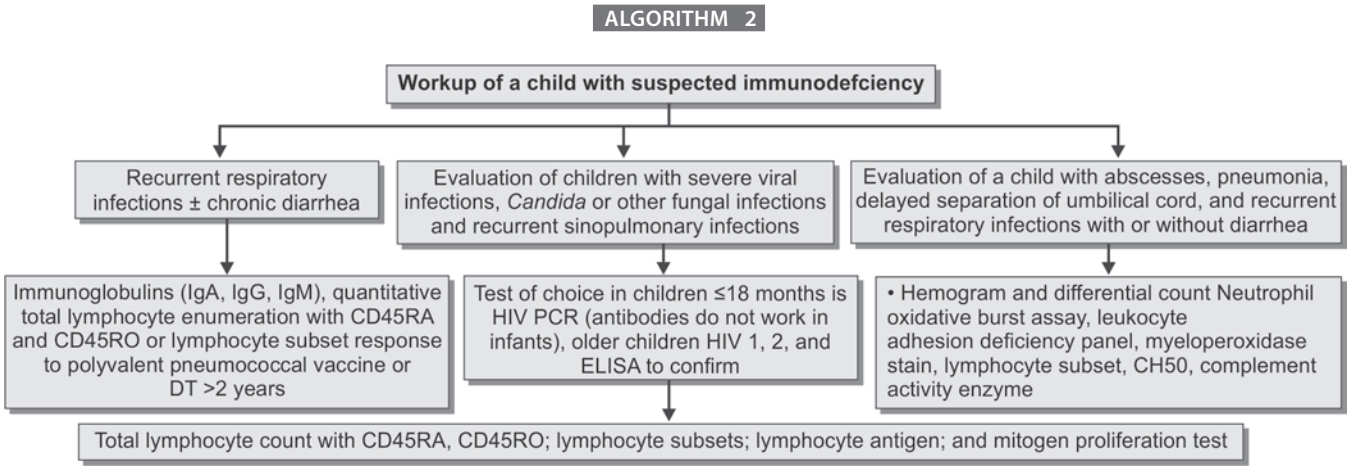
Laboratory evaluation of children with recurrent infection should be directed by history and physical examination findings (Table 1, Box 2, Algorithm 2), before evaluating for primary immunodeficiency diseases exclude secondary immunodeficiency, which are more common. General screening tests should include the following to exclude systemic disease: complete blood count with differential electrolytes, glucose, renal and liver function tests, urinalysis, autoimmune workup, and HIV testing. The evaluation for primary immunodeficiency should focus on the component of the immune system that is most likely to be involved based upon the screening tests.

General Screening Tests

- The total absolute lymphocyte count is a useful test (lymphopenia is defined as a count of <1,500 cells/μL in patients over 5 years and <2,500 cells/μL in younger children). The presence of anemia, thrombocytopenia, or an abnormal differential count warrants further investigation
- Neutropenia and absolute neutrophil count should be checked:

$$\text{ANC} = \frac{\text{WBC (cells/μL)} \times \text{percent (PMNs + bands)}}{100}$$

  Other important blood cells to be evaluated are eosinophils; if increased, suggest an allergic state. Platelet size and number should be seen as they are useful—small platelets seen in Wiskott-Aldrich syndrome, etc. However, thrombocytosis is less specific and only points to chronic inflammation
- Chest X-ray, computed tomography scan: this will assist in documenting serious infections like pneumonia, thymus size, presence of mass in chest predisposing to infection, bronchiectasis, etc. This may suggest a diagnosis of previously unsuspected etiology
- Immunoglobulin levels: immunoglobulin G (IgG), IgM, IgA, and IgE, must be compared with age-matched controls for children. An antibody deficiency is suggested by an IgG less than 200 mg/dL and a total Ig (IgG plus IgM plus IgA) less than 400 mg/dL, or by the complete absence of IgM or IgA (after infancy). A small increase of IgE (>100 IU/mL) can occur due to allergy, eczema, or with phagocytic dysfunction. In hyper IgE syndrome, the level of IgE are generally greater than 2,000 IU/mL



HIV, human immunodeficiency virus; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

- Antibody titers, complement screening test: functional assessment of the antibody system can be done by checking antibody titers to vaccines that the child has been documented to have received. Titers to tetanus, diphtheria, and *Haemophilus influenzae* type b are available for reference. Response to polysaccharide antigens can be determined by measurement of pneumococcal titers (12–14 serotypes) in children over the age of 2 years
- Complement activity needs to be assessed in patients with recurrent sepsis due to neisserial infection. The screening test is a total hemolytic complement determination (CH50). A normal CH50 level excludes nearly all hereditary complement deficiencies.

Diagnostic Tests

Specific testing is indicated when screening tests are abnormal or if there is a convincing history or family history suggestive of an immunodeficiency. The patient should be referred to a special center for diagnostic tests and management.

- Lymphocyte subset analysis: by flow cytometry for CD3 (total T cells), CD4 (T helper), CD8 (T cytotoxic), CD19 (B cells), and CD16/56 (natural killer cells), compared with age-matched controls (B or T cell defect)
- An absolute CD4 count of less than 500 cells/μL in a child over 5 or less than 1,000 cells/μL in younger children (suggests a cellular immunodeficiency)
- An absolute B cell (CD19) count of less than 100 cells/μL can be seen in children with agammaglobulinemia
- Low levels of any lymphocyte subset should be repeated and if still decreased, followed by functional analysis of the respective subset
- Immunoglobulin G subset levels can be tested if the patient has low total IgG levels and poor antibody response to vaccinations. A complete absence of IgG1, IgG2, or IgG3 suggests immune dysregulation, and may indicate the early onset of common variable immunodeficiency. However, a low level of only one or more IgG subclasses does not make a diagnosis if an antibody deficiency, for such a diagnosis functional antibody studies are needed
- Delayed cutaneous hypersensitivity is a good functional *in vivo* test of T cells; however, it is limited in utility as it can be performed only in older children
- Lymphoproliferative assays are *in vitro* assays used to evaluate the cellular immune system. This examines proliferative response of lymphocytes to mitogens (phytohemagglutinin, pokeweed), stimulatory monoclonal antibodies (anti-CD3), etc. Defects in this assay suggest a T cell defect
- Phagocytic oxidative response is evaluated by a fluorescent dye (dihydrorhodamine) by flow cytometry. Chronic granulomatous disease gives a negative test. This is more accurate than the nitroblue tetrazolium dye reduction assays
- Leukocyte adhesion defect testing: cases presumed to suffer from leukocyte adhesion deficiency (LAD) can be evaluated by flow cytometry evaluation of cell surface marker expression of CD11 and CD18. These are absent in LAD I and CD15a is absent in LAD II. However, patients with LAD III have normal integrin expression and demonstration of impaired integrin activation, is needed
- Complement component: if the screening test shows very low or absent CH50 activity on repeat testing then complement component assays are indicated
- Confirmatory diagnostic studies: many immune defects have their molecular tests available; these tests are usually performed in specialized labs. A definite diagnosis by molecular testing helps in treatment, prognosis, and genetic counseling. Genetic diagnosis is available for the majority of disorders commercially and confirmatory tests should be done in conjunction with a specialist as these tests are expensive.

Confirm the neutropenia on a manual peripheral smear stained with Wright-Giemsa stain and perform a bone marrow test. For cyclic neutropenia, there will be recurrent infections and a regular oscillation in the neutrophil count at approximately 21 day intervals. Other causes of neutropenia are given in table 3.

TABLE 3: Causes of isolated neutropenia

Acquired neutropenias	Congenital neutropenias
Postinfectious: mechanisms are sequestration, aggregation, or destruction of neutrophils by the circulating antibodies	Kostmann's syndrome
Drug-induced: immune-mediated destruction, drug-induced antibodies or by direct toxic effects on bone marrow granulocyte precursors	Shwachman-Diamond syndrome
Primary immune disorders: anti-neutrophil antibodies in patients of systemic lupus erythematosus, rheumatoid arthritis	Chédiak-Higashi syndrome
Isoimmune neonatal neutropenia: due to transplacental passage of immunoglobulin G antibodies against specific paternal neutrophil antigens in the infant	Cyclic neutropenia
Chronic autoimmune neutropenia occurs in infants and children and is a benign entity	Rule out other diseases: Fanconi anemia, reticular agenesis, myelodysplastic syndrome (may precede pancytopenia), glycogen storage disease type 1

Clinical Pearls

- Opportunistic infections can be due to neutrophil defects, T cell deficiency, or human immunodeficiency virus
- Recurrent sinopulmonary infections may be due to antibody defects.

KEY POINTS

- ☞ A single episode of unusual infection (rare organism or unusual severity of infection of common organism) should be taken seriously and investigated
- ☞ Early diagnosis and referral is lifesaving.

SUGGESTED READINGS

1. Buckley RH, editor. Diagnostic and clinical care guidelines for primary immunodeficiency diseases: Immune Deficiency Foundation 2006. [online] Available from: www.primaryimmune.org. [Accessed December, 2015].
2. Grüber C, Keil T, Kulig M, Roll S, Wahn U, Wahn V, et al. History of respiratory infections in the first 12 yr among children from a birth cohort. Pediatr Allergy Immunol. 2008;19(6):505-12.
3. Skoda-Smith, S, Barrett, DJ. When earaches and sore throats become more than a pain in the neck. Contemp Pediatr. 2000;17:156.
4. Stiehm ER, Ochs HD, Winkelstein JA. Immunodeficiency disorders: general considerations. In: Stiehm ER, Ochs HD, Winkelstein JA, editors. Immunologic disorders in infants and children. 5th ed. Philadelphia: Saunders/Elsevier; 2004. p. 289.
5. Stiehm ER. Approach to the child with recurrent infections. 2015 [online] Available from: http://www.uptodate.com/contents/approach-to-the-child-with-recurrent-infections. [Accessed December, 2015].
6. Wheeler JG. Evaluating the child with recurrent infections. Am Fam Physician. 1996;54(7):2276-82, 2285-6.

CHAPTER 62

Approach to Persistent Fever with Hepatosplenomegaly in a Child

Anupam Sachdeva, Vinod Gunasekaran

INTRODUCTION

Hepatosplenomegaly is a common clinical finding seen in infants and children presenting with fever. Hepatosplenomegaly can be associated with a variety of clinical conditions including infectious, hematological, malignant, congestive, storage disorders, connective tissue disorders, and other miscellaneous conditions. Fever can be associated in a majority of these conditions. Hence, a thorough history, clinical examination, and relevant laboratory investigations help the clinician in arriving at an early diagnosis and to initiate appropriate treatment. This chapter discusses in detail regarding a practical approach to a child with fever and hepatosplenomegaly and a simplified algorithmic approach is provided in algorithm 1.

HEPATOMEGALY

A liver that is palpable clinically does not always indicate hepatomegaly. Liver can normally be palpable in infants and young children. It can also be displaced inferiorly by pathology involving diaphragm or thoracic organs, giving the impression of hepatomegaly. Hence, the liver span measured by percussion is more reliable and it should be more than the expected for the corresponding age to consider as hepatomegaly. The normal range for liver span by percussion at 1 week of age is 4.5–5 cm. At 12 years, the normal value for boys is 7–8 cm and for girls is 6–6.5 cm. The normal range of liver span in various age-groups include: infants, 5–6.5 cm; 1–5 years, 6–7 cm; 5–10 years, 7–9 cm; and 10–15 years, 8–10 cm. Hepatomegaly generally occurs via five mechanisms:

1. Inflammation
2. Excessive storage
3. Infiltration
4. Congestion
5. Obstruction.

Infections from viruses, bacteria, fungi, and parasites promote inflammation-induced hepatomegaly. Toxins, radiation, autoimmune disease, and Kupffer cell hyperplasia also may cause hepatomegaly by this mechanism. Metastatic infiltration occurs in leukemia, lymphoma, neuroblastoma, and histiocytosis. Extramedullary hematopoiesis and hemophagocytic syndrome cause hepatomegaly due to infiltration by blood cells. Hepatomegaly due to other mechanisms may not be associated with fever usually.

Clinical Pearl

- Liver can normally be palpable in young children. Enlarged liver span signifies hepatomegaly.

SPLENOMEGALY

Spleen becomes clinically palpable only after it enlarges two to three times its normal size. Splenomegaly can be classified into three grades based on the size enlarged below the left costal margin, i.e., mild, (1–3 cm), moderate (4–7 cm), and massive (>7 cm).

Clinical Pearl

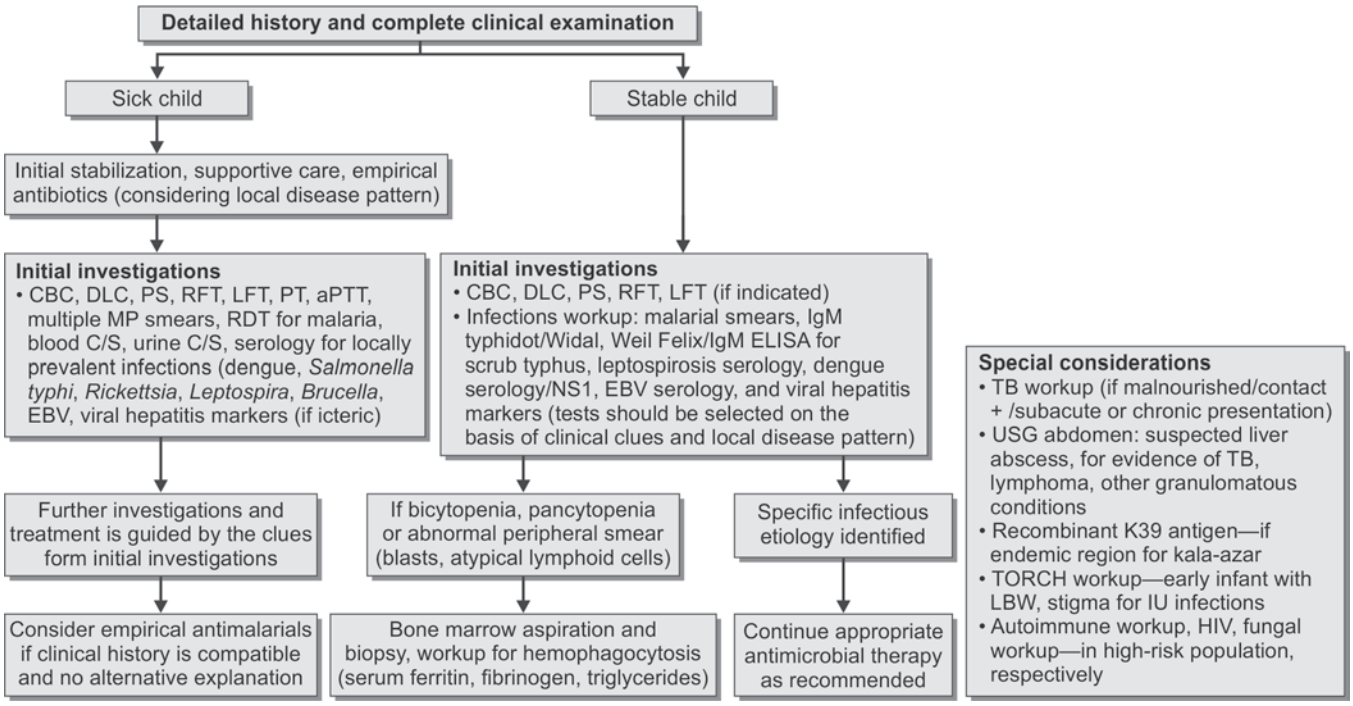
- A soft, thin spleen can be palpable in 15% of neonates, 10% of normal children and 5% of adolescents.

Causes of persistent fever with hepatosplenomegaly in a child:

- Infectious:
  - Viral
    - Infectious mononucleosis
    - Congenital Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, and Herpes Simplex (TORCH) infections
    - Human immunodeficiency virus (HIV)
    - Herpes simplex infections
    - Dengue
    - Viral hepatitis

ALGORITHM 1

Approach to persistent fever with hepatosplenomegaly in a child



CBC, complete blood count; DLC, differential leukocyte count; PS, Peripheral Smear; RFT, renal function test; LFT, liver function test; PT, prothrombin time; aPTT, activated partial thromboplastin time; RDT, rapid diagnostic test; ELISA, enzyme-linked immunosorbent assay; EBV, Epstein-Barr virus; TB, tuberculosis; USG, ultrasound; TORCH, Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, and Herpes Simplex; LBW, low birth weight; HIV, human immunodeficiency virus.

    - Bacterial
        - *Salmonella typhi*
        - Rickettsial infections
        - Leptospirosis
        - Tuberculosis
        - Borreliosis
        - Congenital syphilis
        - Brucellosis
        - Pyogenic liver abscesses
        - Infective endocarditis
        - Bacterial sepsis with disseminated intravascular coagulation (DIC)
    - Parasitic
        - Malaria
        - Kala-azar
        - Toxoplasmosis
        - Toxocariasis
    - Fungal
        - Disseminated histoplasmosis
        - Systemic candidiasis (in immunosuppressed)
- Connective tissue disorders:
    - Systemic lupus erythematosus
    - Systemic onset juvenile idiopathic arthritis
- Hemophagocytic syndromes:
    - Postinfectious
    - Familial
- Malignancies:
    - Acute leukemia
    - Lymphomas
    - Chronic myeloid leukemia
    - Neuroblastoma
- Miscellaneous:
    - Sarcoidosis
    - Chronis granulomatous disease
    - Hemolytic anemia with acute infections.

Among the various causes enumerated, infections like malaria, dengue, tuberculosis, enteric fever, viral hepatitis, septicemia, and rickettsial infections constitute a majority of children presenting with fever and hepatosplenomegaly in tropical countries. Pallor, jaundice, anorexia, rashes, and abdominal distension are the common associated complaints. Lymphadenopathy is a common associated finding. These signs and symptoms help in making a differential diagnosis and guide initial investigations.

Clinical Pearl

- In tropical regions, infections remain the common cause of fever with hepatosplenomegaly.

HISTORY

Evaluating a child with fever and hepatosplenomegaly starts with a complete history. The etiology may differ depending on the patient's age group. Acute leukemia usually presents in the age group of 2–10 years. In an infant, a careful birth history

including birth weight may uncover risk factors for perinatally acquired infections that include hepatitis B, toxoplasmosis, syphilis, cytomegalovirus, rubella, herpes simplex, enterovirus, rubella, and HIV. In older children, careful questioning about travel, insect exposure, ingestion of drugs, and environmental toxins may reveal risk factors for acute hepatitis or certain infections. Epidemiology of the patient gives clue for certain diseases like kala-azar, which is localized to certain parts of the country (Bihar and eastern Uttar Pradesh).

A prodrome of upper respiratory infection is seen in Epstein-Barr virus (EBV) infections. History of myalgia or arthralgia may be seen in viral infections and in leptospirosis. History of bony pain and tenderness is seen in acute leukemia. Acute onset of hepatomegaly associated with hyperbilirubinemia in an older child raises the suspicion of infection with hepatitis A. Previous history of recurrent infections may give a clue to underlying immunodeficiency. History of raw milk consumption may be associated with Brucellosis infection. Systemic symptoms related to chronic inflammatory diseases should be sought in the older child. History of contact with tuberculosis or a person with chronic cough is an important clue for a young child presenting with disseminated tuberculosis. Previous history of repeated transfusions, jaundice, gallstones may be a clue for an underlying hemolytic anemia, now presenting with an acute infection. Family history suggestive of a similar illness or a recent infectious illness may be a clue for a communicable or a hereditarily predisposed illness. Other nonspecific signs and symptoms include fatigue, anorexia, weight loss, blood in the stool, and abdominal distension.

PHYSICAL EXAMINATION

A careful physical examination often narrows the diagnostic considerations. Neonatal history of intrauterine growth retardation, microcephaly, chorioretinitis, and purpura accompanied by hepatomegaly strongly suggests congenital infection. Presence or absence of associated rash and the type of rash give rise to a different set of differential diagnosis. Viral exanthems are by far the most common cause of fever with rash in children. Among them, dengue, dengue-like illnesses, Herpes simplex infections, infectious mononucleosis, etc. can have associated hepatosplenomegaly. Among bacterial infections, *S. typhi*, leptospirosis, rickettsial infections, borreliosis, and brucellosis can have similar set of clinical findings. Connective tissue disorders like systemic lupus erythematosus, juvenile idiopathic arthritis can also manifest skin rashes. Presence of lymphadenopathy is usually seen in the above clinical conditions. Lymphomas can present with fever, hepatosplenomegaly, and lymphadenopathy without other manifestations.

Petechial rash may be seen in dengue hemorrhagic fever and meningococcal infections. Petechial, purpuric, and ecchymotic rashes can be seen in fulminant sepsis with DIC or in malignant conditions like acute leukemia. Bleeding manifestations can be seen in dengue, severe malaria, DIC, and acute leukemia. Other findings to be looked for include pallor, jaundice, edema, and evidence of third spacing, evidence of malnutrition, and involvement of other organ systems.

Clinical Pearl

- Detailed history, complete physical examination, and having knowledge about infections prevalent in the locality and their mode of presentations help in guiding initial investigations.

INVESTIGATIONS

Investigations should be tailored for every patient based on the clinical clues attained from history and clinical examination. Otherwise, investigations may be misleading, diagnosis may be delayed and the treatment cost would increase.

Initial Investigations

Initial investigations in most patients would include:

- Complete blood count with differential count and a peripheral blood smear examination. It gives important information about the cell lines involved and the degree of cytopenia or elevated counts. A peripheral smear might show blasts, activated lymphocytes, evidence of hemolysis, or malarial parasites which may be of diagnostic importance
- Liver functions, renal function tests (if required), in a child with signs of liver or renal dysfunction or in any sick child
- Workup for common infectious causes including blood and urine cultures, serology against infections like *Salmonella*, *Brucella*, *Rickettsia*, leptospirosis, dengue, viral hepatitis markers, and EBV, as indicated by the clinical clues and the current epidemiological pattern of infectious diseases in the patient's locality
- Multiple smears especially during febrile episodes must be sent in a child with compatible clinical picture of malaria. Although *Plasmodium falciparum* is most likely to be identified from blood just after a febrile paroxysm, the timing of the smears is less important than their being obtained several times a day over a period of 3 successive days. A single negative blood smear does not exclude malaria; it may be necessary to repeat the smears as often as every 4–6 hours a day to confirm the diagnosis. Most symptomatic patients with malaria will have detectable parasites on thick blood smears within 48 hours. Rapid diagnostic tests (RDT kits) are available for malaria, that can be done bedside without any equipments with good sensitivity and specificity. Presently, National Vector-Borne Disease Control Programme supplies RDT kits for detection of *P. falciparum* at locations where microscopy results are not obtainable within 24 hours of sample collection.

Imaging of Abdomen

Abdominal ultrasound should be considered early in a child who is toxic with tender hepatomegaly to rule out pyogenic liver abscess. Ultrasound may also give information regarding mesenteric lymphadenopathy, minimal ascites, evidence of intestinal tuberculosis, etc. in selected cases. Granulomatous lesions are detected as hypoechoic lesions in liver and spleen.

Other Investigations

- Congenital Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, and Herpes Simplex screen may be sent in neonate or an early infant with low birth weight
- Workup for tuberculosis including chest X-ray, Mantoux, sputum, or gastric lavage for acid-fast bacilli must be considered in a malnourished child or with a subacute or chronic presentation or a history of contact with an open case
- Human immunodeficiency virus has to be ruled out in a high-risk patient especially if the initial workup is negative
- Recombinant K39 antigen test should be sent in a child from an endemic area for kala-azar. This test has a sensitivity and specificity close to 100%
- Autoimmune etiology should be considered in an older child with rashes, arthralgia, polyserositis, or characteristic rash. Antinuclear antibody and double stranded deoxyribonucleic acid should be sent in such cases
- Fungal workup including fungal cultures from blood and urine, fungal serology, etc. may be considered in child with underlying immunosuppression including those on chemotherapy, myelosuppressive agents, critically-ill patients with multiple indwelling catheters, severely malnourished children, HIV-infected children, etc
- Bone marrow aspiration and biopsy may be indicated in children developing bicytopenia/pancytopenia or showing abnormal cells on peripheral smear in order to rule out hemophagocytosis or malignancy. *Leishmania donovani* bodies in bone marrow confirm the diagnosis of kala-azar
- Fine needle aspiration cytology/biopsy of peripheral lymph nodes or ultrasound-guided aspiration of mesenteric lymph nodes may be of etiological value in case of tuberculosis or lymphoma
- Systemic-onset juvenile idiopathic arthritis is usually a diagnosis of exclusion, which is made only after excluding common infectious etiology, autoimmune, and a malignant process.

TREATMENT

Treatment of the underlying etiology remains the mainstay of therapy. However, in a sick child presenting to emergency with fever and hepatosplenomegaly, initial stabilization, supportive care followed by intravenous (IV) antibiotics against the common infections prevailing in the community like enteric fever and rickettsial infections should be initiated after sending the initial etiological workup. Measures have to be taken to demonstrate malaria parasite before starting empirical antimalarial therapy. However, if clinical presentation indicates severe malaria and there is no alternative explanation these patients should be treated accordingly. Investigations should be continued simultaneously till a definitive diagnosis is made and specific therapy must be initiated.

KEY POINTS

- ☞ Hepatosplenomegaly is a common clinical finding seen in infants and children presenting with fever
- ☞ Fever with hepatosplenomegaly can be caused by infectious (viral, bacterial, parasitic, and fungal), connective tissue disorders, malignancies, hemophagocytic syndromes, and other rare conditions
- ☞ In tropical regions, infections remain the most common cause of fever with hepatosplenomegaly
- ☞ Detailed history, complete physical examination and having knowledge about infections prevalent in the locality and their presentations help in guiding initial investigations
- ☞ Complete blood count with a good peripheral smear examination and workup for common infectious etiologies give a clue to diagnosis in a majority of cases
- ☞ Treatment of the underlying etiology remains the mainstay of therapy. However, in a sick child, initial empirical therapy is justified pending investigation reports.

SUGGESTED READINGS

1. Anusha G, Somaiah G, Siddique AM, Srikanth B, Suresh Babu M, Vamsidhar NS. Study of etiological and clinical profile of hepatosplenomegaly in children between 1 month and 15 years of age. Sch J App Med Sci. 2014;2(2A):554-7.
2. Guidelines for Diagnosis and Treatment of Malaria in India. 2nd ed. New Delhi: National Institute of Malaria Research; 2011.
3. Kliegman RM, Stanton BF, Geme JW, Schor NF, Behrman R, editors. Nelson Textbook of Pediatrics. 19th ed. Elsevier Saunders; 2011.
4. Lakshmanaswamy A. Clinical Paediatrics. History Taking and Case Discussion. 3rd ed. Wolters Kluwer Health/Lippincott Williams and Wilkins (India); 2012.
5. Paul V, Bagga A. Ghai Essential Paediatrics. 8th ed. CBS Publishers; 2013.
6. Sarkar R, Mishra K, Garg VK. Fever with rash in a child in India. Indian J Dermatol Venereol Leprol. 2012;78(3):251-62.
7. Wolf AD, Lavine JE. Hepatomegaly in neonates and children. Pediatr Rev. 2000;21(9):303-10.

CHAPTER 63

Approach to a Bleeding Child

Nitin K Shah

INTERPRETATION OF ALGORITHM

Hemostasis is a delicate balance between fluidity of blood so that it can circulate freely within blood vessels and coagulation so that any breach in continuity of blood vessels can be sealed efficiently and immediately so as not to exsanguinate the body. This delicate balance is maintained mainly by three factors, namely, vascular and extravascular tissues, platelets, and plasma factors. Any disturbance in these three factors will lead to either bleeding or excessive clotting (thromboembolism).

Successful management of an acute bleeding episode in a child mainly depends on the ability to make a rapid diagnosis and prompt implementation of therapeutic measures. Proper detailed history and thorough clinical examination often suggest the presence and type of bleeding disorder. However, accurate diagnosis which is required for specific therapy depends on laboratory tests. A careful history also provides critical information in selecting subsequent tests thus avoiding a battery of investigations. Further workup becomes necessary when there is:

- A recent bout of bleeding: spontaneous or after injury or surgery—usually prolonged and disproportionate to extent of injury
- Family history of bleeding episodes
- Preparation for surgery or invasive procedures
- Systemic diseases known to be associated with bleeding disorders, e.g., liver disorder, renal disorder, disseminated intravascular coagulation (DIC), sepsis, etc.

Whenever a child presents with bleeding episode it is necessary to decide:

- Whether bleeding is significant?
- Whether it is due to local causes, or whether it is a generalized hemostatic defect?
- What is the nature of the bleeding episode? Is it due to vascular, platelet, or a coagulation abnormality or a combination of two or more?
- Is it congenital or acquired?

CLINICAL HISTORY

Local versus Generalized Bleeding

Local cause should be suspected when bleeding is from a single site and recurs often from the same site, e.g. epistaxis with bleeding from left nostril recurring every time from the same nostril. Such bleeding should lead to a suspicion of local causes such as a polyp or a foreign body. However, if bleeding is from both nostrils or from any of the nostrils and patient gives history of hematuria or a past history of excessive bleeding after tooth extraction, then it is more likely to be due to a systemic defect. Common local causes of bleeding are shown in table 1.

In generalized bleeding disorders, bleeding is spontaneous or greater than expected for extent of injury or the site of bleeding and bleeding is from multiple sites like skin and mucous membrane, bleeding into interstitial tissue, muscles, joints, etc.

Platelet/Vascular Type versus Coagulation Type of Bleeding

Bleeding following vascular disorder, thrombocytopenia, or functional platelet disorders is usually in the form of spon-

TABLE 1: Common local causes of bleeding based on site of bleeding

Site of bleeding	Local cause of bleeding
Epistaxis	Deviated septum, hypertrophic turbinate, ectatic vessel
Oral	Poor dental hygiene
Upper gastrointestinal	Swallowed blood in newborn, varices, hemangioma
Lower gastrointestinal	Rectal polyp, Meckel's diverticulum, anal fissure
Hematuria	Cystitis, bladder stone, renal tumor
Umbilicus	Slipped ligature, granuloma

taneous subcutaneous and mucous membrane bleeds like petechiae, purpura, superficial, and few ecchymosis, epistaxis, and menorrhagia. It is often controlled by pressure and once controlled, it usually does not recur. However, in patients with coagulation factor deficiency, hematomas are usually deep (in the muscles) and spreading, bleeding into cavities like joints and retroperitoneal space is known. Post-traumatic bleeds are often delayed, sometimes hours after the injury. This may recur and bleeding may not get controlled by pressure.

Inherited versus Acquired Causes

Inherited Causes

- Age of presentation: inherited disorders usually present in infancy and early childhood with history of bleeding from the umbilical cord, without evidence of sepsis or slipped ligature; spontaneous large cephalhematoma during early neonatal period, bleeding during the eruption or fall of deciduous tooth, etc.; exception being mild hemophilia though inherited cause of bleeding presenting late in life say following a surgery. Whereas acquired bleeding disorders present at any age, usually later in life, like idiopathic thrombocytopenic purpura (ITP) presenting at 3–5 years of age, exception being hemorrhagic disorder of newborn due to vitamin K deficiency though being acquired cause of bleeding presenting in first week of life
- Family history: proper family history of bleeding disorders of at least 2–3 generations on each side of parents (including those who might have died) and noting the pedigree chart helps in realizing the mode of transmission of the disorder such as sex-linked recessive, autosomal recessive or autosomal dominan
    - X-linked recessive inheritance: females are carrier and males are affected. Only male siblings, males on maternal side including maternal male cousins, maternal uncles, and maternal grandfather are affected. This is typically seen in hemophilia A and B or Wiskott-Aldrich syndrome
    - Autosomal recessive inheritance: both parents of affected person are heterozygotes and often there is a history of consanguinity. Siblings of either sex and both maternal as well as paternal cousins of either sex are affected (horizontal transmission). This pattern is typical of disorders of factor II, V, VII, X, XI, XII, and XIII deficiency
    - Autosomal dominant inheritance: there is vertical transmission as the proband is affected, one of the parents is affected and grandparents may be affected with variable penetrance and variable severity within families. This is seen typically in Von Willebrand disease, some types of qualitative platelet defects, dysfibrinogenemia, and hereditary hemorrhagic telangiectasia. Some of the cases may be spontaneous mutation with negative family history
    - Although a positive family history is of great value in the diagnosis of bleeding disorders, a negative family history does not rule out the possibility of inherited bleeding disorders. Family history might be negative, if the coagulation defect is mild or there is a spontaneous mutation, as is seen in 20% of patients with hemophilia A
- Site of bleeding: superficial bleeding is more common in platelet type of bleeding and most common platelet disorder is ITP which is acquired cause of bleeding whereas deep bleeding especially muscle hematoma or joint hematoma are typically seen in coagulation factor deficiency like hemophilia which are inherited causes of bleeding.

Acquired Causes

Conversely, patients with acquired disorders usually present later in life and have a negative family history. They may be associated with underlying systemic disorders like kidney diseases and liver disorders, infections, etc. Previous history of operations like circumcision, dental extraction, tonsillectomy, or major operation practically rules out the possibility of a moderate to severe inherited bleeding disorder. Absence of bleeding from previous trauma, however, does exclude an inherited bleeding disorder. Patients of mild hemophilia with factor level around 10–25% may bleed only after severe trauma. Subject with normal hemostasis may also have bleeding from nonhematological causes as seen in females with menorrhagia or of molar tooth extraction. History of ingestion of drugs like aspirin, in the recent past should lead to the suspicion of a transient drug related hemostatic defect. Similarly, history of oral contraceptives or pregnancy may temporarily increase factor VIII and Von Willebrand factor levels and thus increasing the hemostatic competency in women with Von Willebrand disease.

Associated Underlying Disorders

Certain characteristic hemostatic defects are associated with specific clinical conditions, e.g., liver diseases with factor II, VII, IX, and X deficiency and fibrinolysis due to decreased clearance of activators and hypercoagulable state because of antithrombin III and protein C deficiency. Malabsorption states may be associated with vitamin K deficiency. Acute promyelocytic leukemia is known to be associated with DIC due to increased cellular procoagulant activities. Myeloproliferative disorder may have platelet defects, thrombocytopenia, and thrombocythemia. Amyloidosis may be associated with factor X deficiency and capillary fragility. Systemic lupus erythematosus (SLE) and antiphospholipid antibody (APLA) syndromes may be associated with thrombocytopenia, acquired hemophilia or acquired Von Willebrand disease or on the other hand with hypercoagulable states.

Clinical Pearls

Questions to be asked while history taking in a bleeding child:

- It the bleeding significant?
- Is the bleeding due to local cause or systemic cause?
- Is the bleeding platelets/vascular type or coagulation type?
- Is the bleeding due to congenital or acquired cause?

EXAMINATION

Well versus Sick Child

Well child with no fever, pain, organomegaly, bleeding, bone pains, or weight loss would suggest ITP, whereas sick child would suggest other causes like bone marrow failure or infiltrates.

Pallor and Organomegaly

Sick child with presence of pallor out of proportion of external bleeding would suggest bone marrow suppression like in malignancies and aplastic anemia. Presence of organomegaly like hepatomegaly, splenomegaly and significant lymphadenopathy, weight loss, and bony tenderness would suggest malignancies whereas absence of organomegaly and bony tenderness would suggest aplastic anemia.

Site of Bleeding

Presence of superficial bleeds like petechiae, purpura, and few superficial ecchymosis suggest ITP, vascular cause, or platelet dysfunction. Deep bleeding like muscle hematoma, exsanguinating hematomas, retroperitoneal bleeds, and joint bleeds are pathognomonic of coagulation disorders like hemophilia.

Associated Syndromes

There are some specific systemic disorders which have bleeding as a significant problem and have pathognomonic tell-tale signs as shown in table 2. This includes presence of

- Skeletal deformities, mental retardation, hypogonadism, short stature, hyperpigmentation, and renal anomalies in Fanconi's anemia
- Absent radius in thrombocytopenia with absent radius (TAR) syndrome
- Ataxia, mucosal telangiectasia, and mental subnormality in ataxia telangiectasia
- Partial albinism in Hermansky-Pudlak syndrome
- Syndactyly or lobster hand in factor V deficiency
- Keloids in children with afibrinogenemia and factor XIII deficiency
- Cigarette paper scar, hyperextensible joints, cutis elastic in Ehlers- Danlos syndrome
- Hematochezia, thrombocytopenia, recurrent infection, otitis media, and eczema in a male child with Wiskott-Aldrich syndrome
- Giant hemangioma associated with evidence of clinical and subclinical DIC and thrombocytopenia in Kasabach-Merritt syndrome.

Clinical Pearls

Questions to be asked while examining a bleeding child:

- Is he a well or a sick child?
- Is there organomegaly?
- Are there other systemic disorder signs?
- Are there physical anomalies, especially skeletal deformities?

TABLE 2: Syndromes associated with specific bleeding disorders

Associated condition	Interpretation
Oral or nasal telangiectasia, ataxia	Hereditary telangiectasia
Partial albinism	Hermansky-Pudlak syndrome
Syndactyly	Factor V deficiency
Skeletal malformation, short stature	Fanconi's anemia
Absent radius	Thrombocytopenia-absent radius syndrome
Injury marks, rib fractures, subdural hemorrhage	Battered baby syndrome
Linear purpura at accessible sites	Fictitious purpura
Keloids	Afibrinogenemia
Cigarette paper scar, hypermobile joints	Ehlers-Danlos syndrome
Thrombocytopenia, eczema, ear discharge	Wiskott-Aldrich syndrome
Giant hemangioma	Kasabach-Merritt syndrome

INVESTIGATIONS

No single test is suitable for the laboratory evaluation or the overall process of hemostasis and blood coagulation. Laboratory tests can be conveniently divided into screening tests and special tests. Screening tests are applied only after evaluating the nature and clinical circumstances of bleeding and prior to surgery, so as to know the presence and nature of bleeding disorder so that special tests can be done to confirm the diagnosis thus avoiding a battery of unnecessary tests.

Screening Tests

Screening tests include:

- Complete blood count (CBC) and peripheral smear (PS) examination
- Platelet count
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Thrombin time
- Bleeding time (BT), clotting time, and clot retraction (rarely).

Interpretation of the screening tests is always done together and never in isolation as shown in the table 3.

Complete blood count and PS examination: CBC tells the involvement of red blood cell series (Hb and red cell indices), white blood cell series (total leukocytes and absolute neutrophil count), and platelet series. Peripheral smear examination will confirm all these three cell series involvement and give clue to the probable diagnosis like leukemia, etc. For platelets, PS is more reliable than machine reports. Presence of 10–15 platelets per high power field and presence of platelet clumps will suggest normal platelet counts. Large platelets are seen in regenerative thrombocytopenia as seen in ITP, normal size platelets are seen as in aregenerative cause of

TABLE 3: Interpretation of screening tests for bleeding

Clinical bleeding	aPTT	PT	TCT	Bleeding time	Platelet count	Possible defects
Absent	Abnormal	Normal	Normal	Normal	Normal	High-molecular-weight kininogen, prekallikrein, factor XII, lupus inhibitor
Present	Abnormal	Normal	Normal	Normal	Normal	Factor XI, IX, VIII deficiency
Present	Abnormal	Abnormal	Normal	Normal	Normal	Factor V, X, II, coumarin, vitamin K deficiency, mild hepatic disease
Present	Normal	Abnormal	Normal	Normal	Normal	Factor VII deficiency
Present	Abnormal	Normal	Normal	Abnormal	Normal	Von Willebrand disease
Present	Abnormal	Abnormal	Abnormal	Abnormal	Normal	Afibrinogenemia
Present	Normal	Normal	Normal	Abnormal	Abnormal	Thrombocytopenia
Present	Normal	Normal	Normal	Abnormal	Normal	Qualitative platelet disorder (aspirin, thrombasthenia, Bernard-Soulier syndrome)
Present	Normal	Normal	Normal	Normal	Normal	Factor XIII deficiency
Present	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Disseminated intravascular coagulation, severe liver disease
Variable	Normal	Normal	Abnormal	Normal	Normal	Dysfibrinogenemia, myeloma, fibrinogen/ fibrin degradation products
Present	Abnormal	Normal	Abnormal	Normal	Normal	Heparin

TCT, thrombin clotting time; PT, prothrombin time; aPTT, activated partial thromboplastin time.

thrombocytopenia like aplastic anemia, giant platelets are seen as in Bernard-Soulier syndrome, microplatelets are seen as in Wiskott-Aldrich syndrome, and presence of normal platelets but not in clumps will indicate absence of aggregation, suggesting platelet functional disorder.

Platelet count: it is a simple first step in evaluating the cellular aspect of hemostasis. However, manual count is not reliable and not reproducible and hence platelet count should be done on particle cell counter or using phase contrast microscope. In platelet type of bleeding, if platelet count is normal or marginally low, vascular or platelet functional disorders should be kept in mind.

Prothrombin time, aPTT, and TT: aPTT is an excellent screening test for determining abnormality of intrinsic clotting pathway and common pathways and is sensitive to activities of approximately 20% or less of factor VIII and IX or XI. aPTT is prolonged during deficiency or abnormalities of extrinsic pathway clotting factors like high molecular weight, kininogen, prekallikrein, factor XII, XI, IX, VIII; or of common pathway clotting factors like X, V, II, and fibrinogen; or by inhibitors of blood coagulation such as lupus inhibitors, heparin, and fibrin/fibrinogen degradation product. Activated partial thromboplastin time of test more than 10 seconds over control is considered abnormal.

Prothrombin time measures extrinsic clotting system and the common pathway. It is measured as International Normalized Ratio (INR) and is considered abnormal when INR is more than 1.2, however, if INR is not available it is considered abnormal when test Prothrombin time is more than 3 seconds over control. PT is prolonged with deficiencies of intrinsic pathway clotting factor like VII; or common pathway factors like X, V, II, and fibrinogen and inhibitors of these factors.

Thrombin time measures thrombin induced conversion of fibrinogen to fibrin and is abnormal in patients with hypofibrinogenemia whether acquired or congenital or dysfibrinogenemia and in presence of inhibitors like heparin, myeloma proteins and fibrin degradation products which block either thrombin cleavage of fibrinopeptide or fibrin monomer polymerization.

A prolongation of PT with normal partial thromboplastin time (PTT) that is corrected by adding normal pooled plasma indicates factor VII deficiency that occurs with congenital deficiency, early during oral anticoagulant therapy, vitamin K deficiency, or liver diseases. This is further confirmed by factor VII assay.

A prolonged aPTT with normal PT which is corrected by adding normal pooled plasma will suggest deficiency of factor VII, IX, XI, or XII, however, factor XII deficiency does not manifest clinically with bleeding and in fact presents with thromboembolism hence leaving deficiency of factor VIII, IX or XI as the cause. This can be confirmed further by doing factor VIII, factor IX, and factor XI assay in that order based on their incidence.

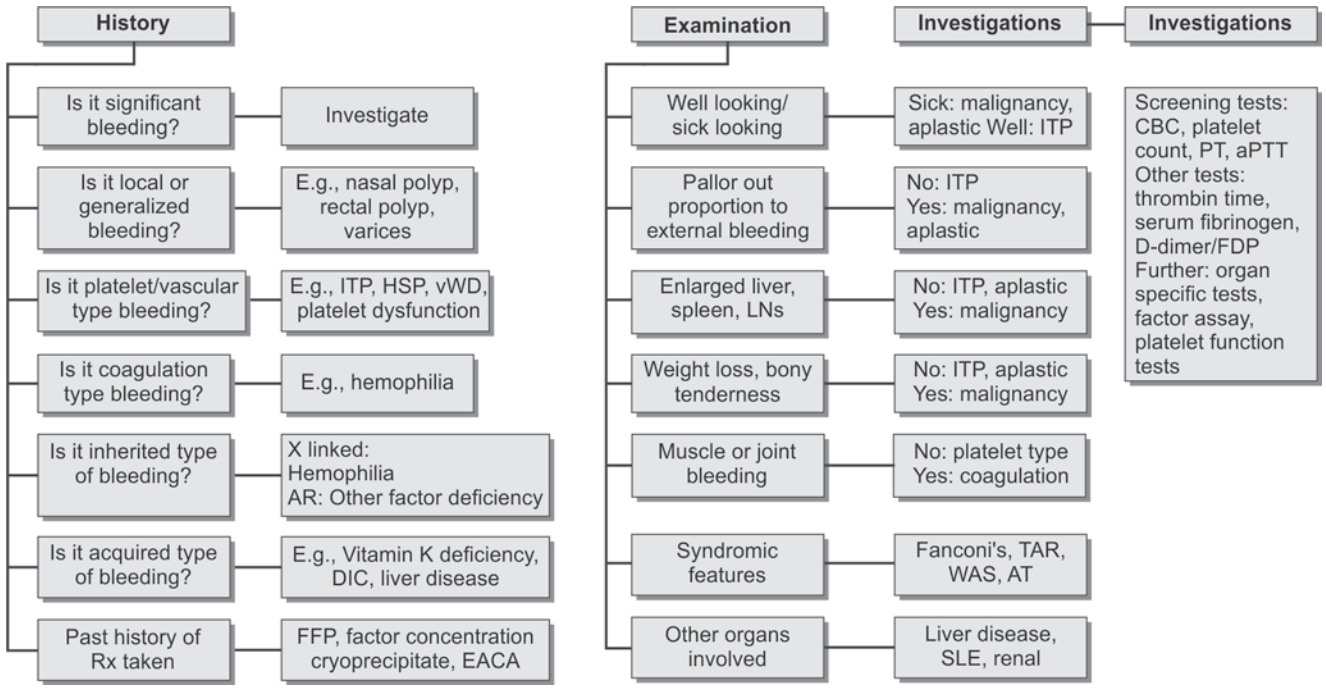
Prolongation of both PT and aPTT would suggest common pathway factor deficiency like factor X, V, II, or fibrinogen; or multiple factor deficiency of intrinsic as well as extrinsic pathways as seen in chronic liver disease or vitamin K deficiency.

Prolonged TT would suggest fibrinogen deficiency or dysfunction. Prolonged TT with normal serum fibrinogen would suggest dysfibrinogenemia, and with low or absent fibrinogen levels would suggest hypo- or afibrinogenemia.

Prolonged aPTT should be screened for presence of inhibitor doing correction study where 1 mL of test plasma is mixed with 1 mL of pooled normal plasma and aPTT

ALGORITHM 1

Approach to a bleeding child



ITP, idiopathic thrombocytopenic purpura; HSP, Henoch-Schönlein purpura; vWD, von Willebrand disease; LN, lymph node; DIC, disseminated intravascular coagulation; FFP, fresh-frozen plasma; EACA, epsilon aminocaproic acid; TAR, thrombocytopenia and absent radius; SLE, systemic lupus erythematosus; CBC, complete blood count; PT, prothrombin time; aPTT, activated partial thromboplastin time; FDP, fibrinogen/fibrin degradation products.

is repeated at zero and 4 hours. If aPTT corrects by more than 50%, it suggests factor deficiency. If aPTT does not correct and even worsens after 4 hours of incubation, it suggests of presence of inhibitor which is then confirmed by doing inhibitor assay. In such cases one must also rule out autoimmune disorders like APLA syndrome and SLE by doing appropriate tests.

Others

Bleeding time: this test evaluates primary hemostatic stage and is ideally done with the help of template. The normal BT is 4–7 minutes and prolongation of BT usually occurs at platelet count less than 50,000/cumm. At counts below 10,000/cumm, BT is usually prolonged and is often 15 minutes or longer and hence BT in severe thrombocytopenia is not required and can be hazardous as it can lead to scarring.

Qualitative platelet disorders have prolonged BT with nearly normal platelet count as seen in Glanzmann's thrombasthenia, Bernard-Soulier syndrome, storage pool disorder, Wiskott-Aldrich syndrome and with various drugs like aspirin and nonsteroidal anti-inflammatory agents like ibuprofen, etc. Even in Von Willebrand disease, BT is usually prolonged as Von Willebrand factor is involved in binding of platelets to matrix protein or to other cells. One can do platelet aggregation study to prove platelet functional disorders as shown in table 4. This can be confirmed by doing

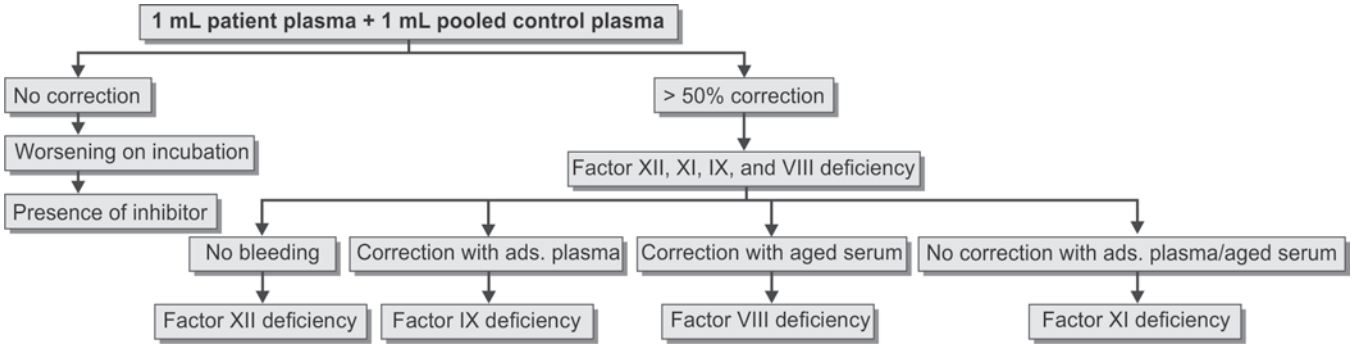
TABLE 4: Platelet aggregation study (for platelet dysfunction)

Disorder	ADP		Collegen	Adrenalin	Restocetin	Arachidonic acid
	Primary	Secondry				
Thrombasthenia	ABN	ABN	ABN	ABN	N	ABN
Bernard-Soulier syndrome	N	N	N	N	ABN	N
Von Willebrand disease	N	N	N	N	ABN	N
Cyclo-oxygenase deficiency Thromboxane synthetase deficiency	N	—	ABN	ABN	N	ABN
Storage pool disorder	N	ABN decreased	ABN	ABN	N	N or decreased
Aspirin defect	N	ABN decreased	ABN	ABN	N	ABN

N, normal aggregation; ABN, impaired aggregation.

ALGORITHM 2

Correction studies when activated partial thromboplastin time is prolonged



aPTT, activated partial thromboplastin time.

platelet surface receptor studies for gpIIB/IIIA or gpIX which are now widely available.

Clot retraction: retraction and exudation of the serum after 1 hour is observed in the clotting tube. Normally, 50% exudation at the end of 1 hour of the original blood volume is taken as normal retraction. However, with the advent of platelet aggregation study and platelet receptor study, this test has become obsolete.

Factor XIII assay: factor XIII deficiency presents with delayed umbilical cord falling, intracranial bleeds, or delayed bleeding from wounds with poor healing. Screening tests for bleeding are normal in such cases; one can do 5 molar urea solubility test to prove factor XIII deficiency.

Clinical Pearls

Never do bleeding time (BT) and clotting time (CT) as screening tests.

Always do following tests:

- CBC with platelets counts and a peripheral smear for platelet morphology
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Thrombin time (TT) with S. fibrinogen.

Bleeding Disorders with Normal Screening Tests

Bleeding disorders not associated with any abnormalities in screening tests are:

- Vascular causes like Henoch-Schonlein purpura, hereditary telangiectasia (Pender-Osler-Weber syndrome), scurvy, Ehlers-Danlos syndrome, senile purpura, simple purpura (seen in 10% of women)
- Factor XIII deficiency
- Fibrinolytic pathway defects like α-2 antiplasmin deficiency
- Amyloidosis (may or may not be associated with factor X deficiency)
- Mild clotting factor deficiency.

MANAGEMENT OF BLEEDING CHILD

Management of a bleeding child will include general supportive care and specific supportive care and treatment of primary disease (the list is vast and beyond the scope of this chapter).

General supportive care: this will include volume expansion using crystalloids and colloids, inotropes for falling blood pressure, oxygen to improve tissue oxygenation, and treatment of primary disease if any.

Specific supportive care: it includes packed red blood cells to maintain hemoglobin in physiological range, platelets to arrest bleeding in a case of thrombocytopenia (mainly in cases due to decreased production), DIC [along with fresh-frozen plasma (FFP)] and platelet dysfunction; FFP in cases with coagulopathy; specific factor replacement in a case of known clotting factor deficiency; use of cryoprecipitate to increase fibrinogen levels; use of factor eight inhibitor bypassing activity or activated prothrombin complex concentrates in hemophilia with inhibitor; plasma exchange in a case of any inhibitors; and activated factor VII for nonresponsive bleeding due to any cause.

KEY POINTS

- ☞ Ascertain whether bleeding is significant, platelet/vascular/coagulation type
- ☞ Ascertain whether the child is well or sick and whether it is inherited or acquired in origin
- ☞ Always to complete screening tests and not bleeding time/clotting time
- ☞ Idiopathic thrombocytopenic purpura is the most common bleeding disorder in children
- ☞ Presence of organomegaly, fever, and anemia out of proportion to bleeding should arouse suspicion of systemic disease.

SUGGESTED READINGS

1. Bachmann HF. Diagnostic approach to mild bleeding disorders. Semin Hematol. 1980;17:292-305.
2. Bithell TC, editor. Bleeding disorders caused by vascular abnormalities. Wintrobe's Clinical Hematology. 9th ed. Philadelphia: Lea & Febiger; 1993. pp. 1374-89.
3. Bowie EJ, Owen CA. Significance of abnormal preoperative hemostatic test. Pros Hemost Thromb. 1980;5:179-209.
4. Fisher S, Rikover M, Noor S. Factor XIII deficiency with severe hemorrhagic diathesis. Blood. 1966;28:34.
5. Gilbert C, White II, Marder VJ, Colman RW, et al. Approach to bleeding patient. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, editors. Hemostasis and Thrombosis. Philadelphia: JB Lippincott Co; 1987. pp. 1048-960.
6. Ingram GI. Investigation of a long-standing bleeding tendency. Br Med Bull. 1977;33:261-4.
7. Lowe GD, Forbes CD. Laboratory diagnosis of congenital coagulation defects. Clin Haematol. 1979;8:79-94.
8. Miller CH, Graham JB, Goldin LR, Elston RC. Genetics of classic von Willebrand's disease. I. Phenotypic variation within families. Blood. 1979;54:117-36.
9. Osler W. On a family form of recurring epistaxis, associated with multiple telangiectases of skin and mucous membranes. Bull John Hopkins Hosp. 1901;7:333-7.
10. Seeler RA. Parahemophilia. Factor V deficiency. Med Clin North Am. 1972;56: 119-25.
11. Uden A. Collagen and bleeding diathesis in Ehlers-Danlos syndrome. Scand J Haematol. 1982;28:425-30.

CHAPTER 64

Clinic Pathological Approach to Coagulation Disorder

Sangeeta S Mudaliar, Bharat Agarwal

INTRODUCTION

Bleeding in a child can be a diagnostic challenge because of the wide range of possible causes. Evaluation of a child presenting with bleeding should include a comprehensive medical and bleeding history, a complete family history, a detailed physical examination, and selected laboratory tests. Investigations and lab tests should be requested based on history and clinical findings.

This chapter will be focussed on the laboratory tests, their interpretation, and significance on arriving at a diagnosis of various bleeding disorders. Bleeding disorders can be inherited or acquired, and include coagulation factor deficiencies, platelet deficiencies and/or dysfunctions, and von Willebrand disease (vWD).

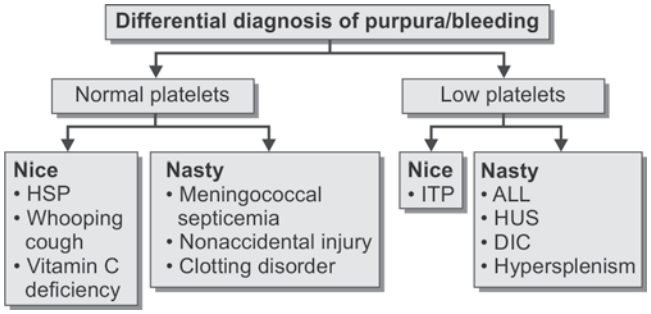
Algorithm 1 represents the differential diagnosis of various clinical conditions which may present with purpura or bleeding. The various disease conditions have been grouped as nice (benign course) or nasty (malignant or life threatening or prolonged course).

Algorithm 2 gives an approach to causes of mucosal and superficial skin bleeding while algorithm 3 gives an approach to conditions which present with large ecchymosis and/or joint bleeding .

Algorithm 4 explains a comprehensive approach to a child presenting with bleeding and/or abnormal coagulation screening test.

ALGORITHM 1

Clinical differential diagnosis of purpura/bleeding in a child



HSP, Henoch-Schonlein purpura; ITP, immune thrombocytopenia; ALL, acute lymphocytic leukemia; HUS, hemolytic uremic syndrome; DIC, disseminated intravascular coagulation.

SCREENING TESTS

Initial tests to screen for bleeding disorders should include a complete blood count (CBC) with platelet counts, blood film, prothrombin time (PT), and activated partial thromboplastin time (aPTT).

Sample collection: improperly collected sample is the most common cause of falsely elevated clotting time. Also, samples collected from indwelling catheters give spuriously abnormal values due to contamination with heparin or intravenous fluids.

Samples should be collected in tubes containing citrate (3.2 or 3.8%) as anticoagulant. The ratio of citrate to whole blood should be 1:9. This needs to be adjusted if patient has high hematocrit. For infants and children, small 3 mL tubes (2.7 mL blood to 0.3 mL citrate) should be used.

Samples should be tested within 2 hours of collection if at room temperature or within 4 hours if kept cold.

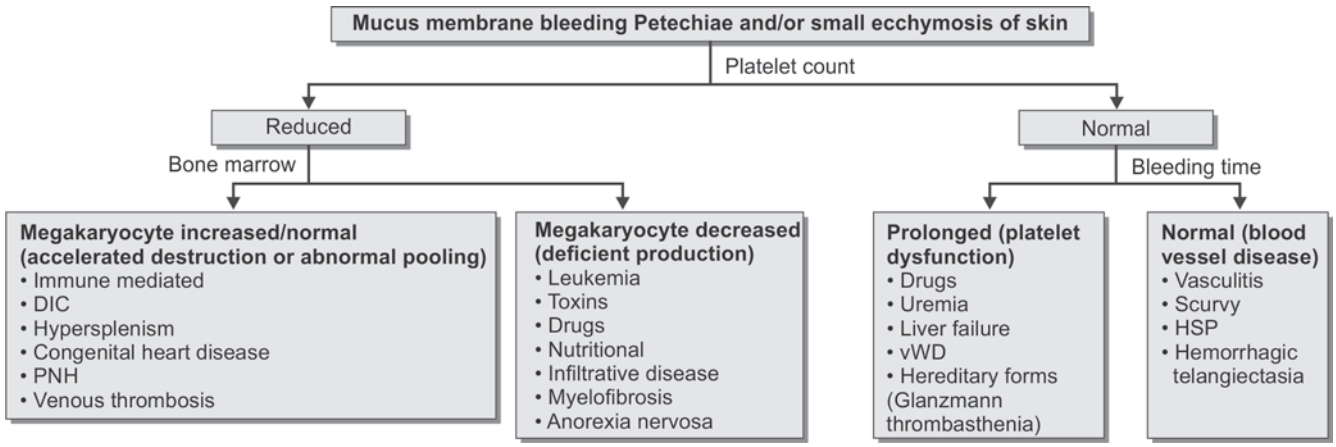
Complete Blood Count

Complete blood count [blood collected into ethylene-diamine tetraacetic acid (EDTA)] is performed to exclude thrombocytopenia. Complete blood count also provides information about additional cytopenias and other white blood cell (WBC) and red blood cell (RBC) abnormalities. Peripheral blood film (blood collected into EDTA) provides additional information regarding platelet number, size, clumping, and granularity (the platelet count can be estimated by the number of platelets per ×100 field multiplied by 20×10^9/L).

Pseudothrombocytopenia resulting from clumping of platelets collected in EDTA anticoagulant can be identified by examination of the blood film, and confirmed by recollecting a specimen in citrate anticoagulant in which clumping

ALGORITHM 2

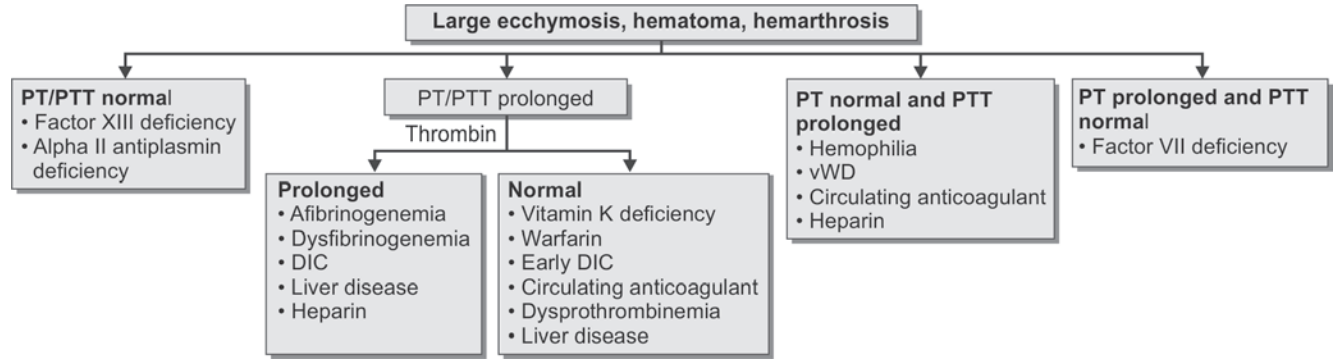
Workup of a patient with a defect in primary hemostatic mechanism



DIC, disseminated intravascular coagulation; PNH, paroxysmal nocturnal hemoglobinuria; vWD, von Willebrand disease; HSP, Henoch-Schonlein purpura.

ALGORITHM 3

Approach to defects in plasma phase lab



PT, prothrombin time; PTT, partial thromboplastin time; vWD, von Willebrand disease; DIC, disseminated intravascular coagulation.

will not occur. If true thrombocytopenia is diagnosed, the next step is to differentiate between new onset acquired thrombocytopenia, chronic acquired thrombocytopenia, and congenital thrombocytopenia.

Evaluation of WBC morphology allows identification of malignant blasts, granulocyte inclusions, such as Dohle-like bodies, or other WBC abnormities. Evaluation of RBC morphology is important to exclude a microangiopathic process as evidenced by presence of fragmented RBCs, microcytosis, macrocytosis, and other RBC abnormalities.

Clinical Pearl

- Improperly collected samples are one of the most common causes of spurious lab results.

Prothrombin Time/International Normalized Ratio

Prothrombin time/International Normalized Ratio (INR) (blood collected into citrate) measures the extrinsic and common pathway in the coagulation cascade (tissue factor, FVII, FX, FV, FII, fibrinogen). Results should be compared with age-specific laboratory reference intervals, and are reported in seconds and/or as a percentage of a normal control sample. The INR is the ratio of a patient's PT to a normal control sample, raised to the power of the ISI value for the analytical system used: INR = (observed PT/control PT) ISI, where ISI = international sensitivity index (sensitivity of thromboplastin).

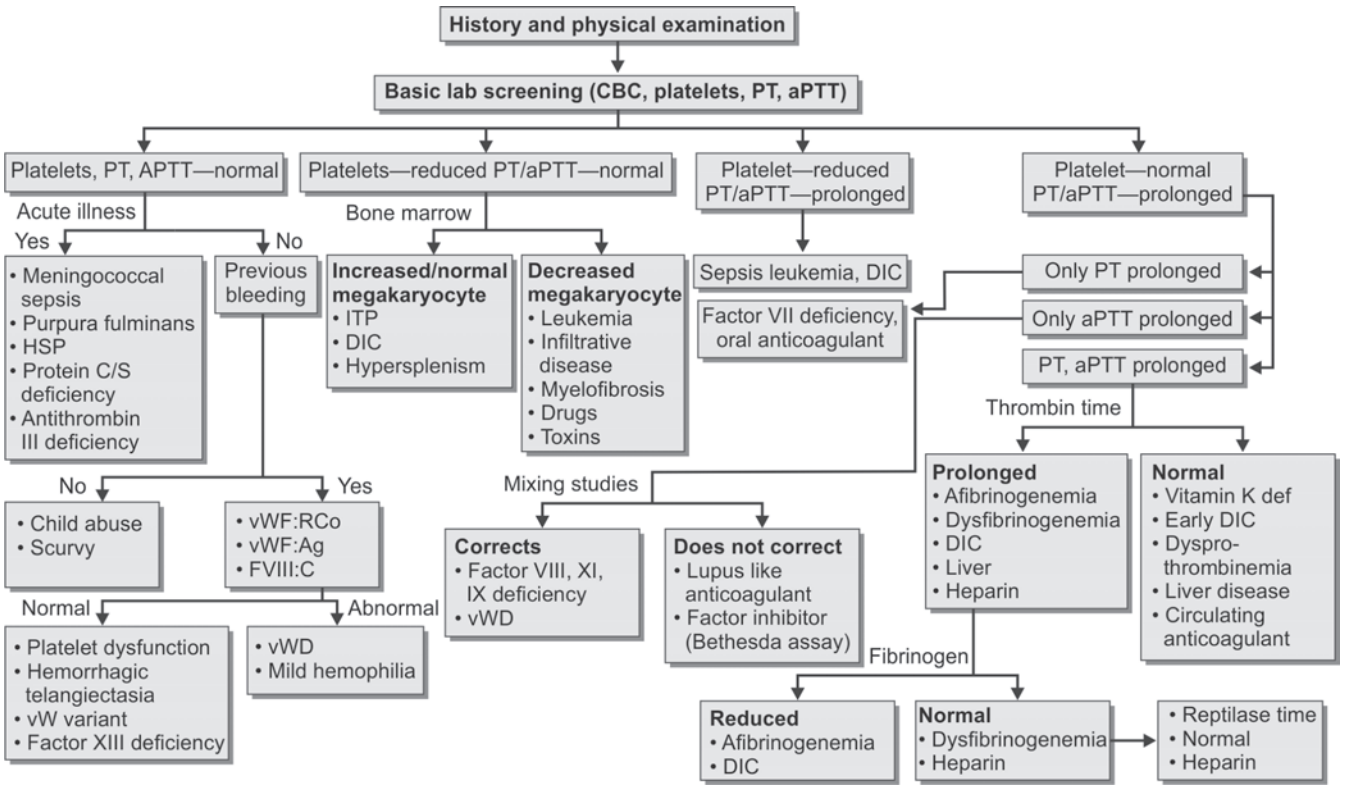
A prolonged PT/high INR (with normal aPTT) suggests FVII deficiency, or use of vitamin K analogs such as warfarin. The PT is performed by adding a thromboplastin reagent that contains calcium chloride to the citrated plasma sample of patient. The time required for clot formation is recorded using an automated instrument.

Activated Partial Thromboplastin Time

Activated partial thromboplastin time measures the intrinsic and common pathways of coagulation (FXII, FXI, FIX, FVIII, FX, FV, FII, fibrinogen). The aPTT is less sensitive than the PT to deficiencies of the common pathway factors. Results should be compared with age-specific laboratory reference intervals, and results are reported in seconds.

ALGORITHM 4

Evaluation of a child with bleeding or abnormal coagulation screening tests



CBC, complete blood count; PT, prothrombin time; aPTT, activated partial thromboplastin time; ITP, immune thrombocytopenia; DIC, disseminated intravascular coagulation; vWF, von Willebrand factor; vWD, von Willebrand disease; vWF:RCo, vWF:ristocetin ; vWF:Ag, vWF:antigen.

An abnormally prolonged aPTT (with normal PT/INR) suggests FVIII, FIX, FXI, or FXII deficiency. An aPTT within the reference range does not reliably exclude mild FVIII, FIX, or FXI deficiency. Therefore, factor assays should be performed if specific deficiencies are suspected.

Factor XII deficiency causes a prolonged aPTT, but is not associated with clinical bleeding. A prolonged aPTT can occur in severe vWD, as a result of the associated FVIII deficiency.

The aPTT is also prolonged in the presence of inhibitors including heparin. Heparin contamination occurs most often in specimens drawn from arterial or central venous catheters. To avoid heparin contamination, an adequate volume of blood should be removed prior to sampling. Where that is not possible, heparin neutralization can be performed, usually by the addition of heparinase to the sample plasma.

Combined prolongation of PT/INR and aPTT can result from inherited deficiencies of individual factors in the common pathway: FX, FV, FII, and fibrinogen, or from the rare inherited deficiency of the vitamin K-dependent coagulation factors. More commonly, combined abnormalities of aPTT and PT/INR are the result of acquired deficiencies of multiple coagulation factors. The aPTT is performed by adding a partial thromboplastin reagent to citrated plasma sample. The sample is preincubated with a surface activating reagent (like celite, kaolin, silica, or ellagic acid) to introduce controlled activation of contact factor (FXI, FXII, prekallikrein, and high-molecular weight kininogen). This mixture is then incubated for 2–5 minutes before adding calcium chloride and recording the time to clot formation by automated instrument.

A summary of clinical conditions presenting with prolonged PT and aPTT are tabulated in table1.

Mixing Study

A mixing study (blood collected into citrate) is done when an abnormal PT and/or an aPTT is identified. The patient's plasma is mixed with normal plasma in a 1:1 ratio, and the screening tests are repeated. This test differentiates between factor deficiency (mixing corrects the PT or aPTT) and the presence of an inhibitor (mixing does not correct the PT or aPTT). The most common inhibitor that results in noncorrection of the aPTT with mixing is a lupus anticoagulant. This is often an incidental finding in children and is not associated with clinical bleeding. Specialized assays will confirm its presence. Specific factor inhibitors also interfere with correction of screening tests by mixing with normal plasma. Confirmation requires specific inhibitor assays.

Prothrombin time and aPTT reagents used for testing have variable sensitivities to coagulation factors and insensitive reagents may result in false negative (i.e., normal) results for mild deficiencies. If there is a strong suspicion of a coagulation factor deficiency, specific factor assays should be performed.

TABLE 1: Causes of prolonged prothrombin time and activated partial thromboplastin time

Prolonged PT	Prolonged aPTT	Prolonged PT and aPTT
Inherited		
Factor VII deficiency	vWF, factor VIII, IX, XI, or XII deficiency	Prothrombin, fibrinogen, factor V, X, or combined factor deficiency
Acquired		
Vitamin K deficiency	Heparin use	Liver disease
Liver disease	Inhibitor of vWF, factors VIII, IX, XI, or XII	DIC
Warfarin use	Antiphospholipid antibodies	Supratherapeutic heparin or warfarin
Factor VII inhibitor	—	• Combined heparin or warfarin use • Inhibitor of prothrombin, fibrinogen, factor V or X • Direct thrombin inhibitor

PT, prolonged prothrombin time; aPTT, activated partial thromboplastin time; vWF, von Willebrand factor; DIC, disseminated intravascular coagulation.

Thrombin Time and Fibrinogen Measurement

Thrombin time measures the thrombin-induced conversion of fibrinogen to fibrin. A prolonged TT suggests a quantitative or qualitative abnormality of fibrinogen or the presence of heparin in the sample. A quantitative measurement of fibrinogen should also be performed.

Prothrombin time, aPTT, and TT do not screen for factor XIII deficiency.

Thrombin time is the time to clot formation after the addition of thrombin to citrated blood. The TT is prolonged by heparin, direct thrombin inhibitors, fibrin degradation products, paraproteins, and fibrinogen deficiency (qualitative and quantitative). Protamine is added to neutralize the heparin so that the TT can be interpreted without heparin interference. This assay has been used to establish the presence of adequate fibrinogen but is not being used as widely now.

Reptilase Time

Reptilase time measures time to clot formation after the addition of reptilase, a thrombin-like snake enzyme, to citrated blood. Unlike the TT, it is not affected by heparin. It can be useful to determine whether heparin is the cause of the prolonged TT.

Urea Clot Lysis Test

Urea clot lysis test (blood collected into citrate) measures the solubility of the clot with the addition of urea. The urea clot solubility test relies on the ability of urea to dissolve unstable clots, which are formed in the absence of factor XIII. Normal clots are not dissolved by urea or monochloroacetic acid, unlike clots in patients with factor XIII deficiency.

An abnormal test suggests severe FXIII deficiency or hypofibrinogenemia. Clot solubility is increased only at very low levels of FXIII levels (<3%) and, therefore, does not detect mild/moderate deficiencies. A quantitative assay of FXIII should be used to confirm the result of this screening test.

Fibrinogen

Fibrinogen's normal levels range from 200 to 400 mg/dL. It is an acute phase reactant and higher levels are seen with acute illness and stress. Fibrinogen levels can be measured immunologically or by a chemical method. The level of function of fibrinogen or fibrinogen activity can also be measured using von Clauss kinetic assay.

Fibrinogen Degradation Products or D-dimer

Fibrin degradation products are fragments resulting from the action of plasmin on fibrin or fibrinogen and reflect high fibrinolysis states [such as disseminated intravascular coagulation (DIC)], when their levels are elevated.

D-dimers are formed when cross-linked fibrin is degraded. They can be measured specifically by enzyme-linked immunosorbent assay. Their level is usually higher in DIC and in thrombotic conditions, such as deep venous thrombosis and pulmonary embolism. Their elevation in the absence of symptoms does not imply the presence of these disorders.

Fibrinolysis Inhibitors

Abnormalities of fibrinolysis inhibitors (blood collected into citrate), such as α2-antiplasmin (α2-AP) and plasminogen activator inhibitor 1 (PAI-1), can cause rare bleeding disorders because of increased fibrinolysis.

Genetic Testing

The genetic mutations associated with inherited hemostatic disorders are gradually being revealed. If available, mutational analysis aids in accurate diagnosis and helps in genetic counseling and prenatal diagnosis.

Specific Coagulation Factors

A specific factor assay measures the clotting time of a mixture of diluted test plasma and a specific factor deficient substrate plasma that supplies all the factors except the one being measured.

Euglobulin Clot Lysis Test

It is a screening test for excessive fibrinolysis. It is shortened in conditions characterized by increased fibrinolysis like systemic fibrinolysis, PAI-1 deficiency, α2-AP deficiency.

Bleeding Time (Using a Device Appropriate for Size of Child)

A lancet device is used to make a standardized cut on the volar surface of the forearm, and the time it takes for bleeding to stop is measured. The bleeding time assesses the function of platelets and their interaction with the vascular wall. The bleeding time test was widely used as a screening test for primary hemostasis disorders, but is less often used now because of difficulties in standardization.

Platelet Function Analyzer

Platelet function analyzer, PFA-100 (blood collected into citrate) is an instrument in which primary, platelet-related hemostasis is simulated. A small sample of anticoagulated whole blood (0.8 mL) is aspirated via a narrow-diameter capillary through a microscopic aperture cut into a membrane coated with the platelet agonists collagen and epinephrine or collagen and adenosine 5'-diphosphate. The high shear rate generated under standardized flow conditions and presence of chemical stimuli result in platelet adhesion, activation, and aggregation at the aperture, building a stable platelet plug. The time required to obtain full occlusion of the aperture is reported as the closure time. The closure time is prolonged by low levels of von Willebrand factor (vWF), thrombocytopenia, decreased hematocrit, and by some platelet function abnormalities (e.g., severe disorders such as Bernard-Soulier syndrome and Glanzmann thrombasthenia).

Due to issues of both sensitivity and specificity, use of the PFA-100® as a routine screening test is still debated. However, the small blood volume needed for this test compared with the much larger volume required for platelet function testing by aggregometry (10 mL or more) is an advantage, especially for screening very young children for vWD or severe platelet function disorders.

Testing for Defects in Primary Hemostasis von Willebrand Factor Antigen and Activity

These tests help in making diagnosis of Von Willebrand disease by measuring the level of von willebrand antigen and ristocetin cofactor activity.

Platelet Function Testing

The most common method of assessing platelet function is light transmission aggregometry, in which the increase in light transmission through a rapidly stirred sample of citrated platelet-rich plasma is recorded as platelets aggregate. As a fresh blood sample is needed for aggregation testing, the patient may have to be referred to a center with a specialized laboratory. Specialized testing includes measurement of granule secretion, dense granule enumeration by whole mount electron microscopy, flow cytometric assessment of surface receptors, and evaluation of platelet ultrastructure by transmission electron microscopy.

Screening platelet function for detecting vWD has a low negative predictive value and may require repeat testing. One also may measure von Willebrand factor antigen (vWF:Ag) by immunoassay and vWF activity by measuring the ability of patient's vWF to agglutinate normal platelets in the presence of ristocetin (vWF:RCo) or by its ability to bind collagen (vWF: CB). Factor VIII:C activity is a functional assay for factor VIII that is measured by mixing normal plasma with factor VIII-deficient plasma. Levels of vWF:Ag and vWF:RCo may be elevated during pregnancy, oral contraceptive use, and liver disease. They may decrease with hypothyroidism and type O blood.

Platelet Aggregometry

The rapidity and extent of platelet agglutination are graphically recorded after adding a variety of agonists [ristocetin, epinephrine, collagen, adenosine diphosphate (ADP), and arachidonic acid].

Platelet aggregation studies remain the most sensitive method for detecting and distinguishing platelet function defects. In these tests, platelet aggregation is tested by measuring changes in optical density as platelets respond to various agents such as ADP, epinephrine, collagen, arachidonic acid, and ristocetin. Different disorders will show different patterns. For example, platelets of patients with Glanzmann thrombasthenia (dysfunctional or deficient glycoprotein IIb/IIIa complex in platelets) only aggregate with ristocetin, whereas platelets of patients with Bernard-Soulier syndrome (absent or decreased glycoprotein Ib complex on platelets) have no aggregation with ristocetin, reduced aggregation with collagen, and normal aggregation with ADP, arachidonic acid, and epinephrine.

Thromboelastography

Thromboelastography provides the whole dynamic process of hemostasis from clot formation to its dissolution and also provides information about platelet function.

KEY POINTS

- ☞ Evaluation of a child with bleeding should include a comprehensive medical and bleeding history, a complete family history and a detailed physical examination
- ☞ Based on history and clinical findings, investigations and lab tests should be requested
- ☞ Initial tests to screen for bleeding disorders should include a complete blood count with platelet counts, blood film, prothrombin time, and activated partial thromboplastin time
- ☞ Faulty sample collection may lead to abnormal results, hence it is extremely important to ensure proper sampling.

SUGGESTED READINGS

1. Leung LK. Antithrombotic therapy: problems and issues. Hematology. 2006;457-62.
2. Revel-Vilk S, Rand ML, Israels SJ. An approach to the bleeding child. In: Blanchette VS, Breakey VR, Revel-Vilk S, editor. SickKids Handbook of Pediatric Thrombosis and Hemostasis. Basel: Karger; 2013. pp. 14-22.
3. Rajpurkar M, Lushar JM. Clinical and laboratory approach to the patient with bleeding. Nathan and Oski's Hematology of Infancy and Childhood. 7th ed. Philadelphia: Saunders Elsevier; 2009.
4. Stasi R. How to approach thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2012;2012:191-7.

CHAPTER 65

Algorithmic Approach to Eosinophilia in Children

ATK Rau, Sangeetha Shenoy

INTRODUCTION

Eosinophilia is probably the second most common hematologic abnormality in children in the tropics after anemia. The normal eosinophil count ranges from 0.04×10^9 to 0.4×10^9/L and the percentage in relation to the total leukocyte count ranges from 1 to 6%.

Eosinophilia is defined as eosinophil count more than 0.4×10^9/L. The count has a diurnal variation, with the lowest value in the morning and the highest being at night.

For standardization, the morning value at 8 am is taken as the baseline eosinophil count.

The count also varies with age (Table 1), exercise, and environmental stimuli (allergen exposure).

Eosinophilia can further be classified as mild (<1.5×10^9/L), moderate ($1.5–5 \times 10^9$/L), and severe (>5×10^9/L). The peripheral eosinophil count does not correlate with the level of organ damage. The counts may be normal in conditions where there is significant recruitment of eosinophils into organs as in eosinophilic pneumonia. On the other hand, a high eosinophil count may not have associated organ damage. But an eosinophil count of more than 1.5×10^9/L is considered the level above which organ damage is more likely to occur. Eosinophilia can also be masked because of pyogenic inflammation which can lower the eosinophil counts, as well as by exogenous administration of medications like corticosteroids, estrogen, and epinephrine.

The development and terminal differentiation of eosinophils are controlled by several cytokines like interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor, and IL-5, of which the IL-5 is the one which is primarily responsible for the production. Hence, diseases like extrinsic asthma and helminthiasis which stimulate the T-helper 2 mediated immune response have associated eosinophilia.

TABLE 1: Eosinophil counts based on age

Age	Eosinophil count × 10^9/L
Birth	0.1–1.0
Day 3	0.1–2.0
1 month	0.2–1.0
2 months to 12 years	0.1–1.0

After transendothelial migration, eosinophils can invade target organs, secreting their products into surrounding tissues causing local inflammation and tissue remodeling. Marked changes in the microenvironment subsequently leading to chronic organ damage may be caused by the eosinophil derived substances. This may lead to fibrosis and/or thrombosis in some of the patients. Certain organs like heart, lung, skin, spleen, gastrointestinal tract (GIT), and central nervous system are the ones predominantly affected.

ETIOLOGY

Causes of eosinophilia can be divided into primary and secondary.

- Primary can further be divided into:
  - Clonal: there can be neoplastic proliferation as part of an underlying myeloid malignancy. There is histologic, cytogenetic, or molecular evidence of underlying myeloid malignancy
  - Idiopathic: this is considered once secondary and clonal eosinophilia is ruled out. It includes hypereosinophilic syndrome (HES)
- Secondary/reactive:
  - Helminthiasis
  - Drugs
  - Allergic vasculitis, eosinophilic pneumonia, allergic bronchopulmonary eosinophilia, allergic angiitis, Churg-Strauss disease
  - Neoplastic diseases as a paraneoplastic syndrome
  - Immunologic disorders
  - Endocrine.

Helminthiasis: worldwide, helminthiasis is the most common cause of eosinophilia. It can be associated with tissue nematodes, cestodes, and trematodes. All parasitic infections, including hookworm, roundworm, tapeworm, filariasis, trichinella, strongyloides, and visceral larva migrans, have moderate to marked eosinophilia. Parasites elicit eosinophilia when they or their products come in contact with immune effector cells in tissues which happen during migration. Hence, it is seen in infestation with worms that migrate through extraintestinal organs. Parasites that are wholly intramural like adult tapeworm or contained in a cystic structure like hydatid cyst do not cause eosinophilia unless the cyst wall ruptures and its contents leak.

Other infections like scabies, fungal diseases like disseminated coccidioidomycosis, and aspergillosis [when presenting as allergic bronchopulmonary aspergillosis (ABPA)] can also be associated with marked eosinophilia. Tropical pulmonary eosinophilia is the result of immunologic hyper-responsiveness to the filarial parasite. It should be considered in a child with the following—residence in or has had a history of travel to a filarial endemic area, raised serum Immunoglobulin E (IgE) (>1,000 U/L), raised antifilarial antibody titers, eosinophilia more than 3×10^9/L, absence of microfilaria in blood, and significant clinical improvement after 3 weeks course of diethylcarbamazine. There is a dramatic fall in the eosinophil count after 7–10 days of treatment. The importance of treatment lies in the fact that untreated tropical pulmonary eosinophilia can lead to progressive interstitial fibrosis and chronic bronchitis.

Allergic diseases: in Western countries, allergic diseases are the leading cause of eosinophilia. Asthma generally is not associated with moderate or severe eosinophilia. If there is moderate to severe eosinophilia in asthma, possibility of Churg-Strauss disease or ABPA has to be considered.

Drug-related eosinophilia: it is a common cause of persistent eosinophilia in parts of the world where helminthiasis is uncommon. It can be asymptomatic or associated with some symptoms as follows:

- Asymptomatic: quinine, penicillin, cephalosporins, and quinolones
- Associated pulmonary infiltrates: nonsteroidal anti-inflammatory drugs, sulfa drugs, and nitrofurantoin
- Hepatitis: tetracyclines, antipsychotics
- DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome: sulfasalazine, hydantoin, carbamazepine, and D-penicillamine.

Neoplastic diseases: lymphoid malignancy (Hodgkin's lymphoma), B or T cell leukemia or lymphoma, Langerhans cell histiocytosis, solid tumors, and mastocytosis are associated with eosinophilia. It could be a paraneoplastic feature of solid tumors like adenocarcinoma of lung, cervix, and GIT because of ectopic production of IL-5 and other cytokines by malignant cells.

Immunologic disorders like Omenn syndrome, hyper-IgE syndrome, graft-versus host disease.

Endocrine: eosinophilia is seen in conditions with hypoadrenalism because of loss of endogenous glucocorticosteroids as in Addison's disease, adrenal hemorrhage, hypopituitarism.

Hypereosinophilic syndrome: it is characterized by persistent eosinophilia more than 1.5×10^9/L for more than 6 months, evidence of end organ damage but no explanation after investigations. It has two variants: myeloproliferative variant hypereosinophilic syndrome (M-HES) and lymphocytic variant hypereosinophilic syndrome (L-HES). Myeloproliferative-HES is associated with other features of myeloproliferative diseases like increased serum vitamin B12 levels, hepatosplenomegaly, anemia, thrombocytopenia, and increased bone marrow cellularity. Lymphocytic-HES is associated with cutaneous manifestations, increased serum IgE levels and hypergammaglobulinemia. There is overproduction of IL-5 by deregulated T cells leading to polyclonal eosinophil expansion.

Clonal eosinophilia: there are two subcategories in World Health Organization classification of hematologic malignancies: chronic eosinophilic leukemia, not otherwise specified and myeloid/lymphoid neoplasms with eosinophilia and mutations involving platelet-derived growth factor receptor, and -β or fibroblast growth factor receptor. It might also be seen in other myeloid malignancies like myelodysplastic syndromes and systemic mastocytosis.

RARE SYNDROMES WITH EOSINOPHILIA

- Gleich's syndrome
- Churg-Strauss syndrome
- Eosinophilia-myalgia syndrome
- Omenn syndrome
- Hyper IgE syndrome.

PULMONARY INFILTRATES WITH EOSINOPHILIA SYNDROME

- Loeffler's syndrome
- Allergic angiitis and granulomatosis
- Hypersensitivity vasculitis
- Allergic bronchopulmonary aspergillosis: asthma, positive skin test to aspergillus and aspergillus precipitating antibodies
- In addition, drug reaction, HES, and parasitic infections may be associated with pulmonary symptoms.

APPROACH TO A PATIENT WITH EOSINOPHILIA (ALGORITHM 1)

Firstly, an attempt should be made to rule out any underlying treatable cause like parasitic infections or drug reaction. Secondly, any evidence of target organ damage should be looked for.

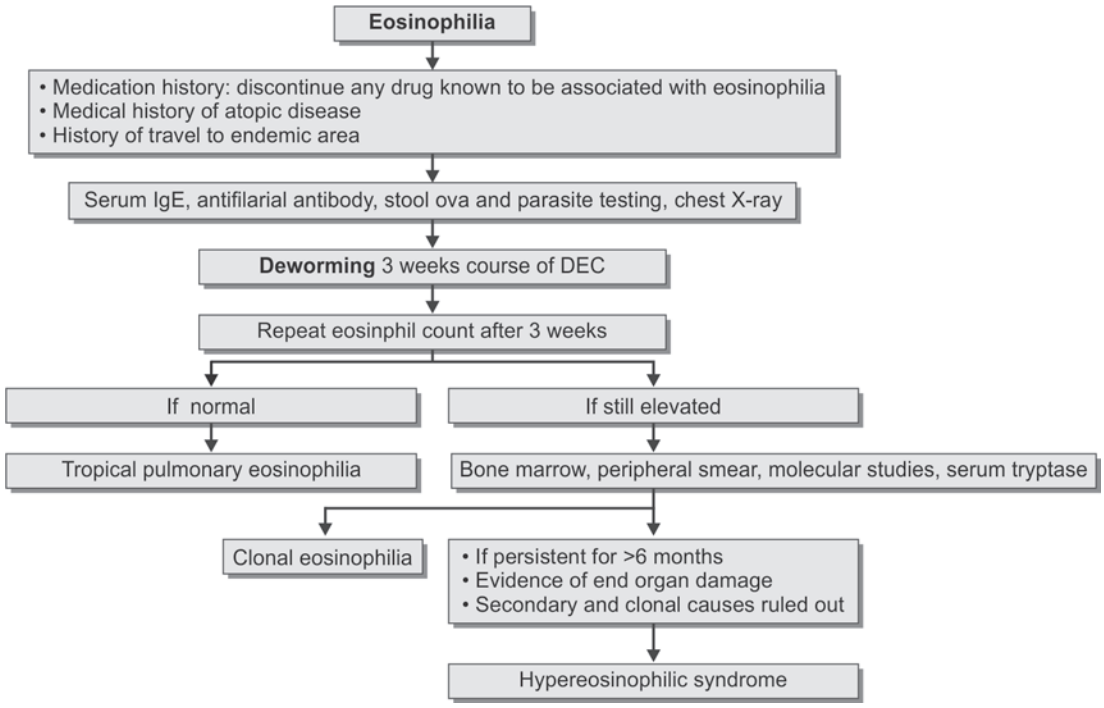
History:

- Travel history
- Occupational history
- Drug history
- Family history
- Allergy history.

Physical examination of skin, liver, spleen, lungs, and soft tissues.

ALGORITHM 1

Approach to a patient with eosinophilia



DEC, diethylcarbamazine

Laboratory investigations: serologic tests (filarial, strongyloides, schistosomiasis, toxocara), stool ova, and parasite testing (hookworm, Schistosoma), chest X-ray.

Once secondary causes are ruled out, the following investigations are performed (Table 2):

- Peripheral smear
- Blood tryptase levels, serum vitamin B12
- Immunoglobulin E
- Bone marrow morphology
- Cytogenetic analysis
- Molecular studies.

The following investigations are done to look for evidence of target organ damage:

TABLE 2: Laboratory investigations in a case of eosinophilia

Peripheral smear	Circulating blasts, dysplastic cells, monocytosis
Bone marrow	—
Cytogenetic analysis	—
Molecular studies	F1L1P1-PDGFRA using FISH or RT-PCR
Serum tryptase	Systemic mastocytosis and other vasculitides
ANCA	Churg-Strauss disease

PDGFRA, platelet-derived growth factor receptor-α; FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase-polymerase chain reaction; ANCA, antineutrophil cytoplasmic antibodies.

- Complete blood count, chest X-ray, echocardiography, troponin levels
- Pulmonary function tests
- Gastrointestinal endoscopy
- Skin biopsy
- X-ray paranasal sinuses
- Neuroimaging.

Clinical Pearls

- An eosinophil count of more than 0.4×10^9/L is considered as eosinophilia and is further classified into mild ($<1.5 \times 10^9$/L), moderate ($1.5–5 \times 10^9$/L) and severe ($>5 \times 10^9$/L) eosinophilia. A count of more than 1.5 X 10^9/L is generally associated with organ damage
- Tropical pulmonary eosinophilia should be considered in a child residing in or with a history of travel to a filarial endemic area with a raised serum immunoglobulin E (>1,000 U/L), raised antifilarial antibody titers, eosinophilia more than 3×10^9/L, absence of microfilaria in blood and significant clinical improvement after 3 weeks course of diethylcarbamazine
- Hypereosinophilic syndrome (HES) is defined by persistent eosinophilia more than 1.5×10^9/L for more than 6 months, evidence of end organ damage but no explanation after investigations. The two variants of HES are myeloproliferative variant HES (M-HES) and lymphocytic variant HES (L-HES).

KEY POINTS

- ☞ The most common cause for eosinophilia worldwide is helminthiasis whereas allergic diseases are the leading causative factor in western countries
- ☞ Untreated eosinophilia can lead to chronic organ damage due to fibrosis and/or thrombosis and hence should be treated
- ☞ A child living in the tropics with eosinophilia should be investigated to rule out tropical pulmonary eosinophilia and treated with deworming and a 3-week course of diethylcarbamazine followed by repeat counts to see the response
- ☞ Presence of moderate to severe eosinophilia in a child with asthma points towards the possibility of Churg-Strauss disease or allergic bronchopulmonary aspergillosis
- ☞ Eosinophilia can also be associated with neoplastic diseases like lymphomas, B or T cell leukemia, Langerhans cell histiocytosis, solid tumors, and mastocytosis which need to be excluded in persistent cases.

SUGGESTED READINGS

1. Ackerman SJ, Bochner BS. Mechanisms of eosinophilia in the pathogenesis of hypereosinophilic disorders. Immunol Allergy Clin North Am. 2007;27:357-75.
2. Aleman K, Noordzij JG, de Groot R, van Dongen JJ, Hartwig NG. Reviewing Omenn syndrome. Eur J Pediatr. 2001;160:718-25.
3. Basara N, Kiehl MG, Fauser AA. Eosinophilia indicates the evolution to acute graft-versus-host disease. Blood. 2002;100:3055.
4. Bass DA. Behavior of eosinophil leukocytes in acute inflammation. I. Lack of dependence on adrenal function. J Clin Invest. 1975;55:1229-36.
5. Beeson PB, Bass DA. The eosinophil. Major Probl Intern Med. 1977;14:1-269.
6. Bousquet J, Chanez P, Lacoste JY, Barneon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. N Engl J Med. 1990;323:1033-9.
7. Dacie JV, Lewis SM. Practical Hematology. 6th ed. London: Churchill Livingstone.
8. Deshpande AD. Eosinophilia associated with scabies. Practitioner. 1987;231: 455.
9. Echols RM, Palmer DL, Long GW. Tissue eosinophilia in human coccidioidomycosis. Rev Infect Dis. 1982;4:656-64.
10. Fulkerson PC, Rothenberg ME. Origin, regulation and physiological function of intestinal eosinophils. Best Pract Res Clin Gastroenterol. 2008;22:411-23.
11. Gleich GJ. Mechanisms of eosinophil-associated inflammation. J Allergy Clin Immunol. 2000;105:651-63.
12. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections-an autosomal dominant multisystem disorder. N Engl J Med. 1999;340:692-702.
13. Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. Immunol Rev. 2005;203:244-50.
14. Harley WB, Blaser MJ. Disseminated coccidioidomycosis associated with extreme eosinophilia. Clin Infect Dis. 1994;18:627-9.
15. Hogan SP, Rosenberg HF, Moqbel R, Phipps S, Foster PS, Lacy P, et al. Eosinophils: biological properties and role in health and disease. Clin Exp Allergy. 2008;38:709-50.
16. Hogan TF, Koss W, Murgo AJ, Amato RS, Fontana JA, VanScoy FL. Acute lymphoblastic leukemia with chromosomal 5;14 translocation and hypereosinophilia: case report and literature review. J Clin Oncol. 1987;5:382-90.
17. Kita H. Eosinophils: multifaceted biological properties and roles in health and disease. Immunol Rev. 2011;242:161-77.
18. Mahmoud AA. Eosinophilia. In: Warren KS, Mahmoud AA, editors. Tropical and Geographical Medicine. New York: McGraw Hill; 1989. pp. 65-70.
19. Moore TA, Nutman TB. Eosinophilia in the returning traveler. Infect Dis Clin North Am. 1998;12:503-21.
20. Ogbogu PU, Rosing DR, Horne MK. Cardiovascular manifestations of hypereosinophilic syndromes. Immunol Allergy Clin North Am. 2007;27:457-75.
21. Ong R, Doyle R. Topical pulmonary eosinophilia. Chest. 1998;113:1673-9.
22. Ottesen EA, Nutman TB. Tropical pulmonary eosinophilia. Annu Rev Med. 1992;43:417-24.
23. Parker RI. Hematologic aspects of systemic mastocytosis. Hematol Oncol Clin North Am. 2000;14:557-68.
24. Robyn J, Noel P, Wlodarska I, Choksi M, O'neal P, Arthur D, et al. Imatinib-responsive hypereosinophilia in a patient with B cell ALL. Leuk Lymphoma. 2004;45:2497-501.
25. Schermoly MJ, Hinthorn DR. Eosinophilia in coccidioidomycosis. Arch Intern Med 1988; 148:895-6.
26. Weller PF. Eosinophilia in travelers. Med Clin North Am. 1992;76:1413-32.
27. Weller PF. Eosinophils: structure and functions. Curr Opin Immunol. 1994;6:85-90.

CHAPTER 66

Approach to a Child with Respiratory Distress

Soumya Tiwari

INTRODUCTION

Respiratory distress is the most common presentation in children visiting a hospital emergency. It initially, may manifest only as fast breathing (rate more than the normal upper limit for that age group; see Table 1), and signs of increased work of breathing in the form of nasal flaring and/or lower chest indrawing, and/or head nodding can follow. It may also be associated with stridor or wheeze suggestive of upper and lower airway obstruction, respectively. There is a need of urgent assessment of airway patency and breathing, when a child with respiratory distress is first evaluated. Stabilization of vital parameters may require proper positioning, oronasal suctioning, and intubation if the airway patency cannot be maintained and use of oxygen by hood/nasal prongs. Supportive therapy in the form of maintaining temperature or correction of hyperthermia/hypothermia; intravenous fluid boluses; correction of hypoglycemia; nebulization with bronchodilator; intercostal tube drainage of any air or fluid collection in the pleural cavity, etc. Such initial treatment coupled with a thorough history, physical examination and relevant investigations, is followed by establishing a provisional diagnosis and instituting appropriate empirical treatment in the emergency ward itself. Uncommonly, a serious terminally sick child may show bradypnea (decreased heart rate) instead of tachypnea.

TABLE 1: The cut offs for respiratory rate marking significant lower chest disease (World Health Organization)

Age group	Respiratory rate cut-off
Young infant (<2 months)	>60/min
Infant (2 months–1 year)	>50/min
Children (1–5 years)	>40/min
School children (>5 years)	>30/min

DEFINITION

Any unusual pattern of breathing, causing a subjective feeling of discomfort, in a previously well child is termed as respiratory distress. It includes abnormally fast or slow breathing, shallow or labored efforts, or noisy breathing.

ETIOLOGY OF RESPIRATORY DISTRESS

Respiratory distress may not always result from a lung disease. Rapid breathing may be physiological, e.g., exercise induced, or pathological due to pulmonary or nonpulmonary causes. The respiratory rate cut offs given in Table 1 are seen in pathological conditions and these could be seen in many different clinical situations as detailed in Box 1.

Box 1: Causes of respiratory distress in children

Upper respiratory tract involvement

- Croup, acute epiglottitis, Ludwig's angina
- Retropharyngeal abscess
- Foreign body aspiration
- Diphtheria
- Laryngospasm

Lower respiratory tract involvement

- Pneumonia
- Bronchiolitis
- Asthma
- Pleural effusion or empyema and hemothorax
- Pneumothorax
- Atelectasis
- Hypersensitivity pneumonitis

Nonpulmonary causes

- Congestive heart failure due to heart disease or severe anemia
- CNS infections, cerebral edema, tumor (raised ICT, compression of the brainstem), spinal cord injury, Guillain Barre syndrome
- Metabolic acidosis
  - Renal failure
  - Renal tubular acidosis
  - Diabetic ketoacidosis
  - Psychogenic hyperventilation, anxiety, and panic attacks

ICT, intracranial tension; CNS, central nervous system.

CLINICAL FEATURES

A child with respiratory distress may have tachypnea with increased work of breathing (suggested by use of accessory muscles), cyanosis and lethargy or altered sensorium. Alteration in sensorium (in the form of irritability, agitation, lethargy, or coma) indicates brain hypoxia and is one of the earliest indicators of impending respiratory failure. While fast breathing is commonly associated with respiratory diseases, it may also occur with fever, crying, or metabolic acidosis. However, normal or decreased respiratory rate may be more ominous if it is associated with severe retractions (paradoxical breathing), cyanosis, grunting, or altered sensorium. Central cyanosis is a late sign but may not be detected in presence of severe pallor (low hemoglobin) and dark skin color.

Stridor is a harsh inspiratory sound that indicates upper airway obstruction. Grunt is a loud noise produced by a forceful expiration against a closed glottis. Grunt and wheeze (a musical sound) are suggestive of lower airway obstruction.

A complete history including the onset, duration, progression of dyspnea, the aggravating and relieving factors as well as the associated symptoms, like fever, cough, sore throat, chest pain, choking episodes, accidental ingestion of poisons, etc. can help in short listing the likely cause (Table 2).

TABLE 2: Clinical feature based diagnostic clues

Clinical features	Diagnosis
Fever, cough, and rapid breathing	Lower respiratory tract infections, like pneumonia, bronchiolitis and virus and associated wheeze
Exercise-induced dyspnea	Asthma, congestive heart failure, severe anemia
Nocturnal cough, orthopnea and dyspnea	Congestive heart failure
Fever, sore throat, stridor	Acute epiglottitis
Severe chest pain with rapid, shallow breathing, decreased air entry	Pneumonia, pneumothorax, pulmonary embolism
Persistent wheezing, recurrent vomiting, failure to thrive	Gastroesophageal reflux disease
Acute respiratory distress after sudden choking, hyperinflated chest	Foreign body inhalation
Fever with altered sensorium, convulsions, fast breathing	Encephalitis involving brain stem
Chest-wall retractions, paraplegia	Acute flaccid paralysis
Acute respiratory distress with vomiting, altered sensorium	Poisoning
Fast breathing usually without other signs of respiratory distress, may be associated with oliguria or anuria	Acute kidney injury/ chronic kidney disease with metabolic acidosis
Fast breathing, altered sensorium, polyuria, dehydration	Diabetic ketoacidosis

Clinical Pearls

Symptoms of impending respiratory failure

- Cyanosis
- Silent chest
- Poor respiratory efforts
- Fatigue/exhaustion
- Agitation or reduced level of consciousness

Preterminal signs

- Bradycardia, desaturation, and altered sensorium.

INVESTIGATIONS

Laboratory investigations help to confirm the diagnosis but the immediate management of a patient should not be delayed pending the reports of the investigations. Use of noninvasive devices, such as pulse oximeter and end-tidal carbon dioxide detector lessen the need for repeated invasive tests for monitoring of the child. Table 3 shows the relevant investigations to ascertain the cause of respiratory distress in a child.

TREATMENT

The management of a child with respiratory distress includes supportive treatment in the form of stabilization of vital parameters, i.e., airway, breathing, and circulation followed by definitive treatment by instituting appropriate respiratory support, antibiotics, chest tube drainage, decongestive measures, etc. The algorithmic approach to management of such a child is shown in algorithm 1.

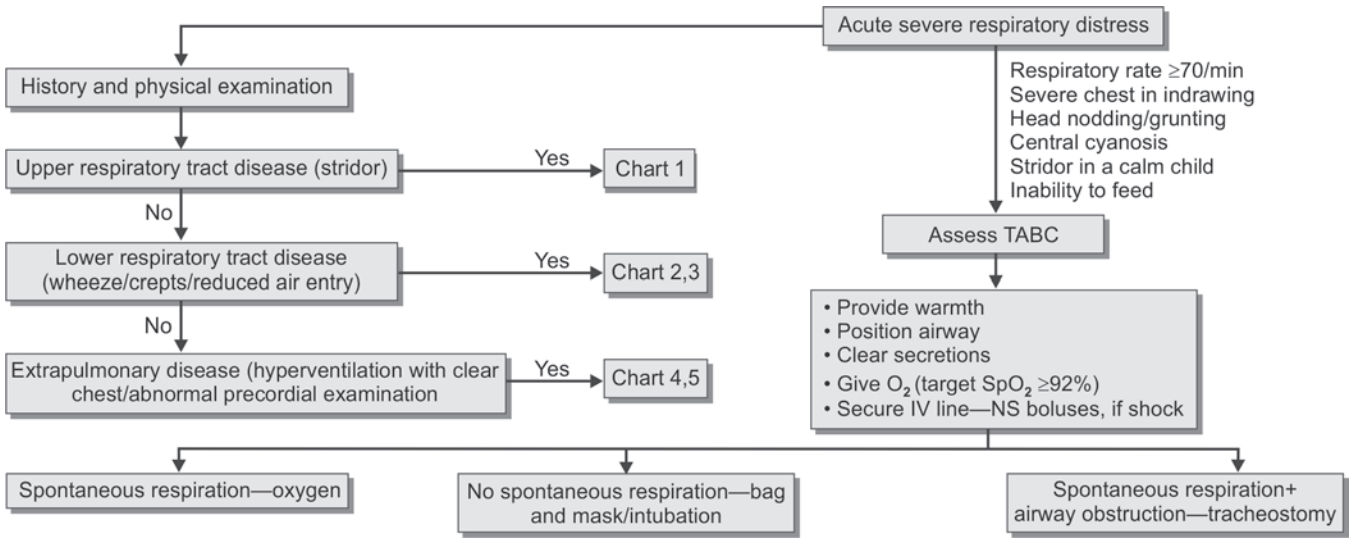
TABLE 3: Laboratory investigations

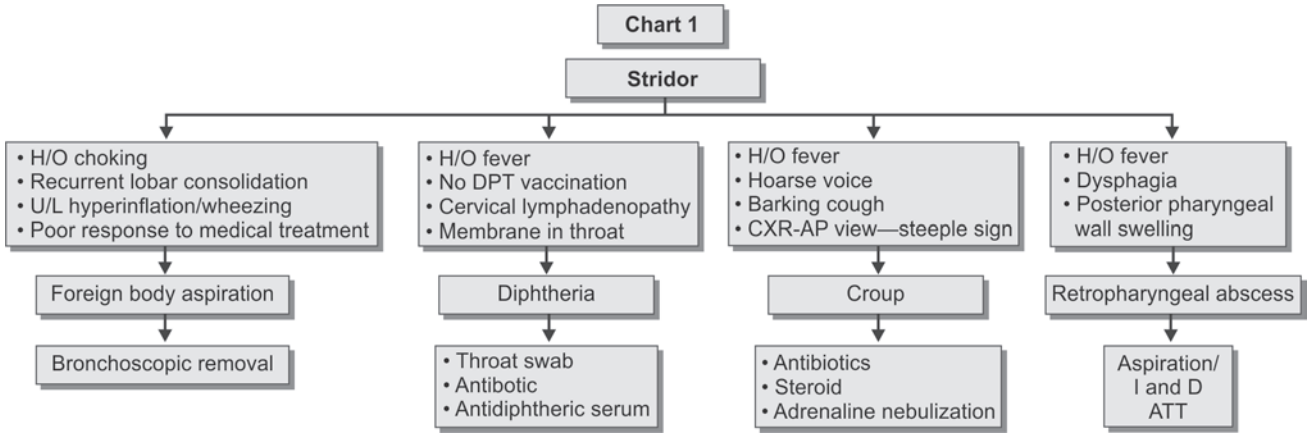
Investigation	Suggested diagnosis
Complete blood count with peripheral smear	Leucocytosis/leucopenia, toxic granules, shift to left, anemia/ polycythemia, eosinophilia-pneumonia, sepsis, TPE
CRP, ESR	Raised-pneumonia, bronchiolitis
Blood culture	Sepsis with pneumonia
Kidney function tests	Acute/chronic kidney disease
Arterial blood gas	Hypoxemia, hypercarbia, acidosis (metabolic/respiratory)—pneumothorax, AKI
Chest X-ray, X-ray soft tissue neck	Pneumonia, pneumothorax, effusion, foreign body, acute epiglottitis, CHF
Bronchoscopy	Foreign body
Echocardiography	Cardiac disease
24-hour pH monitoring	GERD
Pleural tap	Pneumonia (bacterial, tubercular)
Lumbar puncture/ cranial CT scan	Pleocytosis, raised protein and decreased sugar meningoencephalitis/ raised ICT

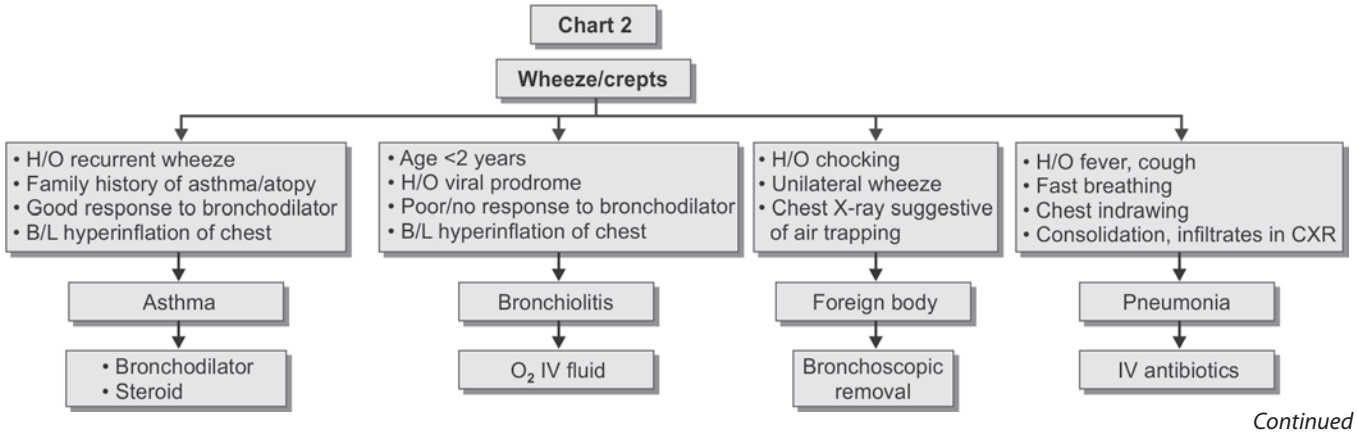
TPE, therapeutic plasma exchange; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AKI, acute kidney injury; CHF, congestive heart failure; GERD, gastroesophageal reflux disease; CT, computed tomography; ICT, intracranial tension.

ALGORITHM 1

Management of a child with respiratory distress

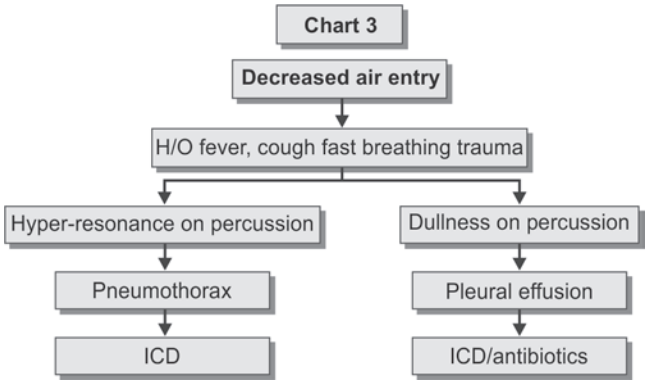


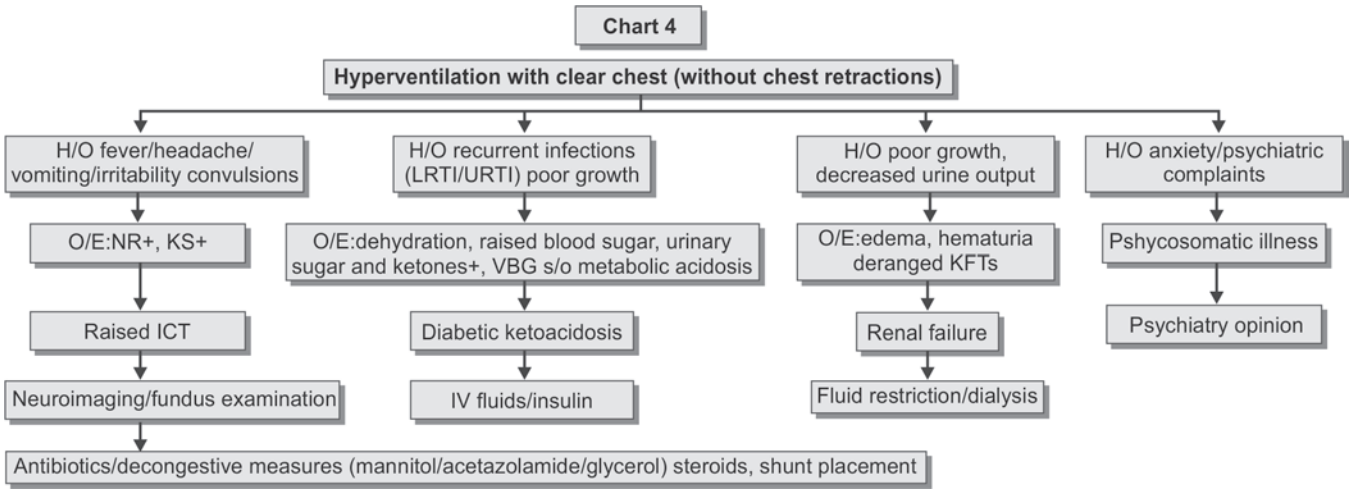


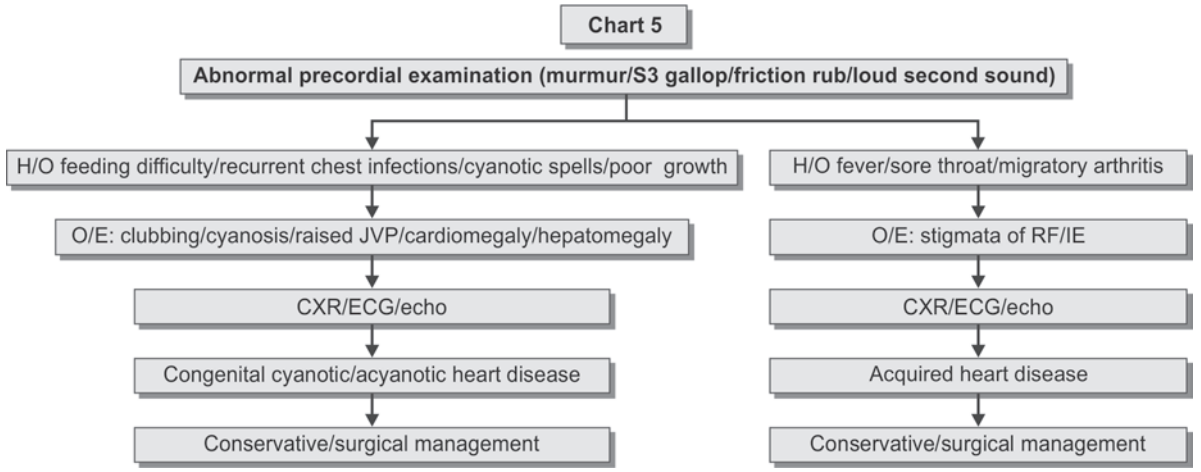


Continued

Continued







TABC, temperament assessment battery for children; NS, normal saline; DPT, diptheria-pertussis-tetanus; CXR, chest X-ray; AP, anteroposterior; ICD, implantable cardioverter-defibrillator; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; ICT, intracranial tension; VBG, venous blood gas; IV, intravenous; JVP, jugular venous pressure; ECG, electrocardiogram; echo, echocardiogram; KFT, kidney function test; I&D, incision and drainage; B/L, bilateral; U/L, unilateral; ATT, antitubercular treatment; RF, rheumatic fever; IE, infective endocarditis.

CONCLUSION

It is essential to promptly triage children with impending respiratory failure and quickly institute supportive management, simultaneously searching for the etiology and planning a definitive treatment. The above mentioned approach will improve the outcome of children, especially the under-five ones, in whom respiratory infections lead to the highest number of mortalities.

KEY POINTS

- ☞ Respiratory distress may not always be due to respiratory diseases, nonpulmonary causes should be carefully evaluated
- ☞ Stabilization of vital signs is the first step in the management of a child with respiratory distress
- ☞ Signs of impending respiratory failure should prompt immediate respiratory support
- ☞ Clinical features guide further investigations and definitive treatment.

SUGGESTED READINGS

1. Fallot A. Respiratory distress. Pediatr Ann. 2005;34(11):885-91.
2. Kilham H, Gillis J, Benjamin B. Severe upper airway obstruction. Pediatr Clin North Am. 1987;34(1):1-14.
3. Mathew JL, Singhi SC. Approach to a child with breathing difficulty. Indian J Pediatr. 2011;78(9):1118-26.
4. Singh V, Tiwari S. Respiratory problems. In: Gupta P (Ed). Textbook of Pediatrics. India: CBS publishers; 2013. pp. 335-68.

CHAPTER 67

Assessing and Managing a Child with Stridor

Dhulika Dhingra, Varinder Singh

INTRODUCTION

Stridor is a harsh, high-pitched vibratory sound caused by partial obstruction of respiratory passages that result in turbulent passage of air through the airways. It can be almost always heard without stethoscope though not uncommonly it may be audible directly to the ear. Stridor is usually heard during inspiration, but sometimes may be biphasic. Inspiratory stridor may result if the child breathes against a closed glottis, expiratory stridor results due to semiapproximated vocal cords causing resistance to exhalation and biphasic stridor may result due to subglottic or glottic anomaly or a severe obstruction of the extra-thoracic airway. Loudness of the sound is poor marker of the degree of obstruction, while its presence even when the patient is quiet or biphasic stridor is associated with significant compromise. Stridor must be differentiated from stertor, which is produced by an obstruction in the nose or nasopharynx.

Stridor is the sound caused by abnormal air passage during breathing. The cause of stridor can usually be located somewhere in extra-thoracic airway (pharynx, larynx, and trachea). Stridor may be acute (caused by inflammation/infection or foreign body inhalation) or chronic. It may be congenital or acquired. Stridor is a sign and not a diagnosis and the cause for which must be ascertained. This chapter aims to educate the pediatrician faced with a child or infant with stridor to determine the severity or respiratory compromise and the need for immediate intervention, to decide based upon history and clinical examination whether a significant lesion is suspected and to understand the consequences and management strategies of the underlying lesion for follow-up and subsequent management of the child.

PATHOPHYSIOLOGY

Gases produce pressure equally in all directions; however, when a gas moves in a linear direction, it produces pressure in the forward vector and decreases the lateral pressure. When air passes through a narrowed flexible airway in a child, the lateral pressure that holds the airway open can drop precipitously (venturi principle) and cause the tube to collapse. A similar process obstructs airflow and produces stridor in cases with upper-airway obstruction.

The most common causes of stridor are summarized in Table 1.

HISTORY AND CLINICAL EXAMINATION

A good history and the clinical examination are the key to localization of the cause of stridor. A child presenting with stridor should be inquired about the onset of stridor (onset in first few months of life usually indicate a congenital cause), postural variation, feeding difficulties, any change in voice quality, pattern of fever, history of foreign body inhalation in form of sudden choking, any neurological symptoms, history of trauma to head and neck (to look for neurogenic stridor),

TABLE 1: Causes of stridor

Acute stridor	Chronic stridor
Laryngotracheobronchitis	Laryngomalacia
Epiglottitis	Congenital or acquired subglottic stenosis
Diphtheria	Laryngeal webs
Bacterial tracheitis	Congenital laryngeal cysts
Retropharyngeal abscess	Tracheal stenosis or complete tracheal rings
Allergic reactions	Tracheomalacia
Vocal cord palsy	Subglottic hemangioma
Acquired subglottic stenosis (following prolonged intubation)	Posterior laryngeal cleft

TABLE 2: Voice changes with localization of site of stridor

Change in voice	Localization of lesion	Differential diagnosis
Hoarseness of voice	Vocal cords	• Laryngeal webs • Abductor palsy • Croup • Retropharyngeal abscess • Diphtheria
Muffled voice	Supraglottic involvement	• Tonsillitis • Parapharyngeal abscess • Peritonsillar abscess
Weak voice	Subglottic obstruction	• Subglottic stenosis (congenital or acquired)

immunization history, and history of similar illness in the neighborhood (diphtheria). It is, however, emphasized that parents may not have noticed the choking episode hence, a high index of suspicion is warranted if stridor has appeared all of a sudden without any other attendant symptoms, like fever, coryza, etc.

Detailed clinical examination may also help in identifying the cause. Onset of stridor, presence/absence of fever, voice change and ability of patient to handle secretions will aid in determining the site. A positional change in severity of stridor may indicate laryngomalacia. A child with choanal atresia may have increased distress as he closes his mouth and with crying his distress may be relieved. Voice quality should also be observed during the examination; however, it must be remembered that a normal voice quality does not rule out laryngeal or pharyngeal pathology though presence of changes in voice quality does. Table 2 summarizes important voice changes associated with different pathologies.

Clinical examination must also include a detailed neurological examination and inspection of the spine to rule out neurogenic stridor. Neck should be examined for any lymph node masses or for any evidence of trauma. Note should also be made of craniofacial anomalies including macrglossia, retrognathia and maxillary hypoplasia. Throat examination may reveal presence of a membrane, tonsillar enlargement, or presence of exudates. Throat examination should not be attempted for a child who is drooling, has high grade fever, and is agitated.

Apart from ascertaining the diagnosis, clinical examination should also aim at assessing the severity of respiratory distress. Retractions/use of accessory muscles are better clinical signs than degree of stridor when assessing degree of respiratory distress. Cyanosis is a late finding and is a sign of impending respiratory failure.

Clinical Pearl

- Onset of stridor, presence/absence of fever, voice change, and ability of patient to handle secretions will aid in determining the diagnosis.

INVESTIGATIONS

Establishing a patent airway is of utmost importance. No laboratory investigation or imaging should take precedence over establishing airway. If the patient has chronic stridor, has no or minimal respiratory distress, he/she may be taken up for flexible laryngoscopy or bronchoscopy to look for underlying abnormalities. The procedure may also rule out secondary airway lesions.

If the child has an acute stridor in the absence of severe respiratory distress, one may go for a chest X-ray or soft-tissue lateral neck imaging depending upon the history. A clinician capable of establishing airway should accompany such a patient to the X-ray department.

Clinical Pearl

- Establishing a patent airway must take precedence over imaging and bronchoscopy in evaluating patients with stridor.

Chest X-ray in a child with history of foreign body inhalation may reveal unilateral hyperinflation or collapse, while radiograph of a child with laryngotracheobronchitis shows subglottic narrowing (steeple sign).

MANAGEMENT

Laryngotracheobronchitis/Croup

Croup is a heterogeneous group of acute and infectious processes in children (between 6 months to 6 years of age) that manifest most commonly with characteristic inspiratory stridor, barking cough, hoarse voice, and varying degrees of respiratory distress. Parainfluenza viruses type 1 (50%), 2 and 3; respiratory syncytial virus, influenza A and B, and rhinovirus account for the majority of cases. The illness usually starts with a common cold, like illness with symptoms of rhinorrhea, cough, sore throat, and fever. Features of upper airway obstruction, i.e., inspiratory stridor, hoarseness, and barking cough develop over next 2–3 days.

Treatment is dependent upon the severity of croup and includes humidified oxygen, oral or parental steroids, and inhaled adrenaline.

- Humidified air: It has been widely advocated in the past without any scientific validation, but it still can be used as home remedy in children with mild croup.
- Oxygen therapy: Oxygen is the most important treatment for a child with moderate or severe croup who has considerable upper-airway obstruction or SpO_2 less than 92%.
- Oral or inhaled steroids: Steroids can improve the symptoms of croup within 6–8 hours after starting the treatment. They also result in shorter duration of hospital stay, lesser need of endotracheal intubation, and decreased need for adrenaline nebulization. Oral corticosteroids are preferred as they are inexpensive, easy to administer, readily available, as effective and produce measurable improvements within hours. The recommended dose of

dexamethasone is 0.15–0.3 mg/kg body weight (oral or IM) and prednisolone (suspension or tablets) is 1 mg/kg body weight. Nebulized budesonide (2 mg) has been shown to be equally efficacious. This can be repeated 12 hourly for up to 48 hours. The choice of route is based upon the cost and the child condition.

- Nebulized adrenaline: It is indicated in children with moderate to severe croup with stridor at rest and marked intercostal or subcostal indrawing. One needs to administer 1:1000 dilution solution of nebulized adrenaline 0.5 mL/kg of body weight (maximum of 5 mL). It has a rapid onset of action on bronchial and tracheal epithelial vascular permeability, thereby decreasing airway edema, which, in turn, increases the airway radius and improves airflow, with improvement in croup severity score within 30 minutes. However, it has a temporary action on the airway obstruction and only gives time for the underlying basic pathology to resolve and may delay or decrease the need for intubation/tracheostomy. If the severity recurs, the dose can be repeated after 2–4 hours.
- Antimicrobials: These have no role in treatment of viral croup, even to prevent secondary bacterial infection.
- Airway management: A severely obstructed airway leading to signs of impending respiratory failure will need either endotracheal intubation or tracheostomy. Intubation with a size smaller than the most appropriate size based on the age of the child is preferred as there is significant edema of the airway. Tracheostomy can often be avoided if an experienced pediatrician/anesthetist is available for a rapid-sequence intubation.
- Discharge: Child can be sent home when there is no stridor at rest. Parents need to be educated for monitoring worsening of symptoms.

Epiglottitis

Epiglottitis is a medical emergency occurring most commonly in children aged 2–7 years, due to fulminant inflammation of the supraglottic structures: epiglottis, arytenoids, aryepiglottic folds, and uvula, due to infection by *Haemophilus influenzae* type B. It is not often reported from India. Clinically, the child appears toxic. The disease is characterized by an abrupt onset of high-grade fever, sore throat, dysphagia, respiratory distress, and drooling of saliva. Establishing an airway by nasotracheal intubation or less often, by tracheostomy is indicated. In general, children with acute epiglottitis are intubated for 2–3 days, because the response to antibiotics is usually rapid.

Diphtheria

Diphtheria is commonly seen in partially or completely unimmunized children. Throat examination reveals a thick pharyngeal membrane spreading to the adjacent larynx. This results in airway obstruction. It is important not to agitate the child as this may precipitate aspiration or airway obstruction. Child may be administered oxygen. Emergency intubation is to be avoided and early tracheostomy to establish a patent airway should be done. Diphtheria antitoxin [80,000–1,20,000 IU, intravenous (IV)] should be administered and child should be treated with crystalline penicillin (40,000 U/kg/dose 6 hourly for 14 days).

Retropharyngeal Abscess

Retropharyngeal abscess is a complication of bacterial pharyngitis observed in children younger than 6 years. The child presents with abrupt onset of high fever, difficulty in swallowing, refusal to feed, sore throat, hyperextension of the neck, stridor and respiratory distress. Most often they are polymicrobial; usual pathogens include group A streptococci, oropharyngeal anaerobic bacteria and *Staphylococcus aureus*. Treatment options include IV antibiotics, like co-amoxyclavulinic acid with or without surgical drainage. Endotracheal intubation is indicated in any child with stridor at presentation.

Allergic Reactions/Angioneurotic Edema

Allergic reaction (i.e., anaphylaxis) occurs within 30 minutes of an adverse exposure. Hoarseness and inspiratory stridor may be accompanied by allergic symptoms (e.g., dysphagia, nasal congestion, itching eyes, sneezing, and wheezing). Oxygen should be administered and endotracheal intubation is indicated in any child with stridor at presentation. Adrenaline (0.01 mL/kg subcutaneous), hydrocortisone (10 mg/kg), and antihistaminics are administered.

Laryngomalacia

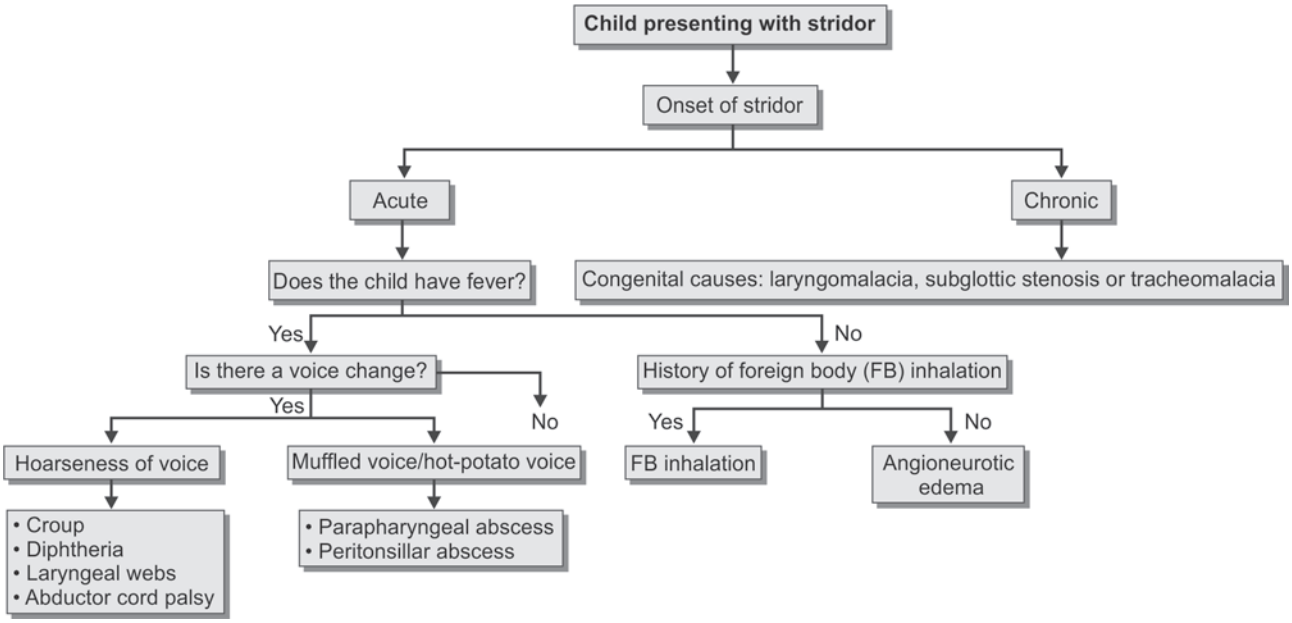
It is the most common congenital laryngeal anomaly and the most common cause of stridor in infants and children. Expectant observation is suitable for most infants because symptoms resolve spontaneously as the child and airways grow. If significant obstruction or failure-to-thrive is present, surgical correction (supraglottoplasty) may be considered which may be warranted in only 10% cases. It is usually a clinical diagnosis however, cases presenting early (under 4 weeks of age) or with severe obstruction should preferably have an early airway examination to rule-out alternative causes, requiring a different treatment approach.

Subglottic Stenosis

It can be congenital or acquired. Congenital subglottic stenosis occurs due to incomplete canalization of the subglottis and cricoid rings leading to narrowing of the subglottic lumen. Acquired stenosis is most commonly caused by prolonged intubation or due to a neglected foreign body. The symptomatology will depend on degree of stenosis. Symptomatic children may be tracheotomized. Definitive surgical management includes endoscopic methods, laser coagulation, or laryngotracheal reconstruction.

ALGORITHM 1

Algorithm for approach to a child with stridor



Vocal Cord Paralysis

Vocal cord paralysis can be congenital or secondary to trauma at birth or during cardiac or intrathoracic surgery. The left vocal cord is more commonly affected as the left recurrent laryngeal nerve may get damaged, secondary to ligation of patent ductus arteriosus. Since vocal cord paralysis usually resolves in 6–18 months in infants, those with bilateral vocal cord paralysis can be managed either by lateralization of the cords or by tracheostomy. In case of nonresolution in follow up, definitive surgical management, such as partial cordotomy and arytenoidopexy may be required.

CONCLUSION

Stridor is a sign and not a diagnosis. Any child presenting with stridor should be evaluated to determine the cause (Algorithm 1). Onset of stridor, presence/absence of fever, voice change and ability of patient to handle secretions will aid in determining the diagnosis. Establishing a patent airway is of utmost priority in such children.

KEY POINTS

- ☞ Stridor is a harsh, high-pitched vibratory sound caused by partial obstruction of respiratory passages that result in turbulent passage of air through the airways
- ☞ Stridor is a sign and not diagnosis. Hence, every effort should be made to identify the cause of this sign
- ☞ Maintenance of airway should take precedence over making a diagnosis
- ☞ A detailed history and clinical examination will help in determining the cause at the earliest
- ☞ Neurogenic stridor is an important entity which is often ignored. Hence, a detailed neurological examination should not be ignored while examining a patient with stridor.

SUGGESTED READINGS

1. Boudewyns A, Claes J, Van de Heyning P. Clinical practice: an approach to stridor in infants and children. Eur J Pediatr. 2010;169:135-41.
2. D' Agostino J. Pediatric airway nightmares. Emerg Med Clin North Am. 2010;28:119-26.
3. Tibballs J, Watson T. Symptoms and signs differentiating croup and epiglottitis. J Paediatr Child Health. 2011;47:77-82.
4. Leung AK, Cho H. Diagnosis of stridor in children. Am Fam Physician. 1999;60:2289-96.
5. Sly PD, Collins RA. Physiological basis of respiratory signs and symptoms. Paediatr Respir Rev. 2006;7:84-8.

CHAPTER 68

Recurrent Wheezing in Infants and Preschool Children

Ankit Parakh, Varinder Singh

INTRODUCTION

Recurrent wheezing in children less than five years of age is a common childhood respiratory problem and possibly the most common indication for referral to pediatric respiratory physicians. Asthma in school-age child is due to cellular airway inflammation and inhaled corticosteroids (ICS) are pivotal to management in school-age children with asthma. However, much less is known about pathophysiology of preschool wheeze and its management has been extrapolated from studies on older children. The present chapter deals with the phenotypes, causes, investigations, and management under-five childhood wheezing with a focus on practical aspects.

PHENOTYPES OF PRESCHOOL WHEEZE

The conventional teaching was to classify children into wheeze associated lower respiratory tract infection and early onset asthma. This distinction was based on whether there were afebrile episodes, personal/family history of atopy and response to bronchodilators. Although this distinction could be useful in clinical practice; a significant overlap between phenotypes made it less useful. These terms, however, are still commonly used in clinical practice.

The largest epidemiological data comes from the work of Fernado Martinez and colleagues from the Tucson children's cohort with a follow up into adulthood. Children were classified as transient early wheezers, late onset wheezers and persistent wheezers. Although this has been extremely important in understanding of childhood wheezing, the classification system is retrospectively based on the follow-up of the child. What a clinician needs and the parents want is to know whether the index case shall develop asthma early in disease. They need a prognostication as soon as possible and not a retrospective epidemiological tool. An Asthma Predictive Index (API) has been suggested based on the association between certain risk factors with certain types of early child wheezing. The API has a moderate positive predictive value and a very high negative predictive value. Hence, an early childhood wheezer with a negative API has very low chance of developing asthma later in life.

European Respiratory Society task force recommended classifying these children in a more pragmatic clinically relevant syndrome based on their temporal pattern, named as episodic viral wheeze (EVW) and multiple-trigger wheeze (MTW) (Table 1). The task force agreed not to use term asthma to describe preschool wheezing illness since there was insufficient evidence showing that pathophysiology of preschool wheezing is similar to childhood asthma. Inflammation has been poorly studied in preschool children and might be absent in very young children who wheeze. However, easy as it seems, yet these divisions do not remain as distinct compartmental entities and there is a shift of phenotypes in many cases. The temporal pattern of wheeze during preschool years (EVW or MTW) is a relatively poor predictor of long-term outcome (transient versus persistent wheeze). Frequency and severity of wheezing episodes are stronger predictors of long-term outcome and should be taken into consideration when deciding treatment. As a result of which GINA guidelines 2015 suggests a probability based approach to assess which under-five children with viral induced wheezing are more likely to have asthma and hence are more likely to respond to controller therapy.

Causes

The forgoing discussion of the under-five wheezers is not for an atypical wheezer. Unlike a typical wheezer, the atypical wheezer is always marking an underlying disorder. A detailed description of various form of atypical wheezing is out of scope of the present chapter but the common differential diagnosis, clinical pointers, and investigations are summarized in table 2.

TABLE 1: New classification of phenotypes of wheezing by the European Respiratory Society

	Episodic viral wheeze	Multiple-trigger wheeze
Definition	Wheezing during discrete time periods, often in association with clinical evidence of a viral cold	Wheezing that shows discrete exacerbations but also symptoms between episodes
Triggers	Viral infections	Viral infections, tobacco smoke, allergen exposure, mist-exposure, crying, exercise
Possible underlying factors	Pre-existent impaired lung function, tobacco smoke exposure, prematurity, atopy	Eosinophilic inflammation?
Continues treatment with ICS	Little or no benefit	Significant fewer days with symptoms
Treatment with montelukast	Moderate benefit	Moderate reduction in exacerbations
Long-term outcome	Declines over time (<6 years), can continue as episodic viral wheeze into school age, can change in multiple-trigger wheeze	Can continue as asthma into adulthood

ICS, inhaled corticosteroid

TABLE 2: Causes of atypical wheezing in preschool children

Differential diagnosis	Clinical pointers	Investigations
Infections		
Protracted bacterial bronchitis (PBB)	Wet cough for >4 weeks, no wheezing, complete response to co-amoxiclav for 14 days	Clinical features usually suffice, cough swabs or BAL might be considered
Chronic suppurative lung disease	Recurrent episodes for wet cough, wet cough lasting for >6 months, clubbing	Usually clinical diagnosis, HRCT chest normal
Bronchiectasis	Recurrent episodes for wet cough with or without wheezing, wet cough lasting for >6 months	HRCT changes of bronchial wall thickening and dilatation
Tuberculosis	Prolonged fever, weight loss, anorexia, contact with TB case	Mantoux, gastric aspirates, chest X-ay
Chronic rhino-sinusitis	Chronic cough with upper airway signs (postnasal drip, chronic pharyngeal congestion) with no wheezing	Sinus X-ray, CT useful but required only in resistant cases for surgical intervention
Adenoid hypertrophy	Chronic mouth breathing, adenoid facies	X-ray lateral soft-tissue neck
Bronchiolitis obliterans	Usually post infectious are viral bronchiolitis, persistent wheezing lasting for >60 days	Pulmonary functions tests suggestive of non-reversible severe obstruction, HRCT pattern of mosaic perfusion, lung biopsy in atypical cases
Congenital problems		
Tracheobronchomalacia	Onset of symptoms since birth, usually symptoms persists during interval periods, monophonic wheezing	Flexible bronchoscopy: dynamic airway compression
Cystic fibrosis	Features of CSLD/bronchiectasis, malabsorption, failure to thrive	Sweat chloride, mutation analysis
Bronchopulmonary dysplasia	Preterm birth, HMD, oxygen requirement during neonatal period, ventilation	Chest X-rays, CT chest
Primary ciliary dyskinesia	Features of CSLD/bronchiectasis, rhinitis since birth, chronic otitis, situs inversus	Ciliary motility and ultrastructural studies
H type tracheoesophageal fistula	Cough with feeding since birth, recurrent pneumonias	Flexible bronchoscopy, contrast study
Vascular airway compression	Onset of symptoms since birth, usually symptoms persist during interval periods, monophonic wheezing, feeding difficulties	Flexible bronchoscopy: non dynamic airway pulsatile compression
Non-vascular airway compression (lymph node, cardiomegaly, tumors, cyst)	Congenital cardiac disease, other suggestion of TB, lymphoma, monophonic wheezing, feeding difficulties	Flexible bronchoscopy, Chest X-rays, CT chest
Mechanical problems		
Gastroesophageal reflux disease (GERD)	Early onset symptoms (<6 months), severe wheezing episodes, gastroesophageal symptoms, features of aspiration on chest X-ray	24 hours pH study, GER scan
Foreign body aspirations	Choking while feeding, monophonic wheezing, lateralizing signs	Flexible bronchoscopy

TB, tuberculosis; CSLD, chronic suppurative lung disease; HMD, hyaline membrane disease; BAL, bronchoalveolar lavage; HRCT, high resolution computed tomography; CT, computed tomography; GER, gastroesophageal reflux

Clinical Pearls

- Preschool wheeze is a very common disorder and usually does not need to be investigated
- Clinicians should try and clinically differentiate these typical wheezers form children having atypical wheezing
- Red flag signs need to be identified
- Children with atypical wheezing would need a pediatric pulmonology referral and will have to be investigated further
- Further investigation can be decided on a case-to-case basis and might need (one or multiple) sweat chloride, studies for gastroesophageal reflux disease, flexible bronchoscopy, immune studies and computed tomography chest.

HISTORY AND EXAMINATION

A detailed history should be obtained including the age of onset of the first episode, frequency of episodes, severity of episodes [requiring out-patient department, and emergency visits, admissions, and intensive care unit (ICU) admissions], association with viral upper respiratory infection (URI), and nature of drugs used including response should be sought. Seasonal variation and severity trend should also be seen. It would be extremely important to elicit details regarding symptoms during interval period (any cough, wheezing, etc.), symptoms with activity, and any aeroallergen sensitization. History of feeding difficulty, choking, and regurgitation of feeds should be asked. History for allergic rhinitis and conjunctivitis should be elicited. A detailed family history including grand parents would also be useful. All details of the previous medicines taken should be recorded.

Examination should focus particularly on the growth velocity of the baby, since children who have failure to thrive could have an underlying serious illness, like cystic fibrosis (CF). Presence of clubbing indicates an underlying suppurative lung disease and should be carefully seen.

Adenoid facies, Dennie-Morgan Folds, transverse nasal creases, nasal examination (nasal mucosa, turbinate, deviated nasal septum) are also important features on physical examination. Respiratory examination should focus on shape of chest (any increased anteroposterior diameter), symmetry, and type of wheeze (monophonic or polyphonic). Presence of monophonic wheeze would indicate a lesion/compression of the intrathoracic airway and if persistent, should be investigated further, e.g., endoscopic evaluation. The examination should also cover the cardiovascular, abdominal, and nervous systems.

INVESTIGATIONS: HOW AND HOW FAR?

Most children with recurring wheezing (EVW or MTW) do not require any investigations. A detailed history and complete physical examination usually is sufficient. As a rule, wheeze should be documented as clinical mimickers, like recurrent or back to back URI (nursery school syndrome) and protracted bacterial bronchitis do not have a wheeze but have ruttles. Children who are asymptomatic during intervals and have a normal examination (normal respiratory rate, no noisy breathing, no wheeze) are unlikely to have any atypical cause of wheeze.

The role of investigations to differentiate the phenotype of preschool wheeze and predict whether this child might go on to develop asthma or remit is still a matter of research. Preschool pulmonary function testing techniques (impulse oscillometry/interrupter technique), fractional exhaled nitric oxide and biomarkers on exhaled breath condensate have been used. Since there is no final conclusion on any of these modalities their routine use in clinical practice needs to wait.

Gastroesophageal reflux disease (GERD) has been evaluated as a cause of wheezing in children but still many questions remain unanswered. Gastroesophageal reflux disease is physiological and whether the "D: the disease" can be attributed to reflux or is just a cotraveler, needs to be defined for each case. Children with severe episodes, especially less than 6 months are more likely to have GERD as the sole or one of the reasons of persistent or recurrent wheezing.

Investigations are required only in children suspected to have atypical causes of wheezing. The red flag signs in Box 1 should prompt referral for a detailed evaluation. Focused investigations would be required and might include GER scan/24 h pH study, flexible bronchoscopy, sweat chloride test, and computed tomography chest.

TREATMENT

Acute Episode

Inhaled short-acting β2-agonists remain the cornerstone of therapy although nebulized and oral route are also acceptable although inferior options. Inhaled or nebulized ipratropium may be added in severe wheezy episodes. Systemic steroids short course (either patient initiated or doctor initiated) have not shown to reduce the symptom scores, hospital admission rate or duration of hospital stay. It might be considered for a very severe episode as a counsel of despair but its routine use is not recommended. Routine use of nebulized steroids has shown to be ineffective and is not recommended.

Recent studies have evaluated the role of pre-emptive therapy, i.e., treatment started at the beginning of a URI to prevent a wheezy episode. Both inhaled fluticasone and oral montelukast have been shown to have an only modest effect on reduction in number of wheezing episodes and the number needed to treat is high. Hence, their routine use is not justified and might be reserved for children with severe EVW episodes.

Box 1: Red flag signs

- Failure to thrive
- Clubbing
- Presence of persistent wet cough
- Persistent wheezing >4 weeks
- Stridor/noisy breathing
- Age of onset <6 months
- Severe wheeze episodes

Regular Prophylaxis

The key issues while considering long-term treatments are:

- Can we identify a child who is more prone to be an asthmatic in the future?
- Can we modify the natural history of the disease with any intervention?
- Can we modify lung function levels in adult life?

Three landmark trials (Peak, Ifwin, and PAC) over the last 10 years have shown that ICS only improves symptoms with no long-term benefit in the form of modification of the natural course of disease or alteration in lung function. Interested readers could refer to these very important studies mentioned under Suggested Readings.

What Does all this Mean in and What are the Implications for Clinical Practice?

Preschool children with recurrent wheeze, selected based on the API do respond to ICSs as a group although the effect size is less as compared to older children with asthma. There are no studies on non-atopic MTW, but recent data showed that the pathology of non-atopic and atopic MTW can be similar. Recent meta-analysis suggests no difference in response between atopic versus nonatopic, although this awaits further studies.

The *NHLBI-EPR 3 Guidelines* has recommended using prophylaxis in the following subset of children with recurrent wheezing less than 5 years of age:

1. Greater than 4 episodes of wheezing in past 1 year lasted more than 1 day and affected sleep and who have risk factors for developing persistent asthma: positive API
2. Consistently require symptomatic treatment more than 2 days per week for a period of more than 4 weeks
3. Second asthma exacerbation requiring systemic corticosteroids within 6 months.

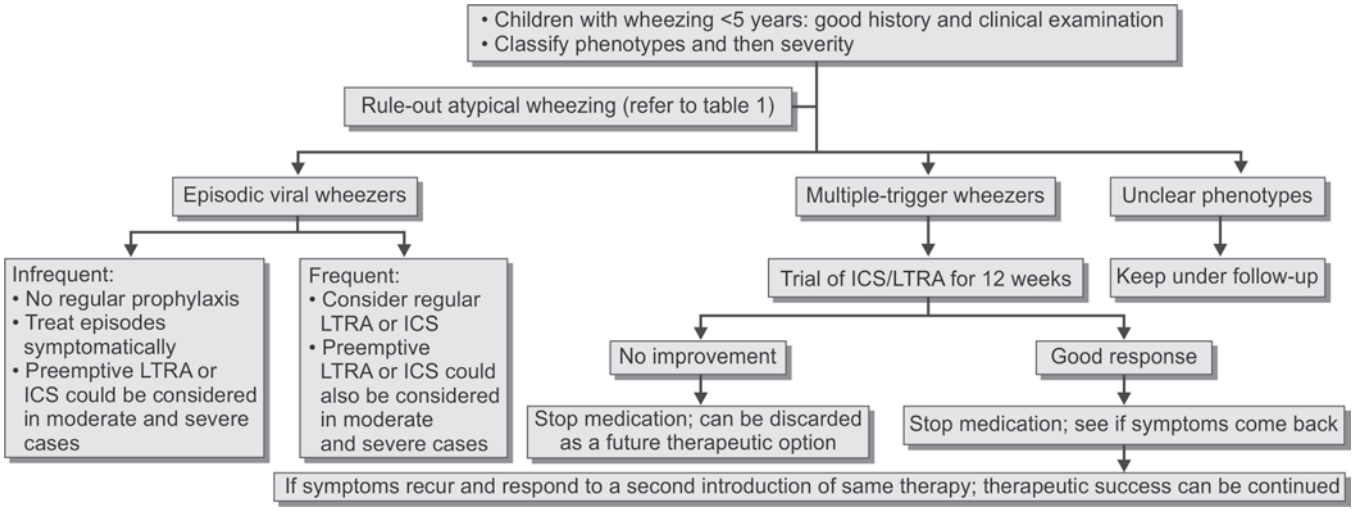
Although, these guidelines are also based on expert opinion but appears to be useful.

There is no clear consensus on the type of ICS, dose at which ICS to be started, maximum dose and when to label therapy as ineffective. Also there are no studies on the addition of leukotriene receptor antagonist (LTRA) to ICS. Since long-acting β-agonist are Food and Drug Administration (FDA) approved for more than 6 years of age due to concerns on safety, there are no studies on the use of LABA in preschool children with wheezing in addition to ICS.

Given the significant shift between the phenotypes, ICS/LTRA may be considered on a trial basis in preschool child with recurrent wheeze (MTW or EVW with severe and recurrent episodes), but should be discontinued if there is no clear clinical benefit. Children treated with a low-dose ICS have an average of 5% fewer days with symptoms (or 18 days per year) than children receiving placebo. Hence, it is arguable whether this increase in symptom-free days is clinically significant. The increase cost of therapy, negative impact on height and other unrecognizable adverse effects should also be considered. Hence, the use of preventer regimen should be reserved for only those with very troublesome symptoms and needing repeated oral steroids. The management algorithm is discussed in Algorithm 1.

ALGORITHM 1

Approach to management of wheezing in preschool children



ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist.

KEY POINTS

- ☞ Most children wheeze only when they have upper respiratory infection, are usually nonatopic, and outgrow symptoms by 6 years of age
- ☞ A good history and physical examination would suffice in most cases. Invasive investigations would be only required for atypical cases
- ☞ Most children would require only symptomatic therapy
- ☞ Some with very frequent or severe symptoms require some prophylaxis: either pre-emptive or regular
- ☞ Inhaled corticosteroids (ICS) do control symptoms but do not seem to alter the natural history of wheezing (benefit not as much as children with school asthma)
- ☞ Efficacy of ICS with episodic viral wheeze remains controversial, while with multiple-trigger wheeze (MTW) appears to be at least somewhat effective. However, the effect size in preschool children with MTW is smaller than the effect size in school-aged children with asthma
- ☞ Treatment of children with recurrent wheezing in <5 years still remains practice imperfect.

SUGGESTED READINGS

1. Bacharier LB, Guilbert TW. Diagnosis and management of early asthma in preschool-aged children. J Allergy Clin Immunol. 2012;130(2):287-96.
2. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008;32(4):1096-110.
3. Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. Eur Respir J. 2014;43(4):1172-7.
4. Castro-Rodriguez JA, Pedersen S. The role of inhaled corticosteroids in management of asthma in infants and preschoolers. Curr Opin Pulm Med. 2013;19(1):54-9.
5. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. Pediatrics. 2009;123(3):e519-25.
6. Global Initiative for Asthma. (2015). Global Strategy for Asthma Management and Prevention. [online] Available from: www.ginasthma.org [Accessed December 2015].
7. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med. 2006;354(19):1985-97.
8. Rosenfeld M, Allen J, Arets BH, Aurora P, Beydon N, Calogero C, et al. An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. Ann Am Thorac Soc. 2013;10(2):S1-S11.

CHAPTER 69

Managing Acute Severe Asthma

Ankit Parakh, Shalu Gupta, Varinder Singh

INTRODUCTION

Acute severe asthma or acute exacerbations are acute episodes of progressive deteriorating shortness of breath, cough, wheezing, chest tightness, or a combination of these symptoms. These acute episodes of asthma are an important cause of morbidity, school absenteeism, and frequent hospital admissions in children. The severity of these episodes varies from mild to severe and each episode has the potential to progress to respiratory failure. The term "critical asthma syndrome" is now used to describe any child who is at high risk of fatal asthma and includes acute severe asthma, refractory asthma, status asthmaticus, and near fatal asthma. Status asthmaticus refers to an acute asthma exacerbation in which bronchial obstruction is severe and continues to worsen or not improve despite the institution of adequate standard therapy, leading to respiratory fatigue and finally to respiratory failure.

A step-wise approach is required for the early recognition, coordinated evaluation, and prompt treatment by an experienced healthcare provider team.

EPIDEMIOLOGY

In USA more than 3.5 million children have greater than or equal to 1 exacerbation/year, resulting in approximate 1.75 million total emergency department (ED) visits, including 0.64 million for children aged 0–17 years. Children younger than 4 years old age have the highest rate of hospitalizations. Children aged 5–17 years missed 10.5 million school days owing to asthma, and activity limitations were reported in 5.5% as well.

In the Indian subcontinent as per the phase 3 ISAAC study, in children aged 13–14 and 6–7 years, the prevalence of asthma increased per year by +0.02 and +0.06%, respectively. Although there is little change in the overall prevalence of the current wheeze, the percentage of children reported to have had asthma increased significantly, possibly reflecting a greater awareness of this condition and/or changes in diagnostic practice. No country wide or large series data exist regarding burden of disease due to acute exacerbations.

CLINICAL FEATURES

A rapid initial assessment is a must to determine degree of airway obstruction and hypoxia. Immediately identify severe or life-threatening attack in children and institute immediate measures to treat it (Box 1).

A detailed and rapid clinical assessment is done on the basis of history, physical examination, and relevant investigations. A clinical history should include episodes/duration of respiratory distress, fever, cough, noisy breathing, abnormal respiratory sounds, episodes of lethargy and cyanosis, records of past treatment and current treatment, any previous hospitalization or intensive care unit admission, use of steroids, and exposure to any allergen or trigger which could have triggered this attack. A child with asthma will present with bouts of cough, wheezing, dyspnea, and increases work of breathing. Because early recognition is important for improving outcomes, various risk factors are defined for early identification of fatal asthma (Box 2).

Detailed clinical examination should include level of consciousness and degree of agitation, respiratory rate, heart rate, temperature, peripheral pulses, blood pressure, pulsus paradoxus, use of accessory muscles including chest retractions and nasal flaring, chest auscultation (wheeze), and oxygen saturation. Categorization of the acute attack can be done into mild, moderate, or severe (Table 1).

Chest radiography is not routinely indicated in a child with previous history of asthma. Indications for chest radiography may include clinical suspicion for pneumothorax, atelectasis, foreign body aspiration, after endotracheal intubation or failure to respond to standard therapy.

Box 1: Identification of life-threatening attack

- Silent chest with increasing respiratory effort
- Agitation with decreased level of consciousness
- Central cyanosis
- Inability to speak
- Diaphoresis
- Inability to lie down
- Hypotension
- Bradycardia

Box 2: Risk factors for potentially fatal asthma in children

- Previous near fatal asthma
- Previous admission to a PICU for asthma
- Admission for asthma in the last year
- Excessive use of or overdependence on β2 agonists
- Current use or recent use of oral corticosteroids
- Repeated attendances at emergency unit for asthma treatment, especially if in the last year
- "Brittle" asthma (sudden onset of acute severe asthma attacks)
- Poor adherence to medication
- Psychosocial and/or family problems

PICU, pediatric intensive care unit.

Source: Adapted from Global Initiative for Asthma, British Thoracic Society/ Scottish Intercollegiate Guidelines Network

Arterial blood gas measurement provides objective assessment of gas exchange. Early in the course of asthma, hypoxemia and hypocapnia are found due to ventilation/ perfusion mismatch and hyperventilation. With the progression of airflow obstruction, $PaCO_2$ measurement returns to normal values, though in a tachypneic and hyperventilating child, a normal $PaCO_2$ value should be interpreted as a sign of early muscle fatigue. With further progression of the disease mixed respiratory and metabolic acidosis occurs. Lactic acidosis indicates a combination of excess production from respiratory muscles, tissue hypoxia (due to hypoxemia and decreased cardiac output), and dehydration (due to decreased intake and increased insensible losses). The decision to intubate a child with severe acute asthma should be based on the child's clinical status and not simply the arterial blood gas values.

Clinical Pearls

- Clinical signs correlate poorly with the severity of airways obstruction. Some children may have very severe airways obstruction without appearing to be obviously distressed
- In a tachypneic and hyperventilating child, a normal $PaCO_2$ value should be interpreted as a sign of early muscle fatigue
- The decision to intubate a child with severe acute asthma should be based on the child's clinical status and not simply the arterial blood gas values.

TREATMENT

There is good evidence supporting recommendations for the initial treatment of acute asthma. Most children would respond to these measures although a small proportion of children would need further therapy. There is less evidence to guide the use of second line therapies to treat the small number of severe cases poorly responsive to first line measures.

The details regarding assessment, first line treatment, second line treatment, algorithm, further evaluation and drug doses should be present in all emergency and pediatric intensive care unit as a ready to use tool. A suggested algorithm is shown in Algorithm 1 and drugs with doses, delivery methods, and adverse effects are summarized in Table 2. After each step in the algorithm the child should be reclassified. Children moving down a category (e.g., severe to moderate) suggest a good response; remaining in the same category (e.g., severe to severe) suggests a partial response; and children moving up a category (e.g., severe to life threatening) suggest a poor response.

TABLE 1: Acute asthma severity assessment

Examination	Mild	Moderate	Severe
Breathing frequency (awake)	Increased	Increased	>30/min
Wheezing	None or mild end expiratory	Throughout expiration	Both inspiratory and expiratory
Work of breathing and use of auxiliary muscles	Normal or minimal retractions	Intercostals retractions	Suprasternal retractions, present
Expiration	Normal or minimally prolonged	Moderately prolonged	Severely prolonged
Pulsus paradoxus	Absent	Can be present	Often present
Pulse pressure fluctuation	<10 mmHg	10–25 mmHg	20–40 mmHg
Air entry	Normal	Decreased at bases	Wide-spread decrease
Breathlessness	With activity or walking	While at rest: For infants: soft or shorter cry, difficulty feeding, prefers sitting	While at rest For infants: stops feeding, sits upright
Talks	Sentences	Phrases	words
Alertness	Alert/can be agitated	May be agitated	agitated
Investigations			
Pulse oximetry (room air)	>95%	91–95%	<91%
$PaCo_2$ (KPa)	<5.6	<5.6	≥5.6
PaO_2 (KPa)	Normal	>8	<8, possible cyanosis
PEF (% of predicted for height)	≥70%	40–69%	<40%

PEF, peak expiratory flow.

TABLE 2: Doses of common drug used in acute severe asthma

	Dose	Available formulations	Adverse effects and comments
Short-acting β-agonists			
Salbutamol	• Nebulized: 0.15 mg/kg (minimum dose 2.5 mg) every 20 min for 3 doses then 0.15–0.3 mg/kg up to 10 mg every 1–4 hour as needed, or 0.5 mg/kg/hour by continuous nebulization • MDI: 2–4 puffs (up to 10 puffs) at the same intervals as above	• Respules: 2.5 mg/2.5 mL; • Respirator solution: 5 mg/mL; • MDI: 100 µg/puff	• Tachycardia, palpitations, headache, hypokalemia, hyperglycemia
Levo salbutamol	• 0.075 mg/kg usage similar to salbutamol	• Respules: Three strengths available 0.31/0.63/1.25 mg/2.5 mL	• Same as above
Terbutaline	• 0.01 mg/kg subcutaneous • Bolus 5–10 µg/kg over 10 minutes followed by 2–10 µg/kg/hour IV (1 mL terbutaline + 50 mL 5% dextrose, thus, 1 mL = 10 µg terbutaline)	• Inj 0.5 mg/mL	• IV terbutaline drip necessitates continuous heart rate and ECG • If heart rate i.e.,180/min or if ECG changes develop, halve the drip rate • Discontinue nebulized β2 agonist if using high infusion rates of IV terbutaline • Dose of IV terbutaline to be halved if concurrently used with theophylline drip
Anticholinergics			
Ipratropium bromide	• 125 µg <1 year; 250 µg >1 year every 20 min for 3 doses, then every 6–8 hours	• Respules: 0.5 mg/2 mL • Respirator solution: 0.25 mg/mL; • MDI: 20 µg/puff	• Dryness of mouth increased wheezing in some • Slower onset of than β2 agonists but may provide additive effect in severe exacerbations
Corticosteroids			
Hydrocortisone	• 10 mg/kg stat followed by 5 mg/kg every 6 hourly IV	• Injection 100 mg/vial	• Oral steroids are equally effective • Shift to oral as soon as the child is able to accept orally • Tapering not required for short courses
Prednisolone	• 1–2 mg/kg in 2 divided doses (maximum 60 mg/day)	• Tablet 5, 10, 20, 30 mg, syrup 5 mg/mL and 15 mg/mL	
Others			
Aminophylline	• 6 mg/kg bolus over 30 min followed by 0.5–1 mg/kg/hour continuous infusion in 5% dextrose	• Injection 250 mg/10 mL	• Omit bolus in children already on oral aminophylline
Magnesium sulfate	• 25–50 mg/kg IV bolus over 20 min (maximum 2 g)	• Injection 50% (500 mg/mL), 1 mL ampoule	• Tachycardia, hypotension, muscle weakness

MDI, metered-dose inhaler; ECG, electrocardiogram; IV, intravenous.

First Line Treatment

Oxygen

All children with severe and life-threatening asthma or SpO_2 less than 92%, should receive supplemental oxygen via a face mask or nasal cannula at sufficient flow rates to achieve normal saturations. Partial rebreathing and non-rebreathing masks are useful in providing high concentration of fraction of inspired oxygen in children not maintaining on simple/venturi face mask.

Short-acting β-2 Agonists

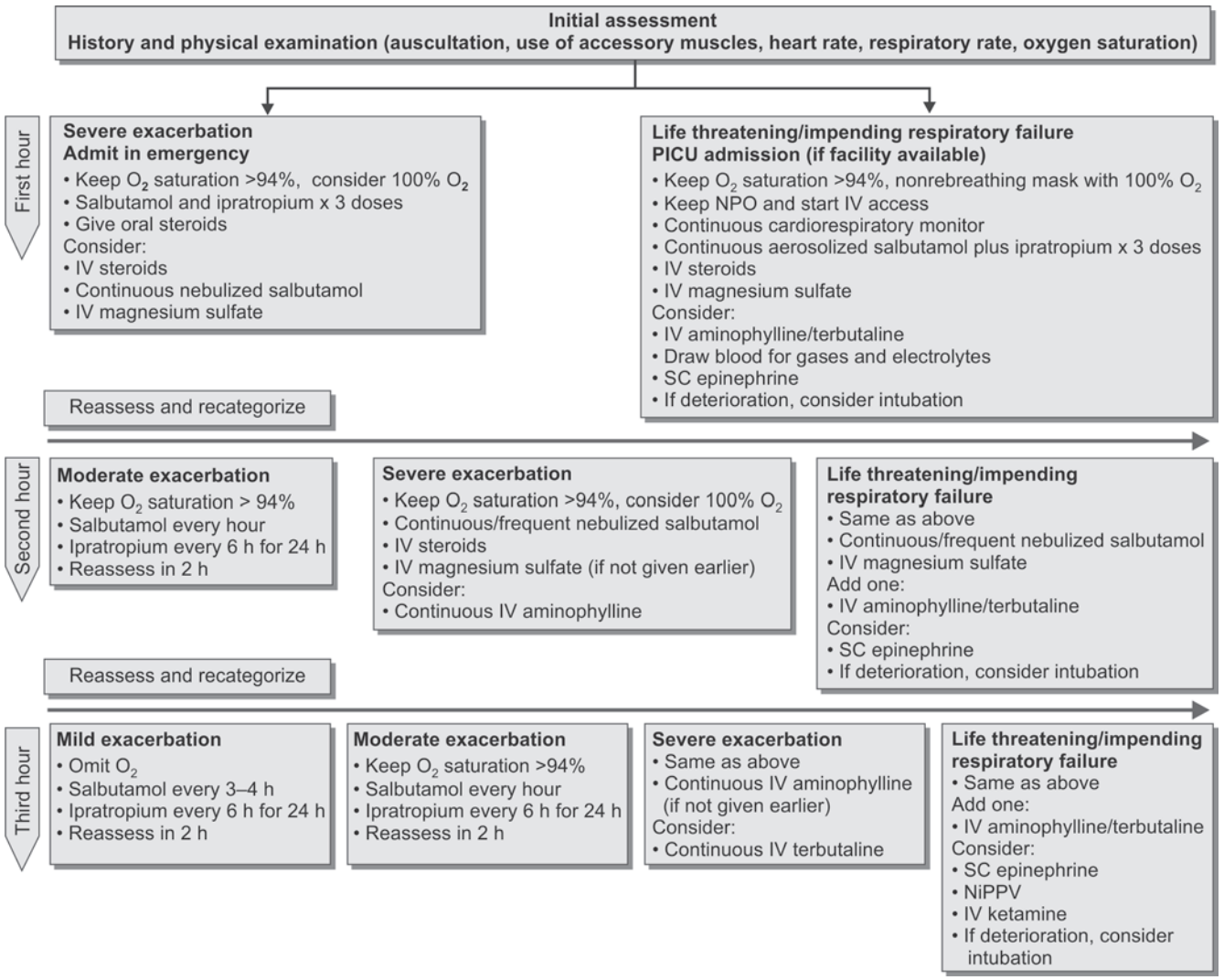
Short-acting β-2 agonists (salbutamol, levosalbutamol, terbutaline) are the bronchodilators of choice for acute exacerbations of asthma across all severity. Children with severe or life-threatening asthma should receive frequent doses of nebulized bronchodilators (2.5–5 mg salbutamol) driven by oxygen, repeated every 20–30 minutes; although metered-dose inhaler with spacers can be used (10–12 puffs of salbutamol 100 µg repeated every 2–4 minutes titrated according to clinical response). Continuous nebulized β2-agonists are of no greater benefit than the use of frequent intermittent doses in the same total hourly dosage.

Anticholinergics

Children with severe exacerbation or moderate exacerbation with poor response to the initial dose of β2-agonists, are usually nebulized with combination with nebulized ipratropium

ALGORITHM 1

Algorithm for management of acute severe asthma



PICU, pediatric intensive care unit; ECG, electrocardiogram; IV, intravenous; NPO, nil per os; IV, intravenous; SC, subcutaneous; NiPPV, nasal intermittent positive pressure inhibitors.

bromide. There is good evidence for the safety and efficacy of frequent doses of ipratropium bromide (every 20–30 minutes) used in addition to β2 agonists for the first two hours of a severe asthma attack. Benefits are more apparent in the most severe patients.

Corticosteroids

Systemic corticosteroids are pivotal in the management of acute severe asthma and reduce the need for hospital admission and prevent a relapse in symptoms after initial presentation. Benefits can be apparent within 3–4 hours. Both oral as well as intravenous (IV) steroids have similar efficacy. Intravenous hydrocortisone (4 mg/kg repeated 4-hourly) should be reserved for severely affected children who are unable to retain oral medication.

Second Line Treatment

Children with continuing severe asthma, despite frequent nebulized β2 agonists and ipratropium bromide plus oral steroids, and those with life-threatening features, need transfer to a high dependency unit or PICU to receive second line IV therapies. There are three options to consider: (1) magnesium sulfate, (2) aminophylline and (3) continuous IV salbutamol/terbutaline.

Intravenous or Nebulized Magnesium Sulfate

Magnesium sulfate is a physiological calcium antagonist that acts by inhibiting the contraction, mediated by the bronchial smooth muscle. In addition, it interferes with the parasympathetic stimulation and prevents acetylcholine release to the axon terminal; therefore promoting a bronchodilating

effect. It has been usually recommended as an add-on therapy after the first hour of treatment with salbutamol and steroids (GINA 2015, Evidence level A). One large open-labeled trail from Argentina has shown that magnesium sulfate when used in the first hour itself can reduce significantly, the percentage of children who required mechanical ventilation support. There is now evidence to support use of nebulized isotonic magnesium sulfate.

Intravenous Aminophylline

There is no evidence that aminophylline is of benefit for mild to moderate asthma and side effects are common and troublesome. One well-conducted study has shown evidence of benefit in severe acute asthma unresponsive to multiple doses of β2 agonists and steroids, although the loading dose used was double that currently recommended in UK and one-third of patients were withdrawn from active medication because of vomiting. Two studies have compared IV β2 agonists with IV theophylline/aminophylline. One demonstrated equivalence. The other resulted in a shorter period of inpatient treatment among the children receiving an aminophylline bolus followed by infusion but in the salbutamol arm of the study an infusion was not given after the bolus dose.

Intravenous Terbutaline

A continuous IV infusion of terbutaline could be used in children not responding to the above mentioned drugs. This should be given in a high dependency unit or PICU with continuous electrocardiogram (ECG) monitoring and twice daily electrolyte monitoring. Nebulized bronchodilators should be continued while the patient is receiving IV bronchodilators. Once the patient is improving the IV infusion should be reduced before reducing the frequency of nebulized bronchodilators. Currently, the availability of this drug is poor across our country.

Other Modalities

Children not responding to the above measures should be considered for noninvasive ventilation, IV ketamine, and if required, intubation and mechanical ventilation.

The use of a helium-oxygen gas mixture is another potentially attractive therapy for the treatment of status asthmaticus in children. The use of helium-oxygen–driven aerosolized therapy increases drug delivery by improving gas exchange to the distal airways.

KEY POINTS

- ☞ Acute asthma management involves prompt recognition of severity and treatment using short-acting β-agonists, anticholinergics, and systemic corticosteroids
- ☞ Children with severe exacerbations should receive high-dose short-acting β-agonists mixed with ipratropium bromide as well as systemic steroids
- ☞ Children with less-severe exacerbations might benefit from systemic steroids
- ☞ Patients not improving after multiple high-dose systemic steroids should receive adjunctive therapy, such as intravenous magnesium
- ☞ Prepare a written asthma action plan. Ensure proper follow-up after discharge with an aim to implement a long-term management plan.

SUGGESTED READINGS

1. Camargo CA Jr, Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department: summary of the National Asthma Education And Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. Proc Am Thorac Soc. 2009;6(4):357-66.
2. Carroll CA, Sala KA. Pediatric status asthmaticus. Crit Care Clin. 2013;29(2):153-66.
3. Kling S, Zar HJ, Levin ME, Green RJ, Jeena PM, Risenga SM, et al. Guideline for the management of acute asthma in children: 2013 update. S Afr Med J. 2013;103(3 Pt 3):199-207.
4. Koninckx M, Buysee C, dee Hoog M. Management of status asthmaticus in children. Paediatr Respir Rev. 2013;14(2):78-85.
5. Nelson KA, Zorc JJ. Asthma update. Pediatr Clin North Am. 2013;60(5):1035-48.
6. Nievas IF, Anand KJ. Severe acute asthma exacerbation in children: a stepwise approach for escalating therapy in a pediatric intensive care unit. J Pediatr Pharmacol Ther. 2013;18(2):88-104.

CHAPTER 70

Management of Bronchiolitis

Preeti Singh, Varinder Singh

INTRODUCTION

Bronchiolitis accounts for significant number of hospital admission worldwide especially less than 2 years of age. The American Academy of Pediatrics Clinical Practice Guideline defines bronchiolitis as "a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than two years of age".

EPIDEMIOLOGY

Bronchiolitis is primarily a disease of infancy, with the first (and the most severe) episodes occuring between 2–6 months of age. Respiratory syncytial virus (RSV) is the most common etiological agent and accounts for 50–80% of cases. In Indian studies, RSV infection was implicated in 30–70% of children with bronchiolitis. Other viruses responsible are rhinovirus, adenovirus, coronavirus, enterovirus, parainfluenza virus type 3, influenza, and the recently identified human metapneumovirus (HMPV). Molecular diagnostic techniques have also revealed that young children with bronchiolitis have mixed viral infections (10–30%) most commonly with RSV and either HMPV or rhinovirus. Bronchiolitis shows a seasonal pattern with highest rates occurring during winter in most locations and in more tropical and subtropical latitudes during rainy season. There has been no evidence for a role of bacteria in etiology of bronchiolitis. Data on synergistic viral-bacterial infections also are unconvincing.

PATHOGENESIS

Bronchiolitis is characterized by acute inflammation of the bronchiolar epithelium, with peribronchial infiltration of white blood cells, mostly mononuclear cells, edema of the submucosa and adventitia, necrosis of small airway epithelial cells, increased mucus production, and bronchospasm. Plugs of sloughed, necrotic epithelium and fibrin in the airways cause partial or total obstruction to airflow. A "ball-valve" mechanism results in air trapping distal to obstructed areas, with subsequent absorption, atelectasis, and a ventilation perfusion mismatch leading to hypoxemia. The degree of obstruction may vary as these areas are cleared, resulting in rapidly changing clinical signs. Certain underlying conditions, such as prematurity, chronic lung disease, cardiac disease, immunodeficiency, and neuromuscular disorders can predispose a child to a more turbulent course while certain clinical clues suggest a more likely stormy course (Table 1).

TABLE 1: Markers of an increased risk and severity of bronchiolitis

Personal risk factors	Environmental risk factors	Clinical clues
• Male gender • Prematurity <34 weeks • Age <6 months • Absence of breast-feeding • Chronic pulmonary disease • Hemodynamically significant congenital heart disease • Immunodeficiency • Family history of asthma • Personal atopy • Congenitally small airways • Airway hyperactivity • RSV-specific IgE responses	• Having older siblings • Passive smoke • Household crowding • Child-care attendance	• Toxic or ill appearance • Oxygen saturation <95% • Respiratory rate ≥70 breaths per minute • Moderate/ severe chest retractions • Atelectasis on chest radiograph

RSV, respiratory syncytial virus; IgE, immunoglobulin E

Clinical Pearl

- Bronchiolitis is primarily a disease of infancy with respiratory syncytial virus being responsible for more than 50% of cases. Host, anatomical immunologic, environmental and nature of the viral pathogen plays an important role in severity of clinical syndrome.

CLINICAL FEATURES AND COURSE

Bronchiolitis typically starts with fever and rhinorrhea. After 1–3 days, a prominent staccato-like cough and wheeze develop. The clinical presentation of bronchiolitis can be quite variable, both over time and between patients. It can range from mild respiratory distress with transient events, such as mucous plugging, to apnea and respiratory failure. Excessive nasal secretions can cause upper airway obstruction, with both inspiratory and expiratory noise on auscultation. Concurrent presence of respiratory symptoms in other family members is common. On examination child has tachypnea, varying degree of hypoxemia due to ventilation perfusion mismatch and increased work of breathing manifested as nasal flaring, intercostal retractions, subcostal retractions, and use of accessory muscles. Upon auscultation, diffuse bilateral wheezes and crackles are often present; the expiratory phase of respiration can also be prolonged. The liver and spleen can be palpable due to hyperinflation of the lungs secondary to air trapping. Other manifestations of upper respiratory tract infection (URTI), like mild conjunctivitis, otitis media, and pharyngitis may be present.

The mean duration of illness with bronchiolitis is 15 days, and the majority of these infections resolve uneventfully within 3–4 weeks. The mortality rate is less than 1%, being attributable to apnea or respiratory failure. The association of bronchiolitis with the subsequent wheezing is not clearly established as causal. While RSV bronchiolitis actually leads to long-term changes in the lungs in a proportion of patients while in others who continue to wheeze later, RSV infection simply may serve as a marker for a genetic or physiologic/anatomic predisposition to wheezing.

DIAGNOSIS

The diagnosis of bronchiolitis is essentially clinical and does not require diagnostic testing, but the differential diagnosis is broad and multifactorial which warrants consideration (Box 1). The use of complete blood counts has not proved to be useful in either diagnosing bronchiolitis or guiding its therapy. A blood gas (capillary, venous, or arterial) can aid with assessment of gas exchange in a child with moderate to severe respiratory distress. If a child has poor oral intake, one can assess electrolyte abnormalities and extent of dehydration by measuring the plasma blood urea nitrogen, creatine, and electrolytes. The typical findings on chest radiograph are hyperinflation and peribronchial thickening. Areas of atelectasis are not uncommon. Indian Academy of Pediatrics and American Academy of Pediatrics does not recommend the routine use of chest radiography for diagnosis and management of bronchiolitis. It may be useful when the hospitalized child does not improve at the expected rate, if the severity of disease requires further evaluation, or if another diagnosis is suspected. Laboratory testing of nasopharyngeal aspirates for identification of viruses can support patient diagnosis, aid with syndromic surveillance, but has limited utility and does not aid individual case management.

Box 1: Differential diagnoses for acute bronchiolitis

- Virus-induced wheeze of infancy
- Viral and bacterial pneumonias
- Other pulmonary infections (e.g., *Mycoplasma*, *Chlamydia*, tuberculosis)
- Gastroesophageal reflux disease
- Congestive heart failure
- Structural abnormalities, like congenital vascular ring, laryngotracheomalacia, mediastinal mass, bronchogenic cyst, etc.
- Tracheoesophageal fistula
- Foreign body aspiration
- Cystic fibrosis

Clinical Pearl

- The diagnosis of bronchiolitis is essentially clinical, particularly in a previously healthy infant with first episode of wheezing.

MANAGEMENT

The treatment of bronchiolitis is often debated and no consistently effective therapy has shown to alter the course of the disease or its major outcomes. It is critical to remember that most infants with mild bronchiolitis improve and resolve spontaneously and hence can be successfully treated at home. The cornerstone of therapy for bronchiolitis is supportive care. Infants with moderate to severe respiratory distress need hospitalization for management of this life-threatening condition. The need for treatment is either hypoxemia necessitating supplemental oxygen or the inability to take adequate fluids by mouth. Monitoring the child with bronchiolitis for disease progression and complications is a vital part of supportive care. Table 2 details the current evidence for the management of acute bronchiolitis.

Supportive Care

Fluid and Hydration Management

Children with bronchiolitis often have potential problem of dehydration because of decreased intake and increased needs (due to fever and tachypnea), so fluid and hydration status should be properly maintained. Care should be taken not to overhydrate them because edema is an important part of the pathology of bronchiolitis (excessive antidiuretic hormone production), which can lead to pulmonary congestion. Breast feeding should be encouraged as it provides hydration and confers immunological protection. Nasogastric feedings may be considered for a child who has decreased oral intake, with mild to moderate respiratory distress. In infants with diificulty in feeding, persistent vomiting or with moderate to severe respiratory distress intravenous fluids should be considered to maintain hydration. Usual maintainence fluids are needed.

Oxygen Supplementation

The keystone of therapy for bronchiolitis is the administration of oxygen because hypoxemia is seen in moderate to severe

TABLE 2: Evidence-based recommendations for treatment of bronchiolitis

Intervention	Recommendation
• Supportive-care fluid and hydration management • Use of supplemental oxygen if SpO_2 <90%	• Strong recommendation
• Nebulized bronchodilators (epinephrine/salbutamol)	• Consider trial under strict monitoring but use of either drug continued only if proven benefit
• Nebulized hypertonic saline	• May reduce length of inpatient hospitalization but no recommendation
• Corticosteroids	• Not recommended for routine use
• Antibiotics	• Specific indications in case of coexisting bacterial infection
• Ribavarin	• Not recommended for routine use
• CPAP, mechanical ventillation, surfactant, heliox	• Possibly effective for most severe cases and areas of future research
• Leukotriene receptor antagonists/montelukast • Oral bronchodilators • Chest physiotherapy • Inhaled furosemide/inhaled interferon α-2a/inhaled recombinant human DNase	• Possibly ineffective so no recommendation

CPAP, continuous positive airway pressure; DNase, deoxyribonuclease.

cases due to ventilation perfusion mismatch. Humidified oxygen should be administered using nasal cannula, face mask, or head box and the patient's respiratory status monitored by pulse oximetry. In an irritable child one may have to accept the least threatning but most acceptable manner of oxygen therpy (like nasal blow by) in which the baby tolerates it. The American Academy of Pediatrics (AAP) recommends supplemental oxygen if the hemoglobin oxygen saturation is persistently below 90%. Their suggested point of discontinuation of oxygen therapy is when the child's oxygen saturation can be maintained at or above 90% with room air and the child is feeding well, with minimal respiratory distress. Premature or low birth weight infants, as well as those with chronic lung disease or congenital heart disease have lower tolerance for hypoxemia and a higher likelihood of severe disease, so need to be careful while discontinuing oxygen.

Nasal Decongestion

Children with bronchiolitis suffer from nasal blockade due to thick copious nasal secretions. Cleaning of nostrils by instilling saline drops and gentle suction may help to relieve nasal block and facilitate feeding. Parents should be taught this effective self-clearing of the nasal passages before discharge from hospital.

Clinical Pearl

- The cornerstone of therapy for bronchiolitis is supportive care with maintenance of adequate hydration and nutrition, ensuring adequate oxygenation, and nasal decongestion using nasal saline washes.

Bronchodilators

The evidence to support the routine use of bronchodilators in the management of bronchiolitis is not very strong, and the practice remains controversial. The Cochrne review does not show any benfit of short-acting β-2 agonists in the management of bronchiolitis. Another meta-analysis demonstrated superiority of epinephrine compared to placebo for short-term outcomes for outpatients.

If the decision is made to use an inhaled bronchodilator, it should be based on personal or family history of atopy or asthma; if present, salbutamol inhalation may be given, otherwise a trial of epinephrine inhalation may be given. Further doses of either medication may be continued only on documentation of improvement.

Corticosteroids

The use of systemic corticosteroid in bronchiolitis is still controversial. A recent Cochrane review conducted in 2010 including 17 trials with a total of 2596 infants did not demonstrate a benefit in significantly reducing outpatient visits, hospital admission rate, clinical score after 12 hours and length of stay for inpatients. Combined dexamethasone and epinephrine may reduce outpatient admissions, but result from this single study at best be called exploratory and safety data is limited. Currently, there is no definitive evidence to support the use of inhaled corticosteroids for acute or long-term benefit in bronchiolitis.

Mucolytics

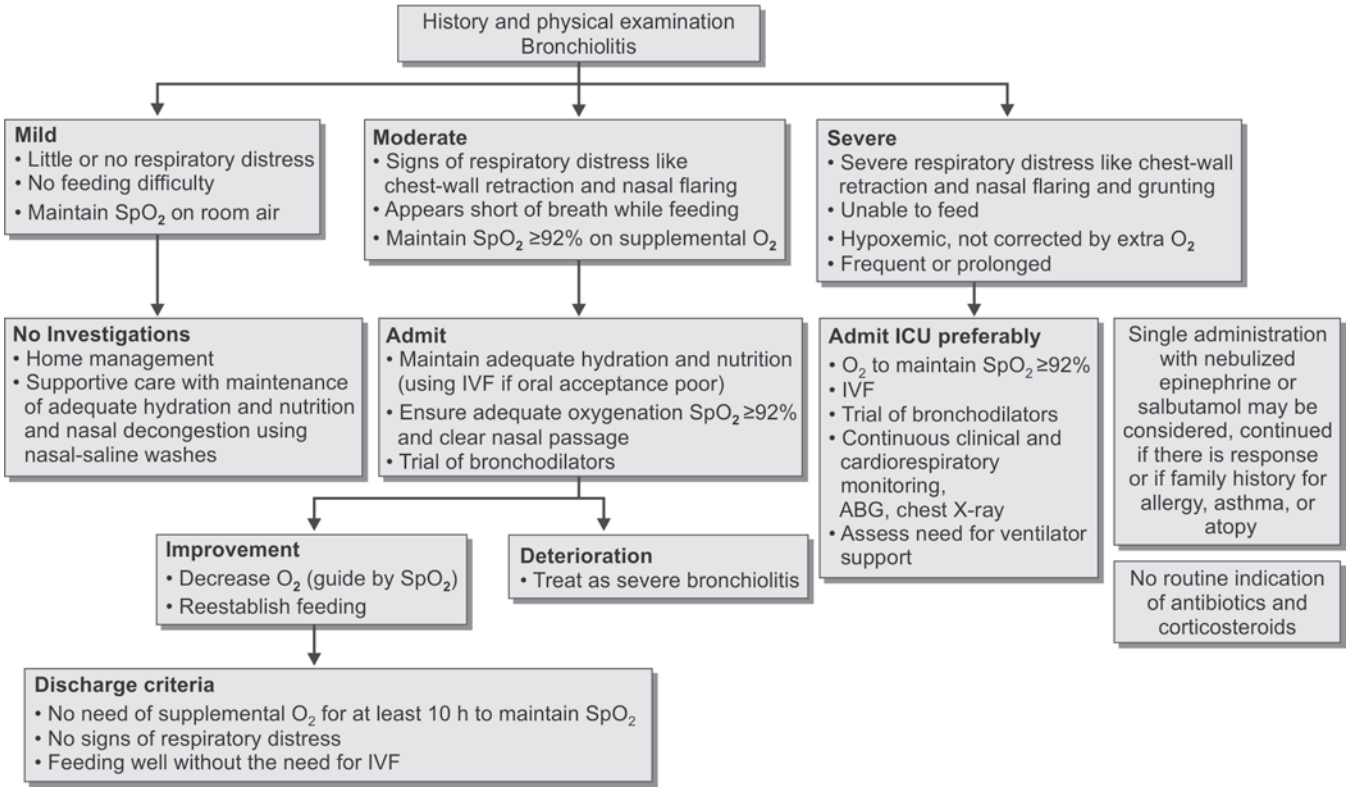
Mucous plugging plays a significant role in the small airway obstruction of bronchiolitis and interventions, like hypertonic saline and deoxyribonuclease (DNase) decrease epithelial edema and elasticity and viscosity of mucus which could improve clinical outcomes. Hypertonic saline inhalation may be considered as potential treatment for bronchiolitis. Recent randomized controlled trial reported that high volume normal saline was as effective as 3% saline in children with mild bronchiolitis.

Antibiotics

As bronchiolitis is a viral disease, antibiotics are not useful or necessary. Institution of antibiotics should be considered only when a change in course of illness suggests the possibility of secondary bacterial infection. A recent review did not find sufficient evidence to support the use of antibiotics for bronchiolitis, but concluded that research may be justified to identify a subgroup of patients who may benefit from antibiotics. It also stressed that the future research should

ALGORITHM 1

Algorithmic approach and management of a child with bronchiolitis



IVF, *in vitro* fluid; ICU, intensive care unit; ABG, arterial blood gas.

focus on determining the reasons that clinicians use antibiotics so readily for bronchiolitis, so that the antibiotic usage in bronchiolitis is reduced and also the clinician anxiety about not using antibiotics is reduced.

Mechanical Ventilation and Continuous Positive Airway Pressure

Assisted ventilation is indicated in infants with moderate to severe bronchiolitis with progressive clinical deterioration, i.e. increasing respiratory distress, apnea and poor peripheral perfusion. In severe bronchiolitis early intervention in form of continuous positive airway pressure (CPAP) did not produce any conclusive evidence to decrease the need for intubation. Current evidence is inconclusive regarding routine use of CPAP in children with acute bronchiolitis. The use of chest physiotherapy is discouraged in children with bronchiolitis as it did not reduce supplemental oxygen requirement, or length of hospital stay rather it may increase the distress and irritability of ill infants.

Antiviral

Ribavarin is the only antiviral agent licensed for use with RSV bronchiolitis. Routine use of ribavirin is not recommended for children with bronchiolitis. It may be considered in high risk infants (immunocompromised and/or hemodynamically significant cardiopulmonary disease) and in infants requiring mechanical ventilation.

Others

Current evidence suggests that surfactant therapy may have potential use in acute severe bronchiolitis requiring mechanical ventilation in decreasing duration of mechanical ventilation and intensive care unit stay. There is a need for larger trials with adequate power and to establish beneficial role of administration of surfactant in infants with severe bronchiolitis. Currently, there is insufficient evidence to recommend leukotriene modifier and heliox use for bronchiolitis.

PREVENTION

There is no effective therapy that can improve outcome, if administered early in course of bronchiolitis. Hand decontamination is the most important step in preventing nosocomial spread of RSV. Clinicians should educate health personnel and family members on hand sanitation.

Currently, no vaccine exists for the prevention of RSV infection. Passive immunoprophylaxis using palivizumab [humanized mouse immunoglobulin G1 (IgG1) monoclonal antibody] to high-risk infants (Table 3) before RSV season has documented marked reduction in the severity of illness and rate of hospitalization after RSV infection. It is administered

TABLE 3: Recommendations for respiratory syncytial virus immunoprophylaxis with palivizumab

High-risk group	Details
Prematurity	• Infants born at 28 weeks of gestation or earlier who are younger than 12 months of age at the start of the RSV season • Infants born at 29–32 weeks of gestation who are younger than 6 months of age at the start of the RSV season • Infants born between 32 and 35 weeks of gestation, who have 2 or more of the following risk factors (child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease) and are younger than 6 months of age at the start of the RSV season
Chronic lung disease (CLD)	• Required medical therapy for CLD within 6 months before onset of RSV season
Congenital heart disease	• Cyanotic heart disease • Taking medications for congestive heart failure

RSV, respiratory syncytial virus.

intramuscularly at a dose of 15 mg/kg monthly (every 30 days) during the RSV season with maximum of 5 doses being required for prophylaxis during one season.

KEY POINTS

- ☞ Bronchiolitis is a disease of infancy with essentially clinical diagnosis
- ☞ The cornerstone of therapy for bronchiolitis is supportive care with maintenance of adequate hydration and nutrition, ensuring adequate oxygenation, and nasal decongestion
- ☞ Bronchodilators should not be routinely used in the management of bronchiolitis. A carefully monitored trial of either α or β adrenergic inhalation is an option
- ☞ Hand decontamination is the most important step in preventing nosocomial spread of RSV
- ☞ Breastfeeding is recommended to decrease a child's risk of having LRTI.

SUGGESTED READINGS

1. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. Pediatrics. 2006;118(4):1774-93.
2. Anil AB, Anil M, Saglam AB, Cetin N, Bal A, Aksu N. High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. Pediatr Pulmonol. 2010;45(1):41-7.
3. Beem M, Wright FH, Fasan DM, Egerer R, Oehme M. Observations on the etiology of acute bronchiolitis in infants. J Pediatr. 1962;61:864-9.
4. Bharaj P, Sullender WM, Kabra SK, Mani K, Cherian J, Tyagi V, et al. Respiratory viral infections detected by multiplex PCR among pediatric patients with lower respiratory tract infections seen at an urban hospital in Delhi from 2005 to 2007. Virol J. 2009;6:89.
5. Bisgaard H, Flores-Nunez A, Goh A, Azimi P, Halkas A, Malice MP, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. Am J Respir Crit Care Med. 2008;178(8):854-60.
6. Davison C, Ventre KM, Luchetti M, Randolph AG. Efficacy of interventions for bronchiolitis in critically ill infants: a systematic review and meta-analysis. Pediatr Crit Care Med. 2004;5(5):482-9.
7. Donlan M, Fontela PS, Puligandla PS. Use of continuous positive airway pressure (CPAP) in acute viral bronchiolitis: a systematic review. Pediatr Pulmonol. 2011;46(8):736-46.
8. Farley R, Spurling GK, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev. 2014;10:CD005189.
9. Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev. 2010;(10):CD004878.
10. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database of Syst Rev. 2014;6:CD001266.
11. Gupta S, Shamsundar R, Shet A, Chawan R, Srinivasa H. Prevalence of respiratory syncytial virus infection among hospitalized children presenting with acute lower respiratory tract infections. Indian J Pediatr. 2011;78(12):1495-7.
12. Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, et al. Epinephrine for bronchiolitis. Cochrane Database Syst Rev. 2011;6:CD003123.
13. Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. Cochrane Database Syst Rev. 2012;9:CD009194.
14. Jat KR, Mathew JL.Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. Cochrane Database Syst Rev. 2015;1:CD010473.
15. Liet JM, Ducruet T, Gupta V, Cambonie G. Heliox inhalation therapy for bronchiolitis in infants. Cochrane Database Syst Rev. 2010;4:CD006915.
16. Loda FA, Clyde WA Jr, Glezen WP, Senior RJ, Sheaffer CI, Denny FW Jr. Studies on the role of viruses, bacteria, and M. pneumoniae as causes of lower respiratory tract infections in children. J. Pediatr. 1968;72(2):161-76.
17. Maitreyi RS, Broor S, Kabra SK, Ghosh M, Seth P, Dar L, et al. Rapid detection of respiratory viruses by centrifugation enhanced cultures from children with acute lower respiratory tract infections. J Clin Virol. 2000;16(1):41-7.
18. Mansbach JM, Clark S, Christopher NC, LoVecchio F, Kunz S, Acholonu U, et al. Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department. Pediatrics. 2008;121(4):680-8.
19. McConnochie KM, Roghmann KJ. Parental smoking, presence of older siblings, and family history of asthma increase risk of bronchiolitis. Am J Dis Child. 1986;140(8):806-12.
20. Meissner HC. Selected populations at increased risk from respiratory syncytial virus infection. Pediatr Infect Dis J. 2003;22(2 Suppl):S40-4.
21. Mejías A, Ramilo O. Review of palivizumab in the prophylaxis of respiratory syncytial virus (RSV) in high-risk infants. Biologics. 2008;2(3):433-9.
22. Paranhos-Baccalà G, Komurian-Pradel F, Richard N, Vernet G, Lina B, Floret D. Mixed respiratory virus infections. J Clin Virol. 2008;43(4):407-10.
23. Pickering, Baker CJ, McMillanassociate JA (Eds). Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed. Elk Grove, Illinois: American Academy of Pediatrics; 2006.
24. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, et al. Epinephrine and dexamethasone in children with bronchiolitis. N Engl J Med. 2009;360(20): 2079-89.
25. Shaw KN, Bell LM, Sherman NH. Outpatient assessment of infants with bronchiolitis. Am J Dis Child. 1991;145(2):151–5.
26. Smyth RL, Openshaw PJ. Bronchiolitis. Lancet. 2006;368(9532):312-22.
27. van Steensel-Moll HA, Hazelzet JA, van der Voort E, Neijens HJ, Hackeng WH. Excessive secretion of antidiuretic hormone in infections with respiratory syncytial virus. Arch Dis Child. 1990;65(11):1237-9.
28. Verma N, Lodha R, Kabra SK. Recent advances in management of bronchiolitis. Indian Pediatr. 2013;50(10):939-49.
29. Voets S, van Berlaer G, Hachimi-Idrissi S. Clinical predictors of the severity of bronchiolitis. Eur J Emerg Med. 2006;13(3):134-8.
30. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. J Pediatr. 1995;126(2):212-9.
31. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study. II. Lower respiratory tract illness in the first year of life. Am J Epidemiol. 1989;129(6):1232-46.
32. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev. 2013;7:CD006458.

CHAPTER 71

Management of Bronchiectasis

Kana R Jat

INTRODUCTION

Bronchiectasis is a disease of conducting airways characterized clinically by chronic moist or productive cough, airway hyperreactivity, recurrent respiratory infections, and failure to thrive and radiologically by dilated airways. Chronic suppurative lung disease (CSLD), is a broad category with sign and symptoms similar to bronchiectasis with or without radiological evidence of dilated airways. There is lack of consensus whether bronchiectasis and CSLD represent a spectrum of common disease or are different entities. Empyema and lung abscess are considered different from both bronchiectasis and CSLD.

Clinical Pearl

- Never ignore a child with chronic wet cough.

The prevalence of bronchiectasis had decreasing trend in developed countries, but it is still an important chronic respiratory disease in developing countries including India. In early 90s, bronchiectasis was present in approximate 1% children at pediatric respiratory centers in developed countries.

CAUSES OF BRONCHIECTASIS

Bronchiectasis is secondary to many diseases or conditions that injure the conducting airways with recurrent respiratory infections (Table 1). Bronchiectasis may be grouped in two major categories: (1) associated with cystic fibrosis (CF); and (2) non-CF bronchiectasis. The both group may differ in age of onset, airway colonization, disease severity and distribution, extra pulmonary manifestations, treatment strategies, and overall prognosis. Bronchiectasis is mainly secondary to CF in industrialized countries, whereas in developing countries postinfectious bronchiectasis forms a major chunk. In a study from Korea, the underlying etiology was identified in 85.8% (79/92) patients that included bronchiolitis obliterans (32.6%), childhood respiratory infection (20.6%), interstitial lung disease (17.3%), immunodeficiency (8.6%), primary ciliary dyskinesia (PCD) (4.3%), and CF (2%).

PATHOPHYSIOLOGY OF BRONCHIECTASIS

Bronchiectasis is characterized by tortuous and dilated airways filled with infected secretions with airway obstruction. There

TABLE 1: Causes of bronchiectasis

Causes of bronchiectasis*		
Postinfectious: after severe LRTI: tuberculosis, pertussis, measles, and severe viral pneumonia	Airway obstruction (intraluminal or external compression): foreign body, granulation tissue, lymph node, tumor, vascular ring	Yellow nail lymphedema syndrome
Primary ciliary dyskinesia	Bronchiolitis obliterans (postviral, posttransplant)	Marfan syndrome
Immune deficiencies: both primary and secondary	Cystic fibrosis	Usher syndrome
Congenital airway malformation: tracheomalacia, bronchomalacia, etc.	Recurrent aspiration: tracheoesophageal fistula, gastroesophageal reflux	Alpha-1 trypsin deficiency
Allergic bronchopulmonary aspergillosis	Neuromuscular weakness	Eosinophilic lung disease
Interstitial lung disease	Asthma	Idiopathic

LRTI, lower respiratory tract infection.

Note: * Not in order of incidence or prevalence.

is neutrophilic inflammation, peribronchial fibrosis, and accompanying pulmonary and bronchial vascular changes. Pathologically, bronchiectasis may be classified as cylindrical (or tubular), varicose (or fusiform), and cystic (or saccular). Cystic bronchiectasis mostly reflects advanced irreversible disease.

CLINICAL FEATURES

Chronic wet sounding cough with or without sputum expectoration is hallmark of bronchiectasis. Other clinical features include failure to thrive, hemoptysis, exertional dyspnea, wheezing, recurrent respiratory infections, clubbing and/or chest hyperinflation. Auscultation of chest may reveal coarse crackles, and/or rhonchi or it may be normal. Cyanosis and pulmonary hypertension are late ominous signs of bronchiectasis.

Clinical Pearl

- Every wheezing child does not have asthma and every asthmatic child does not wheeze. Clinical examination is a never ending weapon for a physician: Get alerted if you find clubbing and coarse crackles in a child with respiratory symptoms.

Bronchiectasis may be generalized or localized to one or more lobes. In localized form, left lower lobe is most commonly affected followed by right upper lobe. Airway hyperreactivity is not uncommon in children with bronchiectasis ranging from 26–74%. Presence of cough and wheezing may not always suggest asthma, rather it may be due to airway obstruction and increased secretion in bronchiectasis. Gastroesophageal reflux disease (GERD) may coexist with bronchiectasis and should be looked for and treated when clinically indicated. Complications of bronchiectasis may include pulmonary hypertension with/without cor pulmonale, hypertrophic osteoarthropathy, systemic amyloidosis, scoliosis, and social problems.

DIAGNOSIS

Once bronchiectasis is suspected clinically, child should be evaluated to confirm the diagnosis, to find extend and severity of disease, and to identify underlying cause. Bronchiectasis may be suspected on chest X-ray but high-resolution computed tomography (HRCT) scans of the chest is investigation of choice to diagnose and to define extend of bronchiectasis. Chest X-ray may reveal peribronchial thickening, bronchial crowding, atelectasis, and persistent infiltrates in early stages; and cystic spaces, air-fluid levels, dilated thick-walled bronchi, and mucus plugging in advanced stage.

Diagnostic criteria for bronchiectasis are based on HRCT chest findings. A dilated bronchus having size greater than nearby artery is considered diagnostic of bronchiectasis in HRCT chest (Fig. 1). This appears as signet rings or tramlines depending on precise orientation of bronchi to the plane of section.

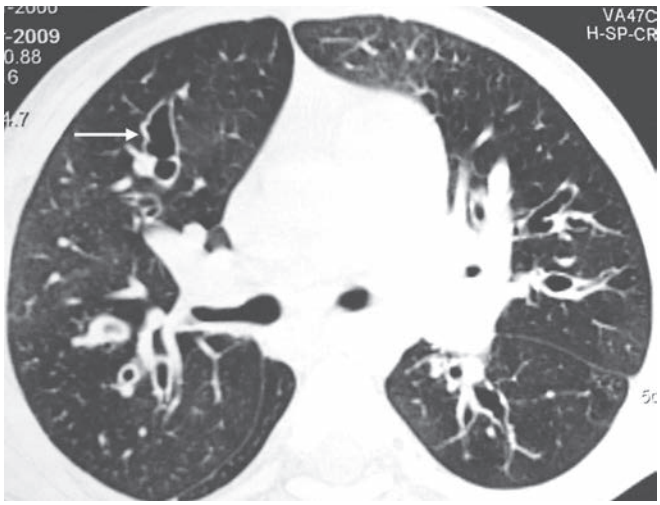


Fig. 1: Bronchiectasis in a child with allergic bronchopulmonary aspergillosis (Arrow: dilated central bronchus)

Clinical Pearl

- High-resolution computed tomography chest (HRCT) is useful to confirm and to define extent of bronchiectasis, but do not delay treatment if facility for HRCT is not available. If treated at very early stage, much of the disease can be reversed.

Other HRCT chest findings in bronchiectasis may include mucus plugs, bronchial wall thickening, lack of normal airway tapering towards lung periphery, visualization of the peripheral bronchi within 1 cm of the costal pleural surface, air-fluid levels in dilated bronchi, a linear array or cluster of cysts, mosaic perfusion, string of pearls (ectatic bronchi with beaded appearance), and air trapping.

After diagnosing bronchiectasis, try to identify underlying etiology by performing sweat test, immunological workup, sputum analysis, workup for tuberculosis and other infections, bronchoscopy, tests for primary ciliary dyskinesia, gastroesophageal reflux (GER), or allergic bronchopulmonary aspergillosis (ABPA), as suggested by associated clinical features. There are many scoring systems to assess severity of bronchiectasis based on chest X-ray and HRCT chest findings, but later one are preferred (Bhalla HRCT score, Reiff scoring system, etc.). Pulmonary function tests (PFTs) may also be performed to assess the severity of bronchiectasis, but there is lack of good correlation between PFTs and HRCT scores. A parent cough-specific quality of life questionnaire is available to assess quality of life in children with bronchiectasis.

Isolation rate for micro-organism from sputum or broncho-alveolar lavage (BAL) in children varies between 53–67%. Common pathogens isolated in children with bronchiectasis include *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Hemophilus influenzae* non-type b, *Pseudomonas aeruginosa*, and *Moraxella catarrhalis*. Exacerbation in bronchiectasis may be suggested by increased sputum production, purulent sputum, increase in cough severity, and/or cough changing from dry to weight.

TREATMENT

Therapy for bronchiectasis may be needed for acute exacerbations and chronic therapy for persistent bronchiectasis. The chronic therapy is different for CF- and non-CF-related bronchiectasis. Early diagnosis and aggressive treatment of bronchiectasis and underlying etiology has paramount importance in reducing morbidity and mortality associated with bronchiectasis.

Clinical Pearl

- If you diagnose bronchiectasis, do not look for higher center; it may reasonably be managed at any center.

Management of bronchiectasis requires a team approach comprising pediatrician, nurse, physiotherapist, social worker, nutritionist, etc. The general management for bronchiectasis is discussed here. The therapeutic options for bronchiectasis include: (1) rational use of antibiotics (for maintenance and exacerbation), (2) airway hydration and mucoactive drugs, (3) effective chest physiotherapy (airway clearance methods), (4) use for anti-inflammatory and antisecretagogues, (5) bronchodilators, (6) good nutritional support, (7) treatment of comorbid conditions and complications, (8) surgical intervention if required, (9) education and social support, and (10) prevention.

Rational Use of Antibiotics

Long-term antibiotics may be used as aerosol or orally for bronchiectasis. Data regarding efficacy of antibiotics for chronic maintenance in children with non-CF-bronchiectasis are limited. Till further evidence is available, chronic maintenance antibiotics should be used for a group of selected children only, e.g., with frequent exacerbations, children having severe lung disease with documented pseudomonas endobronchial infection (inhaled tobramycin may be useful) and CF. Long term use of oral macrolide therapy is found to be beneficial for both CF and non-CF children with bronchiectasis; mainly because of its anti-inflammatory and antisecretagogue properties, rather than due to antimicrobial properties. Acute exacerbations must be treated with antibiotics based on isolated pathogen and local antibiotic sensitivity pattern.

Airway Hydration and Mucoactive Drugs

Mucus clearance is impaired more in children with CF and PCD as compared to idiopathic bronchiectasis. Use of inhaled hypertonic saline (6–7%) is associated with decreased exacerbation and improved lung function in CF bronchiectasis, but data is limited for non-CF bronchiectasis. Risk of bronchospasm following hydrating agents can be minimized with pre-treatment with inhaled salbutamol. To further enhance mucus clearance, mucolytic agents may be used. Recombinant human deoxyribonuclease (rhDNase) is efficacious in CF, but is contraindicated in non-CF-related bronchiectasis as it had worsening of symptoms in non-CF bronchiectasis. Alternative to rhDNase is N-acetylcysteine, but there is lack of evidence for its efficacy. Role of anticholinergics and bromhexine is not established either.

Chest Physiotherapy (Airway Clearance Methods)

Airway clearance techniques (ACTs) with spontaneous or directed cough help in improving mucus clearance. A recent Cochrane review revealed that ACTs appear to be safe and beneficial for both adults and children with stable bronchiectasis. The role of these techniques in people with an acute exacerbation of bronchiectasis is unknown. There are many ACTs, but data is lacking to suggest superiority of one over other and choices may be individualized. Regular physical activity is also encouraged for children with bronchiectasis.

Anti-inflammatory Agents

There is lack of evidence for or against use of inhaled non-steroidal anti-inflammatory agents in the management of bronchiectasis in adults or children; one small trial of inhaled indomethacin in adults reported a reduction in sputum production and improved dyspnea. Use of high-dose ibuprofen for 4 years in children with CF showed a reduction in the rate of lung function decline and improved weight gain but no change in the frequency of pulmonary exacerbations. There are no randomized controlled trials regarding efficacy of oral nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with non-CF bronchiectasis. Inhaled corticosteroids (ICS) failed to benefit in adults with stable bronchiectasis; therefore routine use is not recommended. There is lack of trials of ICS for children and for acute exacerbation of bronchiectasis. Inhaled corticosteroids may be beneficial if there is associated asthma. Long-term oral steroids in CF-bronchiectasis improved lung function, but with significant adverse effects; therefore not recommended to treat CF-related bronchiectasis. There is lack of trials for use of oral steroids in acute and stable non-CF bronchiectasis both in children and adults except for ABPA, where steroids are indicated whether bronchiectasis is present or absent. Thus, steroid therapy in children with bronchiectasis is related to etiology and it's use should be individualized.

Bronchodilators

There is insufficient evidence for or against use of short or long acting β-2 agonists, adrenergics, and leukotriene receptor anta-agonists for management of bronchiectasis and their use should be individualized. Increased cough or wheezing in children with bronchiectasis should be treated as exacerbation at first instance.

Data regarding use of conventional sequence of bronchodilator, hypertonic saline, DNase, ACT, and aerosol antibiotics, frequently used in CF patients, are lacking for non-CF-related bronchiectasis in children and treatment in these patient must be individualized.

SURGICAL TREATMENT

There are no randomized trials comparing medical versus surgical treatment. Usual indication of surgery is failure of medical therapy in localized disease. Other indications for surgery may include severe persistent hemoptysis uncontrolled by bronchial artery embolization, severe chronic symptoms, and growth failure in localized disease. Surgery should not be considered for generalized disease, children below 6 years of age and in bronchiectasis with mild to moderate symptoms. At present, perioperative morbidity and mortality is minimum after lobectomy or pneumonectomy. Outcome after lung transplantation in children with non-CF bronchiectasis is not available.

PREVENTION

Children with bronchiectasis should receive routine vaccination as per national schedule. Limited evidence suggests that routine 23-valent pneumococcal vaccination in children with bronchiectasis may be useful, though robust trials are needed. Role of new 13-valent pneumococcal vaccine requires further trials for young children. Although, there is neither evidence for, nor against, routine influenza vaccination for children and adults with bronchiectasis, it may be used if affordability is not the problem. Children with bronchiectasis should have no/minimal environmental tobacco-smoke exposure as it increases susceptibility to respiratory infections.

An approach to a child with suspected bronchiectasis is shown in algorithm 1.

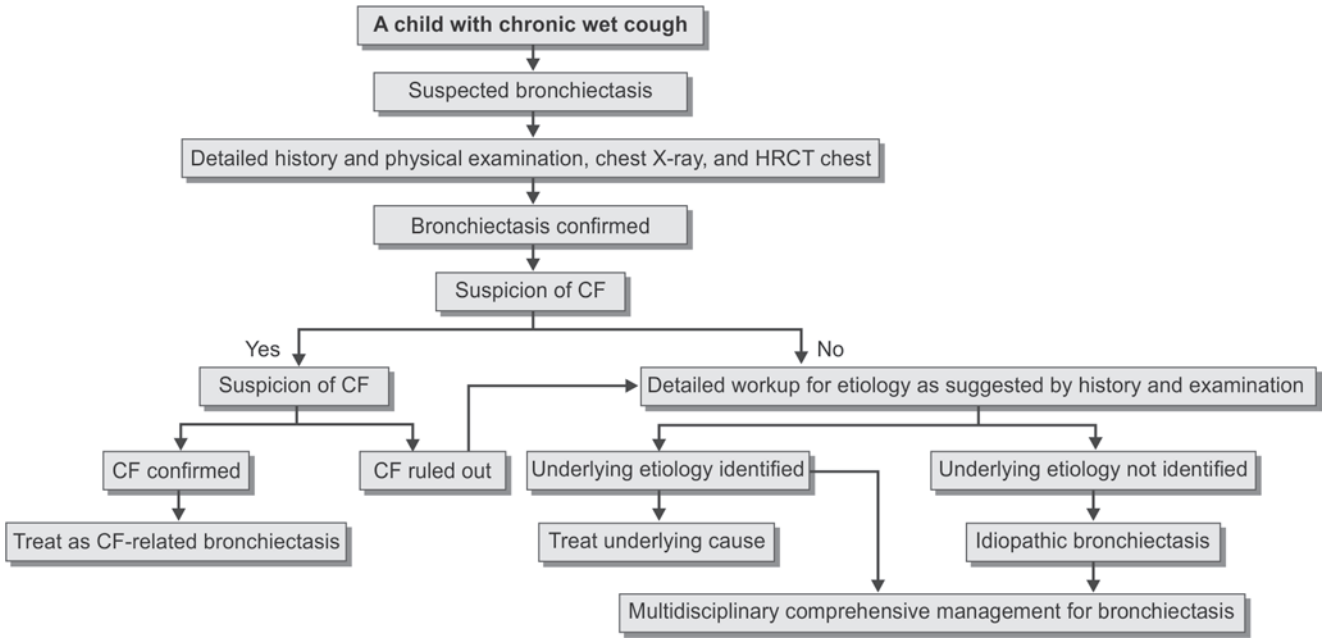
Prognosis of bronchiectasis depends on underlying etiology; extent and severity of disease at diagnosis, frequency of exacerbations; base-line lung function; rate of decline in FEV1, bacterial density and neutrophils in sputum; and nature of treatment. Delayed diagnosis, presence of asthma, bilateral lung involvement, and saccular bronchiectasis are some of poor prognostic factors. Bronchiectasis may be reversible in certain situations, e.g., after removal of chronic foreign body. Although lack of mortality data for pediatric bronchiectasis; nearly one-fourth children had respiratory failure in an about 7 years follow-up. With availability of better and inhaled antibiotics, ACTs, and good nutrition support, the prognosis of bronchiectasis has improved with time.

CONCLUSION

Bronchiectasis is chronic disease of conducting airways with a variety of underlying conditions. Data is lacking for effective treatment in children with non-CF bronchiectasis. Early diagnosis and aggressive multidisciplinary therapy with good nutritional and social support has improved prognosis of bronchiectasis in children. More robust clinical trials for various treatment options are required especially for children with non-CF bronchiectasis. In developing countries, control of infectious diseases is needed to curb the load of post-infectious bronchiectasis.

ALGORITHM 1

Approach to a child with suspected bronchiectasis



HRCT, high-resolution computed tomography; CF, cystic fibrosis.

KEY POINTS

High index of suspicious is required to diagnose bronchiectasis at early stage in children.

- ☞ Multidisciplinary comprehensive management is key for both CF- and non-CF-related bronchiectasis
- ☞ Pathogen-directed inhaled antibiotics, inhaled hypertonic saline, and oral macrolides are important component of therapeutic regimen for children with CF-related bronchiectasis
- ☞ Data is lacking for use of inhaled antibiotics, airway hydrating treatments, mucolytic agents, inhaled anti-inflammatory agents, and bronchodilators in children with non-CF-related bronchiectasis.

SUGGESTED READINGS

1. Chang CC, Morris PS, Chang AB. Influenza vaccine for children and adults with bronchiectasis. Cochrane Database Syst Rev. 2007;(3):CD006218.
2. Chang CC, Singleton RJ, Morris PS, Chang AB. Pneumococcal vaccines for children and adults with bronchiectasis. Cochrane Database Syst Rev. 2007;(2):CD006316.
3. Evans DJ, Bara AI, Greenstone M. Prolonged antibiotics for purulent bronchiectasis in children and adults. Cochrane Database of Syst Rev. 2007;(2):CD001392.
4. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2007;176(10):957-69.
5. Kim HY, Kwon JW, Seo J, Song YH, Kim BJ, Yu J, et al. Bronchiectasis in children: 10-year experience at a single institution. Allergy Asthma Immunol Res. 2011;3(1):39-45.
6. Lee AL, Burge A, Holland AE. Airway clearance techniques for bronchiectasis. Cochrane Database of Syst Rev. 2013;5:CD008351.
7. Newcombe PA, Sheffield JK, Chang AB. Parent cough-specific quality of life: development and validation of a short form. J Allergy Clin Immunol. 2013;131(4):1069-74.
8. Redding GJ. Bronchiectasis in children. Pediatr Clin North Am. 2009;56(1):157-71.
9. Reiff DB, Wells AU, Carr DH, Cole PJ, Hansell DM. CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. AJR Am J Roentgenol. 1995;165(2):261-7.
10. Southern KW, Barker PM, Solis A. Macrolide antibiotics for cystic fibrosis. Cochrane Database Syst Rev. 2004;(2):CD002203.
11. Wilson JF, Decker AM. The surgical management of childhood bronchiectasis. A review of 96 consecutive pulmonary resections in children with nontuberculous bronchiectasis. Ann Surg. 1982;195(3):354-63.

CHAPTER 72

Management of Congestive Heart Failure in Infants and Children: An Algorithmic Approach

M Zulfikar Ahamed

INTRODUCTION

Heart failure in infancy and childhood is "a clinical syndrome which reflects the inability of the heart to pump blood to meet the metabolic requirements of the body, including those needs incurred by growth; or able to do so at a higher filling pressure". It is a complex syndrome that can result from any structural or functional disorder that can impair the ability of ventricle(s) to fill with or eject blood.

While adult congestive heart failure (CHF) is often due to coronary artery disease (CAD), hypertension, valvular heart diseases, and cardiomyopathies, infants and children have CHF primarily due to congenital heart disease (CHD), valvular heart diseases, and cardiomyopathies. Overall, 75% of CHF in pediatric population is due to CHD and the rest due to acquired heart diseases. About 80% of CHF occurs in infants (<1 year). While in market economies, cardiomyopathies, CHD, and postoperative CHD cause CHF in that order, in India, the leading causes of pediatric CHF are CHD, rheumatic fever/rheumatic heart disease (RF/RHD), and cardiomyopathies.

Pathophysiologically, CHF can be divided into three types, which are as follows:

- Type I: CHF due to abnormal loading conditions. It can be due to preload abnormality or afterload problem. This is the most common variety of CHF in infants
  - Preload: ventricular septal defects (VSD), patent ductus arteriosus (PDA), mitral regurgitation (MR)
  - Afterload: aortic stenosis (AS), coarctation of aorta
- Type II: CHF due to abnormality of contractility (inotropy)—dilated cardiomyopathy
- Type III: CHF due to abnormality of diastolic function (lusitropy)—hypertrophic cardiomyopathy

In addition, heart rate abnormalities (very slow rate or very fast rate), such as complete heart block (CHB), and supraventricular tachycardia (SVT), can also cause CHF.

Type I Congestive Heart Failure

- Left to right shunt: VSD, PDA, aortopulmonary window (APW), atrioventricular septal defect (AVSD)
- Admixture CHD: total anomalous pulmonary venous connection (TAPVC), single ventricle, double outlet right ventricle (DORV), truncus arteriosus
- Valvular regurgitation: MR, aortic regurgitation
- Left ventricular outflow tract (LVOT) obstruction: AS, coarctation of aorta
- Rheumatic fever, carditis.

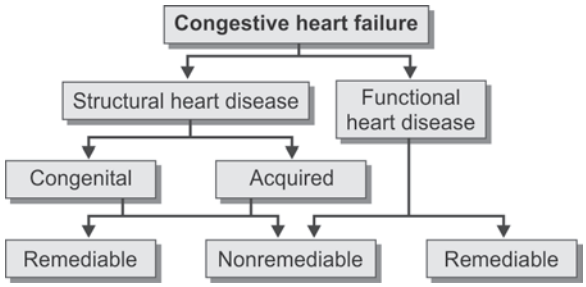
Type II Congestive Heart Failure

- Dilated cardiomyopathy
- Myocarditis
- Postoperative CHD
- Tachycardiomyopathy
- Chronic RHD with left ventricular dysfunction.

Congestive heart failure can be caused mostly by structural lesions. Occasionally, functional heart diseases can also cause CHF. They could be either remediable or nonremediable (Algorithm 1).

ALGORITHM 1

Congestive heart failure broad classification



Most congenital structural heart diseases are remediable either surgically or by intervention. Many acquired heart diseases are also amenable to correction, e.g., mitral stenosis, MR; some are not—dilated cardiomyopathy and hypertrophic cardiomyopathy. Tachycardiomyopathy is a functional heart disease which is remediable, by conversion to sinus rhythm.

CAUSES

Causes of CHF in infancy and childhood have a chronological order. This phenomenon is quite useful, looking for and identifying a cause for CHF in childhood.

Fetal Causes

- Congenital heart disease: Ebstein anomaly, systemic arteriovenous fistula
- Others: intrauterine myocarditis
- Arrhythmia: CHB, SVT.

Day One Causes (0–24 h)

- Ebstein anomaly, systemic arteriovenous fistula, absent pulmonary valve syndrome, severe MR, myocarditis
- Complete heart block, SVT.

First Week Causes (1–7 Days)

- Critical left heart obstruction: AS, hypoplastic left heart syndrome, coarctation of aorta, interrupted aortic arch
- Obstructed TAPVC
- Extension of day one causes.

1–4 Weeks Causes

- Large left to right shunts: VSD, PDA, AVSD
- Admixture lesions: TAPVC, DORV, single ventricle, truncus arteriosus
- Less critical CHD: coarctation, AS
- Rare defects: Pompe, anomalous origin of the left coronary artery arising from the pulmonary artery (ALCAPA), endocardial fibroelastosis (EFE).

1 Months–1 Year Causes

- Left to right shunts: PDA, APW, VSD, AVSD
- Admixture lesions
- Acquired: SVT, dilated cardiomyopathy, and myocarditis.

1–6 Years Causes

- Viral myocarditis, dilated cardiomyopathy
- Left to right shunts with complications
- Infective endocarditis.

6–12 Years Causes

- Rheumatic fever/RHD
- Infective endocarditis
- Congenital heart disease: postoperative
- Viral myocarditis/dilated cardiomyopathy.

Manifestations of CHF are also age and etiology dependent. It may present as:

- Shock: in new born, conditions presenting are duct dependent left sided critical lesions, sepsis, hypoxemic ischemic problems, and arrhythmia
- Acute/subacute CHF: occurs in post tricuspid left to right shunts, obstructive lesions, admixture lesions, and cardiomyopathies
- Chronic CHF: occurs due to cardiomyopathies, valvular heart disease, and moderate left to right shunts.

RECOGNITION OF CONGESTIVE HEART FAILURE IN INFANTS

Clinical recognition of CHF in infancy (Box 1) is different from that of an older child. The classical quartet of findings are tachycardia, tachypnea, tender hepatomegaly, and cardiomegaly. Others are S3 gallop, prolonged capillary refill time, and bibasal crepitation. Elevated jugular venous pressure (JVP), pedal edema, and hypotension are less common manifestations.

Functional assessment in an infant or child with CHF will be based on New York Heart Association (older child) or Ross (infants) classification.

Ross (2002) classification:

1. No symptom, no feeding difficulty, normal growth
2. Tachypnea on feed, sweating on feed, normal growth
3. Significant tachypnea/sweating on feed, retractions at rest, growth failure
4. All the above on rest also.

EVALUATION

Evaluation of CHF includes recognition and characterization of CHF and investigations (Algorithm 2).

Investigations

The investigations can be either definitive or nondefinitive.

One has to decide whether CHF is acute or chronic. Acute CHF could be either primary or decompensated. Both chronic and acute CHF can be either responsive or nonresponsive (refractory) (Algorithm 3).

Investigations can be either definitive or nondefinitive (Algorithm 4).

Box 1: Recognition of congestive heart failure in infants

Key items

- Tachypnea
- Tachycardia
- Tender hepatomegaly
- Cardiomegaly

Important items

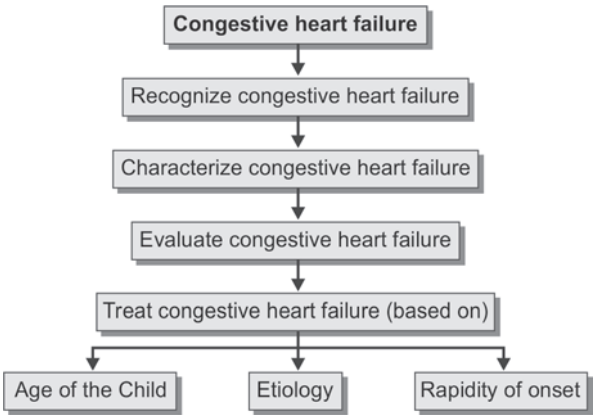
- S3 gallop
- Bibasal crepitations
- Prolonged capillary refill time

Less common items

- Edema
- Elevated jugular venous pressure
- Hypotension

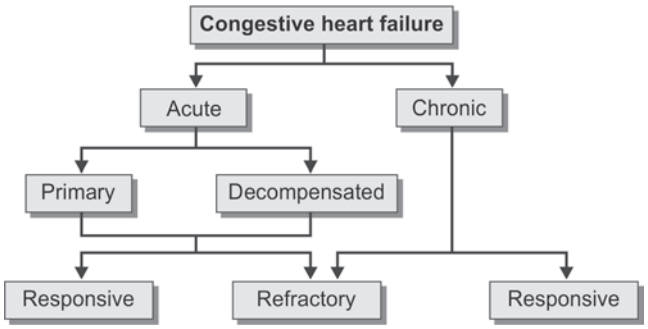
ALGORITHM 2

Evaluation and treatment of congestive heart failure



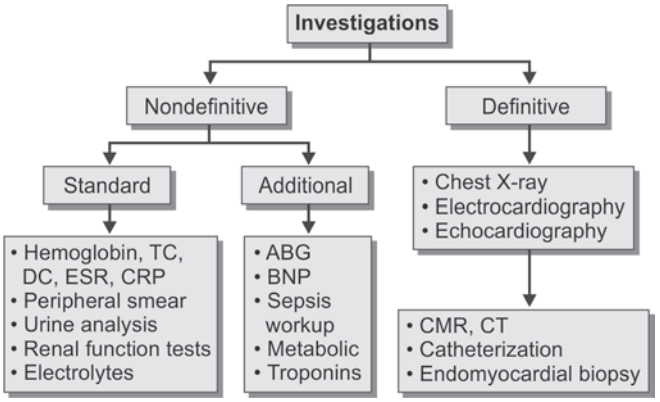
ALGORITHM 3

Congestive heart failure types



ALGORITHM 4

Evaluation of congestive heart failure



CMR, cardiac magnetic resonance imaging; CT, computed tomography; TC, total count; DC, differential count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ABG, arterial blood gas; BNP, brain natriuretic peptide.

Chest X-ray

Chest X-ray is still useful in preliminary evaluation of CHF at any age. It looks at heart size, lung blood flow, presence of pulmonary arterial hypertension (PAH) and the 'typical' look (e.g., figure of "8" in TAPVC). It can also sort out primary or additional lung issues.

Practically, all causes of CHF in infancy will cause cardiomegaly (cardiothoracic ratio >50% in a child, >55% in infants, >60% in neonates). The exceptions could be obstructed TAPVC or cor triatriatum.

Electrocardiography

A 14-lead electrocardiography (ECG) with or without a rhythm strip (lead II) is quite useful. It is a must in all forms of CHF. Electrocardiography can be a pointer to a specific CHD (e.g., biventricular hypertrophy in large VSD) or characteristic of a CHD (e.g., left deviation of the QRS axis and right ventricular hypertrophy in AVSD). It can diagnose tachyarrhythmia as cause of CHF (e.g., SVT leading to "dilated cardiomyopathy" like picture) and can pick up drug toxicity (e.g., digitoxicity).

Echocardiography

It is the most useful tool in evaluating CHF in infants and children. It can virtually diagnose all structural heart lesions, both congenital and acquired. It can pick up diastolic abnormalities and hemodynamic problems such as PAH (Table 1).

Others

Brain natriuretic peptide is useful in assessing CHF in infants, especially recent onset (acute). It will help in differentiating between cardiac and respiratory causes of distress. The normal value is less than 30 pg/mL. Abnormal value (>100 pg/mL) will indicate cardiac cause of respiratory distress with high sensitivity and specificity.

Troponins, either troponin T or troponin I can be useful in conditions like myocarditis.

Radionuclide studies, cardiac magnetic resonance imaging, and computed tomography are occasionally useful in evaluating cause of CHF, especially in adult CHD. Postoperative catheterization and endomyocardial biopsy could also be utilized in evaluating cause of CHF.

TREATMENT

Treatment of CHF involves three facets, which are as follows:

1. Treating the cause
2. Treating the precipitating cause
3. Treating the congestive state.

TABLE 1: Echocardiography

Looks for	Conditions
Structural congenital heart disease	Coarctation of aorta, ventricular septal defect
Ventricular day function	Dilated cardiomyopathy, myocarditis
Pulmonary arterial hypertension	Persistent pulmonary hypertension of the newborn, idiopathic pulmonary arterial hypertension
Mechanical heart disease	Acute aortic and mitral regurgitation

Mostly, causes of CHF in infancy are mechanical problems which need mechanical solutions—either surgical or interventional.

Monitoring is an important factor in treating CHF. We can monitor:

- Heart rate, respiratory rate, blood pressure, capillary refill time
- Cardiomegaly, S3, murmur, lungs
- Urine output, pulse oxymetry/arterial blood gas, renal function.

Drug therapy in CHF in infants and children is a temporizing measure which could be a short-term or long-term bridge. It is also an initial lifesaver. In addition, some drugs may eventually "correct" the abnormality, e.g., prostaglandin E1 (PGE1) or adenosine (Algorithm 5).

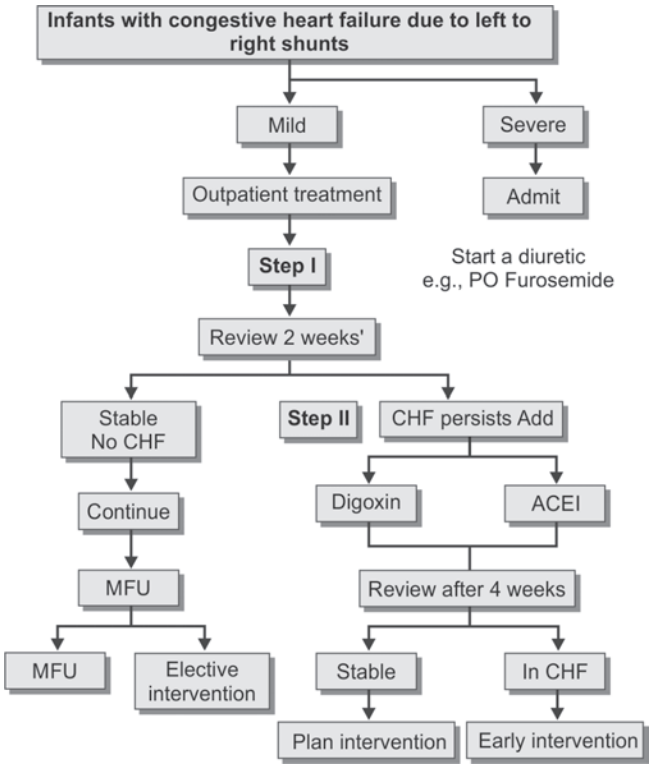
Following examples of CHF treatment in specific satuation algorithms 6 and 7, table 2.

Management of Chronic/Subacute Congestive Heart Failure

It is the most common situation. It can be treated in the wards or as outpatient department. Initial general measures include rest, fowler position, oxygen when indicated, correction of electrolytes and hemoglobin abnormalities, and volume depletion. Drug therapy primarily uses four drugs: diuretics,

ALGORITHM 5

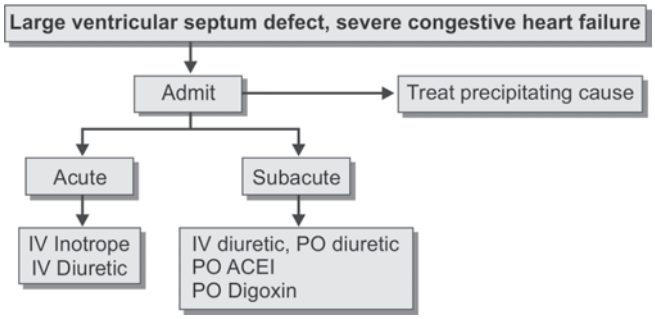
Congestive heart failure treatment protocol



CHF, congestive heart failure; MFU, medical follow-up; ACEI, angiotensin converting enzyme inhibitors, PO, per oral.

ALGORITHM 6

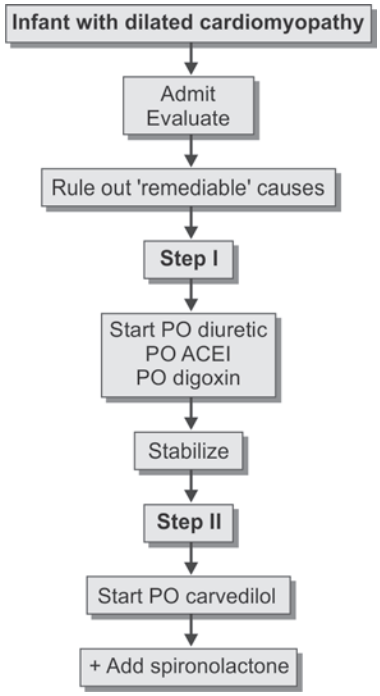
Treating left to right shunts



ACEI, angiotensin converting enzyme inhibitor; PO, per oral, IV, intravenous.

ALGORITHM 7

Treating dilated cardiomyopathy



PO, per oral; ACEI, angiotensin converting enzyme inhibitors.

TABLE 2: Dilated cardiomyopathy treatment protocol

Drug	Functional class			
	I	II	III	IV
Diuretic	0	+	+	+
Digoxin	+	+	+	+
ACEI	+	+	+	+
Carvedilol	+	+	+	+
Spironolactone	0	+	+	+

ACEI, angiotensin converting enzyme inhibitors.

digoxin, angiotensin converting enzyme (ACE) inhibitors and β-blockers.

Management of Acute Congestive Heart Failure

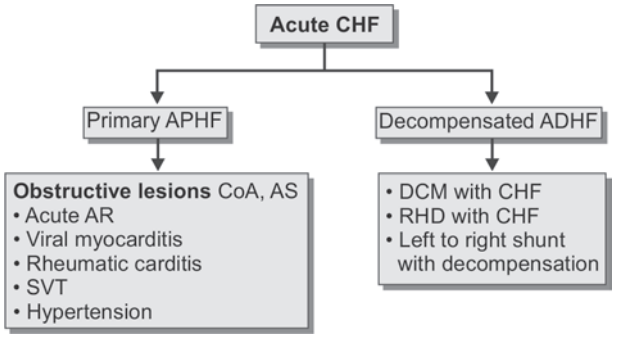
Acute CHF can be either primary or decompensated (Algorithm 8).

Management of acute CHF will include admission into pediatric intensive care unit. General measures include temperature control, oxygen supply, alkali therapy, sepsis management, and metabolic correction.

Specific measures will be by using intravenous (IV) inotrope, IV diuretic, and IV vasodilators. Targeted therapy will be using phosphodiesterase inhibitors, sildenafil, adenosine, or ibuprofen, according to indications. Additional measures will be IV access, multiorgan protection, and mechanical ventilation (Algorithms 9 and 10).

ALGORITHM 8

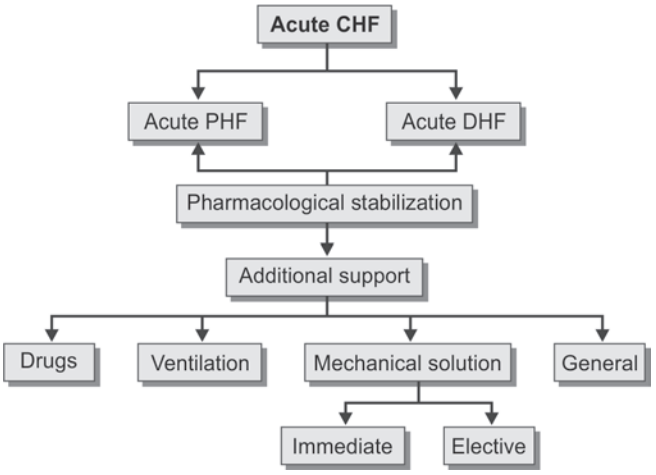
Acute congestive heart failure types



APHF, acute primary heart failure; ADHF, acute decompensated heart failure; DCM, dilated cardiomyopathy; CHF, congestive heart failure; CoA, coarctation of aorta; AS, aortic stenosis; RHD, rheumatic heart disease; MR, mitral regurgitation; AR, aortic regurgitation; SVT, supraventricular tachycardia.

ALGORITHM 9

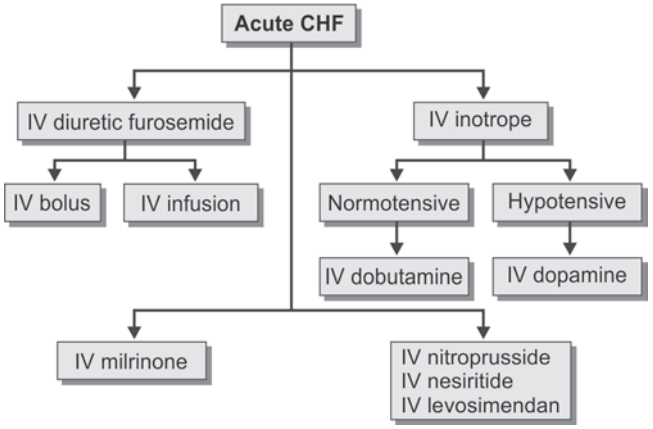
Principles of management



CHF, congestive heart failure; DHF, decompensated heart failure; PHF, primary heart failure.

ALGORITHM 10

Pharmacotherapy of acute CHF



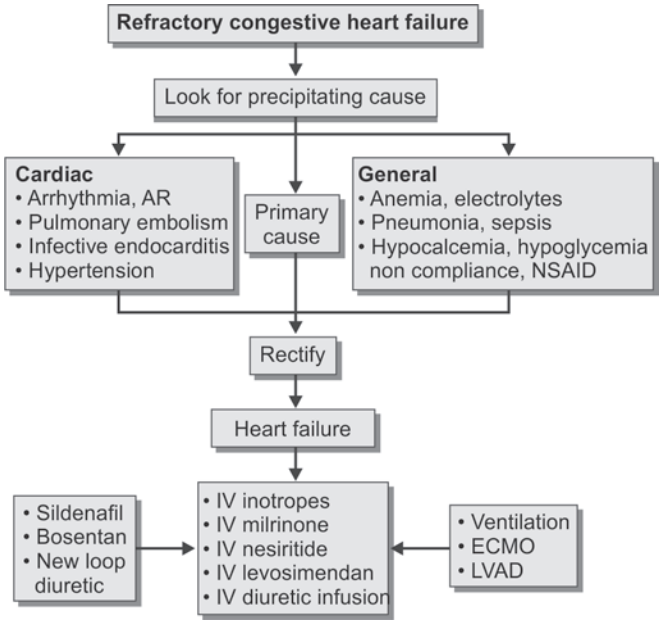
CHF, congestive heart failure; IV, intravenous.; *Hypotension. Newborn: <60 mmHg; infant: <70 mmHg; child: <80 mmHg; adolescent: <90 mmHg.

Management of Refractory Congestive Heart Failure

Refractory CHF is the one not responding to (favorably) conventional medical management (diuretics, digoxin, ACE inhibitors) (Algorithms 11 and 12).

ALGORITHM 11

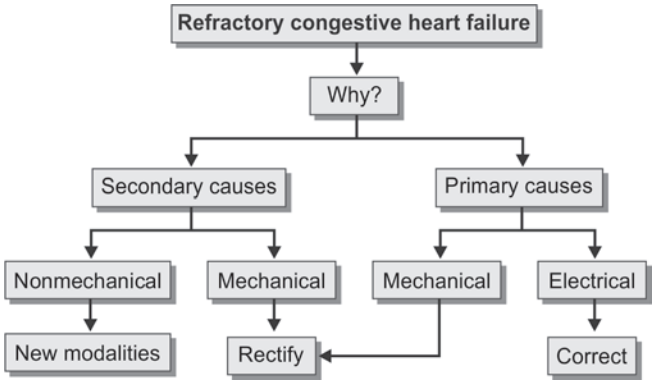
Treating refractory congestive heart failure



IV, intravenous; AR, aortic regurgitation; NSAID, nonsteroidal anti-inflammatory drug; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device.

ALGORITHM 12

Refractory congestive heart failure of causes



Specific Situations

- Newborn with CHF and persistent pulmonary hypertension of the newborn: IV milrinone, IV sildenafil
- Newborn with CHF and CHB: IV dobutamine
- Newborn with CHF and sepsis: IV dobutamine
- Newborn with CHF and preterm PDA: indomethacin/ibuprofen
- Postoperative CHD-CHF, PAH: IV milrinone, sildenafil, nitric oxide
- Hypertensive CHF: IV sodium nitroprusside (NTP), IV diuretic
- Infective endocarditis, acute MR: IV NTP, IV antibiotics
- Dilated cardiomyopathy on β-blockers, CHF: IV milrinone
- Viral myocarditis CHF: IV immunoglobulin
- Postoperative ventricular dysfunction: ACE inhibitor.

DRUGS AND DOSES

Drugs employed in the management of CHF and the respective doses are provided in table 3.

TABLE 3: Drugs employed in the management of CHF and the respective doses

Drugs	Doses
Furosemide	• PO: 1 mg/kg OD/BD/TID • IV: 1 mg/kg OD/BD/TID • Infusion: 0.1–1.0 mg/kg/h
Torsemide	• PO: 0.25–0.5 mg/kg • IV: 2.5–5 mg OD
Bumetanide	• PO: 0.45 – 0.1 mg/kg BD
Digoxin (maintenance)	• PO: ○ Preterm newborn: 5 mg/kg OD ○ Term newborn: 7.5 mg/kg OD ○ Infant: 10 mg/kg BD ○ 2–10 years: 7.5 mg/kg OD ○ >10 years: ½–1 tab OD
Captopril	• PO: 1–4 mg/kg/day TID
Enalapril	• PO: 0.1–0.3 mg/kg/day as OD/BD
Carvedilol	• PO: 0.1–0.5 mg/kg/day BD
Dobutamine	• IV: 2–20 mg/kg/h for 72–96 h
Milrinone	• IV: 50 mg/kg/bolus (10–15) • Infusion: 0.375–0.75 mg/kg/min
Nesiritide	• IV: 1–2 mg/kg/bolus • Infusion: 0.01–0.03 mg/kg/min
Levosimendan	• IV: 6–12 mg/kg/bolus • Infusion: 0.05–0.60 mg/kg/min
Dopamine	• IV: 2–20 mg/kg/h for 72–96 h

IV, intravenous; PO, per oral; OD, once a day; BD, twice a day; TID, thrice a day; tab, tablet.

SUGGESTED READINGS

1. Beggs A, Thompson R, Nash A, Tompson G, Petersen RE, Shaddy LY, et al. Chronic heart failure in children. In: Allen HD, Driscoll DJ, Shaddy RE, Felters TF (Eds). Moss and Adams' Heart Disease in Infants, Children and Adolescents, 8th edition. Philadelphia: Lippincott Williams Wilkins; 2013.
2. Beggs S, Thompson A, Nash R, Tompson A, Peterson G. Cardiac failure in children. 17th Expert Committee on the Selection and Use of Essential Medicines. Geneva: World Health Organization; 2009.
3. Burch M. Heart failure in the young. Heart. 2002;88(2):198-202.
4. Chaturvedi V, Saxena A. Heart failure in children: clinical aspects and management. Indian J Pediatr. 2009;76(2):195-205.
5. Kantor PF, Lougheed J, Dancea A, McGillion M, Barbosa N, Chan C, et al ; Children's Heart Failure Study Group. Presentation, diagnosis and medical management of heart failure in children: Canadian Cardiovascular Society Guidelines. Can J Cardiol. 2013;29(12):1535-52.
6. Kay JD, Colan SD, Graham TP Jr. Congestive heart failure in pediatric patients. Am Heart J. 2001;142(5):923-8.
7. Opie LH, Gerst BJ. Drugs for the Heart, 7th edition. Philadelphia: Elsevier-Saunders; 2009.
8. Ross RD. Medical management of chronic heart failure in children. Am J Cardiovasc Drugs. 2001;1(1):37-44.
9. Shaddy RE, Penny DJ. Chronic cardiac failure: physiology and treatment. In: Anderson RH, Baker EJ, Penny DJ, Redington AN, Rigby ML, Wernovsky G (Eds). Paediatric cardiology, 3rd edition. Philadelphia: Churchill Livingston/Elsevier; 2010.
10. Working Group on Management of Congenital Heart Diseases in India, Saxena A, Juneja R, Ramakrishnan S. Drug therapy of cardiac diseases in children. Indian Pediatr. 2009;46(4):310-38.

CHAPTER 73

Approach to a Child with Chest Pain

Vikas Kohli, Neeraj Agarwal

INTRODUCTION

Chest pain is not an uncommon complaint with which children present to the pediatric outpatient. It is not easy to differentiate the cardiac form non cardiac chest pain. Cardiac origin of chest pain is not the most common cause, but, it is definitely one of the most serious causes, and potentially can result in mortality also rarely. Definitely chest pain with exertion indicates cardiac origin and postural chest pain may indicate pericardial effusion.

This chapter helps localise the cause of chest pain and focuses of cardiac origin of chest pain.

CAUSES OF CHEST PAIN

Chest pain in a child is often benign, but cardiac and serious life-threatening causes do exist. The differential diagnosis is exhaustive and in most of the cases, etiology can be found out by thorough history and examination. Major causes of chest pain can be grouped as: musculoskeletal, pulmonary, psychological, gastrointestinal, cardiac, and idiopathic (Box 1).

In general, the most frequent cause reported is musculoskeletal pain. Approach to pain lies in history and examination leading to source of pain. Specific features which pinpoint to an organ system should be remembered.

Chest Wall

Chest wall trauma or a new strenuous physical activity are a frequent cause for chest pain. New intense physical activity is an important source and such type of pain peaks in 48 hours of activity. This pain is reproducible by palpation or by repeating the particular action. Chest wall deformities, like pectus excavatum/carinatum, can also be associated with musculoskeletal chest pain and thorough general examination should pick up these findings.

Precordial catch syndrome is a clinical diagnosis described as a sharp pain of sudden onset localized to the anterior chest wall that occurs mostly at rest. It tends to last from a few seconds to 3 minutes and may be exacerbated by taking a deep breath.

Breast tenderness can be physiologic during thelarche, or caused by infectious or inflammatory conditions such as mastitis.

Cutaneous chest wall pain may occur during an episode of herpes zoster, in a unilateral dermatome distribution and may precede the development of characteristic skin findings by several days.

Costochondritis is pain localized to costal cartilage and can be elicited by tenderness at costochondral junction. There is no joint inflammation, involves two to four joints, is unilateral, and exacerbated by deep breathing. Tietze syndrome is a specific form of costochondritis characterized by localized, painful, nonsuppurative costochondral swelling involving single costochondral junction.

Slipping rib syndrome is an unusual cause of lower chest pain that results when the medial fibrous attachments of the 8^{th}, 9^{th}, or 10^{th} ribs are inadequate or ruptured. Pain can be reproduced by hooking the fingers under the lowest costal cartilages and drawing them anteriorly and superiorly.

Hypersensitive xiphoid syndrome is uncommon in children and can be diagnosed easily because digital pressure on the xiphoid process reproduces the pain.

Pulmonary

Most common pulmonary causes are reactive airway diseases; auscultation, chest X-ray, or a pulmonary function test (PFT) can get the diagnosis. Pleurodynia (caused by coxsackie virus) is characterized by fever, pleuritic chest pain, and pleural rub. Pleuritis can be seen in children with infections, collagen vascular disease, and malignancy.

Clinical Pearl

- Chest pain only during exertion is a significant indicator of heart disease, but exercise induced asthma will also present only during exertion. However, asthma mostly will be associated with coughing followed by chest pain.

Box 1: Causes of chest pain in pediatrics

Chest wall and musculoskeletal
- Chest wall strain/trauma (exercise, overuse injury, forceful coughing, myositis, rib fracture)
- Skeletal anomaly (chest wall or thoracic spine, cervical ribs, slipping rib, osteomyelitis, thoracic outlet obstruction)
- Costochondritis/Tietze syndrome
- Slipping rib syndrome
- Precordial catch syndrome
- Breast tenderness
- Cutaneous (e.g., herpes zoster)

Cardiovascular
- Arrhythmias
- Coronary artery disease (anomalous coronary arteries), acute Kawasaki disease (coronary arteritis), premature atherosclerosis (e.g., dyslipidemia), congenital coronary artery aneurysm, coronary artery vasospasm (toxicologic ingestion as cocaine/marijuana)
- Structural [hypertrophic cardiomyopathy, valvular stenosis (pulmonary, aortic), mitral valve prolapse, ruptured sinus of Valsalva, coarctation of aorta], aortic aneurysm or dissection (Marfan, Turner, and Noonan syndromes), congenital absence of pericardium
- Myocarditis, pericarditis, endocarditis
- Pulmonary hypertension

Respiratory
- Reactive airway disease, pneumonia, pneumothorax/pneumomediastinum
- Pulmonary embolism
- Pleuritis/pleural effusion (e.g., systemic lupus erythematosus), pleurodynia (coxsackievirus)
- Chronic cough, foreign body aspiration

Abdominal and gastrointestinal
- Esophagitis (gastroesophageal reflux disease, eosinophilic esophagitis, bulimia, pill esophagitis)
- Gastritis, pancreatitis
- Esophageal spasm/dysmotility
- Foreign body
- Hiatus hernia
- Referred pain from abdominal trauma (Kehr's sign)

Neurologic
- Migraine, spinal nerve root compression

Psychiatric
- Anxiety, phobia, somatoform disorder (e.g., conversion), depression, emotional stress

Hematologic and oncologic
- Sickle cell disease (crisis) and tumor (chest wall, thoracic, or mediastinal)

Pneumothorax or pneumomediastinum may occur after an episode of bronchiolitis, choking/aspiration, or after inhalation of cocaine/marijuana. Pneumothorax should be suspected in a child with unexplained dyspnea, tachypnea, or decreased breath sounds. Pneumomediastinum should be suspected if subcutaneous emphysema or Hamman sign (precordial crackles that correlate with the heartbeat) are present.

Clinical Pearl

- Normal auscultation of lung fields and heart sounds significantly rules out a life-threatening cause of chest pain.

Pulmonary embolism is rare in healthy children, but may be seen in the presence of risk factors, such as coagulopathy, a central venous catheter, malignancy, nephrotic syndrome, major surgery, trauma, or sepsis. Ventilation perfusion scan is usually diagnostic. It should be suspected in cases who present with dyspnea, cyanosis, or hemoptysis.

Gastrointestinal

Chest pain due to gastric causes is common in childhood and a detailed history for dietary pattern, abdominal signs/symptoms like burning epigastric pain, constipation, high intake of fast food, irregular dietary behavior, relationship of pain with meals, and epigastric tenderness should point towards gastric etiology. Gastroesophageal reflux disease is the most frequent gastric cause for chest pain in children.

Eosinophilic esophagitis may cause chest pain because of esophageal inflammation, dysmotility, and reflux.

Coins and other objects lodged in the esophagus typically present with chest pain that is often accompanied by drooling and dysphagia.

Pill esophagitis is chemical irritation of the esophageal mucosa from certain medications, particularly iron preparations, tetracyclines, and chronic usage of nonsteroidal anti-inflammatory agents. The pill esophagitis is common in young adolescent patients who typically ingest a tetracycline capsule with too little water and present with chest pain, dysphagia, and occasionally hemoptysis.

Cardiac

Cardiovascular disease is identified in only 2–5% of pediatric patients with chest pain. The presence of dyspnea on exertion, palpitations, or abnormal cardiac auscultation has been found to be statistically significantly related to a cardiac etiology.

Acute myocardial infarction has been described in association with coronary artery anomalies, congenital heart disease, Kawasaki disease, familial hypercholesterolemia, sickle cell disease, cardiac myxoma, hypercoagulable states, substance abuse, and certain metabolic conditions such as homocystinuria and mucopolysaccharidosis. It is diagnosed by classical symptoms (persistent crushing chest pain may/may not radiate to neck/arm, sweating, and dyspnea), serial electrocardiography (ECG), and elevated cardiac enzymes (troponin I/creatine phosphokinase-MB).

Congenital coronary artery abnormalities mainly involve anomalous origin of the left coronary artery from the pulmonary artery. It is often identified when the pulmonary artery pressure declines, usually around 2–3 months of age. Patients may present with crying, poor feeding, and signs of congestive heart failure. Anomalous origin of the left coronary artery from the pulmonary artery may also present in later childhood with angina pain. The typical ECG pattern is that

of an anterolateral infarction with large and wide Q waves, ST changes, and T wave inversion in leads I, aVL, V5, and V6. Other coronary artery abnormalities, including anomalous origin of the left main coronary artery or right coronary artery from the contralateral sinus of Valsalva and hypoplastic coronary arteries may also present in childhood. Coronary artery abnormalities can be picked up or suspected by echocardiography and later confirmed by angiography. Kawasaki disease has been associated with myocardial infarction both in the acute and subacute phases and as a long-term consequence. Infarction can occur during the acute phase caused by coronary arteritis/aneurysmal rupture or during resolution caused by obstruction or stenosis.

Arrhythmias are one of the more common causes of cardiac-related chest pain in children. Tachyarrhythmias may cause chest pain because of a reduction in myocardial blood flow. Hyperthyroidism should be ruled out in all patients with tachyarrhythmia.

Structural heart disease in form of obstructive lesions mostly presents with a pathological heart murmur. Left ventricular outflow obstruction caused by aortic stenosis or hypertrophic cardiomyopathy causes pain that is typically exertional and is caused by subendocardial ischemia. In hypertrophic cardiomyopathy/obstruction, the physical examination is characterized by a harsh systolic ejection murmur. Myocardial ischemia has also been reported in children with sickle cell disease. In a study of pediatric sickle cell patients with a history of chest pain, heart failure, abnormal ECG, left ventricular dilation, or hypokinetic left ventricle, 64% had perfusion defects on thallium-201 single-photon emission computed tomography (CT). Three children who were started on hydroxyurea therapy underwent repeat single-photon emission CT, and all showed improvement. No occlusion of coronary arteries was found, suggesting that pathology of the microcirculation is responsible for the defects.

Myocarditis is a rare, but serious cause of chest pain in children. Children present with symptoms of chest pain, palpitations, dyspnea, sweating, giddiness, syncope, and signs of heart failure (congestive cardiac failure). Electrocardiography and chest radiography is mostly suggestive of diagnosis. Laboratory abnormalities include elevated troponin, elevated creatine kinase, and elevated erythrocyte sedimentation rate. Diagnosis can be confirmed with echocardiography. Pericarditis is diagnosed by pericardial rub or distant heart sounds and endocarditis is suspected with prolonged fever.

Partial or complete congenital absence of the pericardium is rare, but may produce murmur that is heard best at the apex and lower left sternal border. An increase in the intensity of the murmur is seen when the patient assumes an upright posture from a squatting, sitting, or supine position, and with the Valsalva maneuver. A decrease in intensity is heard after going from a standing to a sitting or squatting position, or with passive elevation of the legs. The decrease in intensity occurs when increased ventricular filling increases the size of the outflow tract and decreases the gradient across the obstruction.

Mitral valve prolapse has been reported in pediatric patients with chest pain. It has been hypothesized that severe mitral valve prolapse could cause pain because of papillary muscle ischemia. Children with severe pulmonary stenosis or pulmonary hypertension are also at risk for myocardial ischemia. Pain in such cases often occurs with exercise. Most common associations are dyspnea on exertion and syncope.

Aortic aneurysm and dissection have been described both in healthy pediatric patients and in those with known risk factors such as bicuspid aortic valve, coarctation of the aorta, and valvular aortic stenosis. Other causes include Marfan syndrome, Ehler-Danlos syndrome, Turner syndrome, trauma, cocaine use, and weight lifting. Pectus excavatum may be associated with aortic root dilation, even when other stigmata of Marfan syndrome are absent. The pain of aortic dissection is often described as severe and tearing. It tends to be located in the anterior or posterior chest, neck, jaw, or shoulder. Patient usually presents with hypotension. The chest radiograph is likely to show mediastinal widening, pleural effusion, abnormal aortic contour, or cardiomegaly. Diagnosis can be confirmed by echocardiography.

Psychiatric

Chest pain has been attributed to a psychiatric cause in approximately 5–9% of cases and incidence may be rising in recent years. A history of a preceding stressful event, such as death or hospitalization in the family, family separation, or school changes, has been reported. Other reported psychiatric causes include anxiety disorders, depression and social phobia, and sleep disturbances. Features of depression may be visible and hyperventilation may be a presenting sign in such cases.

Clinical Pearl

- Young adolescent or children should be evaluated privately for psychosomatic disorders and spending time alone with kids in a friendly manner will mostly yield the results.

APPROACH

The primary goals in evaluation of a child with chest pain are to rule out cardiac and other serious life-threatening causes and to classify the origin of the pain. In cases in which the cause remains unclear or if concerning features are identified, further evaluation and sometimes, referral are warranted (Box 2).

Box 2: Danger signs which need further diagnostic workup

- Pain associated with exercise, palpitations, or syncope
- Dyspnea
- Pain preventing daily activities/play of child
- Pain awakens the child from sleep
- Substance abuse
- Presence of prothrombotic conditions
- Features of Kawasaki disease
- Family history of sudden death or early cardiac death
- Abnormal vital signs or physical findings

The history should begin with the onset of pain, with the knowledge that acute pain is more likely to be caused by an identifiable organic cause. The pain that makes child awaken from sleep has a higher likelihood of an organic cause. The family should be asked about events that may have precipitated the pain such as exercise, trauma, eating, potential foreign body ingestion, or psychological stressors.

Characteristic pain patterns have been described with certain conditions. Chest wall pain is often localized and sharp, and exacerbated by deep breath/palpation. Pleural or pulmonary pain may also be accentuated with inspiration or cough, although pain is less likely to be well-localized than musculoskeletal pain, and less likely to be reproduced with palpation. Pleuritic pain is often sharp and superficial, whereas pulmonary pain, such as that associated with asthma, is more likely to be diffuse and deep. A description of midsternal or precordial pain that worsens after eating or when lying down may be esophageal. The classic description of cardiac pain is that of pressure, crushing, or a squeezing sensation that may radiate to the neck or arm. There is little information on whether this classic description is typical in pediatric cases. Pain that is relieved by sitting up and leaning forward may be caused by pericarditis. The presence of blood or other irritants in the peritoneal cavity may cause referred chest or shoulder pain (Kehr's sign). Psychogenic pain is expected to be vague, poorly localized, varying in location, and associated with other somatic complaints. Pain associated with palpitations, dyspnea, or syncope should be considered a possible indicator of cardiac disease, and pain associated with exertion could be either cardiac or related to a respiratory cause such as exercise induced asthma. A history of fever is likely to be reported with pneumonia, but may also be present with myocarditis, pericarditis, or pleural effusion. A history of drooling or reluctance to swallow may be present in a child with an esophageal foreign body. The presence of joint pain or rash may suggest collagen vascular disease. The patient and family should be asked about emotional stressors or presence of anxiety or depression. Adolescents should be asked about use of medications, especially oral contraceptives and pills that have been associated with esophagitis such as tetracycline. They should also be interviewed privately and asked about use of illicit substances such as cocaine or marijuana. Past medical history, such as Kawasaki disease, asthma, sickle cell disease, diabetes, or connective tissue disorders (Marfan syndrome etc.), should be ruled out. The family history should focus on history of unexplained or sudden death, serious underlying conditions, and whether family members have a history of chest pain or heart disease. The examination should include vital signs and an assessment of the general appearance, noting level of alertness, color, and presence of distress or anxiety.

Fever may suggest the presence of infectious or inflammatory condition, and tachycardia or tachypnea suggests the possibility of serious organic etiology.

The chest wall should be inspected for signs of trauma, asymmetry, pectus carinatum or excavatum, or costosternal swelling. Tenderness of the chest wall, costochondral or costosternal junctions suggests a musculoskeletal etiology. Auscultation of the lungs for crepts, wheezes, and decreased breath sounds may suggest pneumonia, asthma, or pneumothorax. Pneumomediastinum may cause subcutaneous emphysema, which can be detected by crepitus on palpation of the supraclavicular area or neck.

The heart should be auscultated to identify the presence of an irregular rhythm, murmur, rub, gallop, or muffled heart sounds. The rub of pericardial effusion is best appreciated when the patient is leaning forward. Patients with myocarditis may have tachycardia, gallop rhythm, displaced point of maximal impulse, or a murmur of mitral regurgitation. If coarctation or aortic dissection is suspected, four-limb blood pressures should be obtained.

Palpation of the abdomen may reveal epigastric tenderness in patients with a gastrointestinal cause for their pain. The skin and extremities should be examined for evidence of trauma, chronic disease, or dysmorphology. Xanthomas on the hands, elbows, knees, and buttocks are characteristic of familial dyslipidemia. Markers for Marfan syndrome or other connective tissue disorders should be searched.

INVESTIGATIONS

A chest radiograph should be obtained if there is unexplained pain of acute onset, respiratory distress, abnormal pulmonary or cardiac auscultation, fever, significant cough, history of drooling or foreign body ingestion, or significant underlying medical conditions.

A 12-lead ECG should be obtained if there is pain or syncope with exertion, abnormal cardiac auscultation, a clinical suspicion for myocarditis or pericarditis, or serious underlying medical conditions that carry an increased risk of cardiac disease**.**

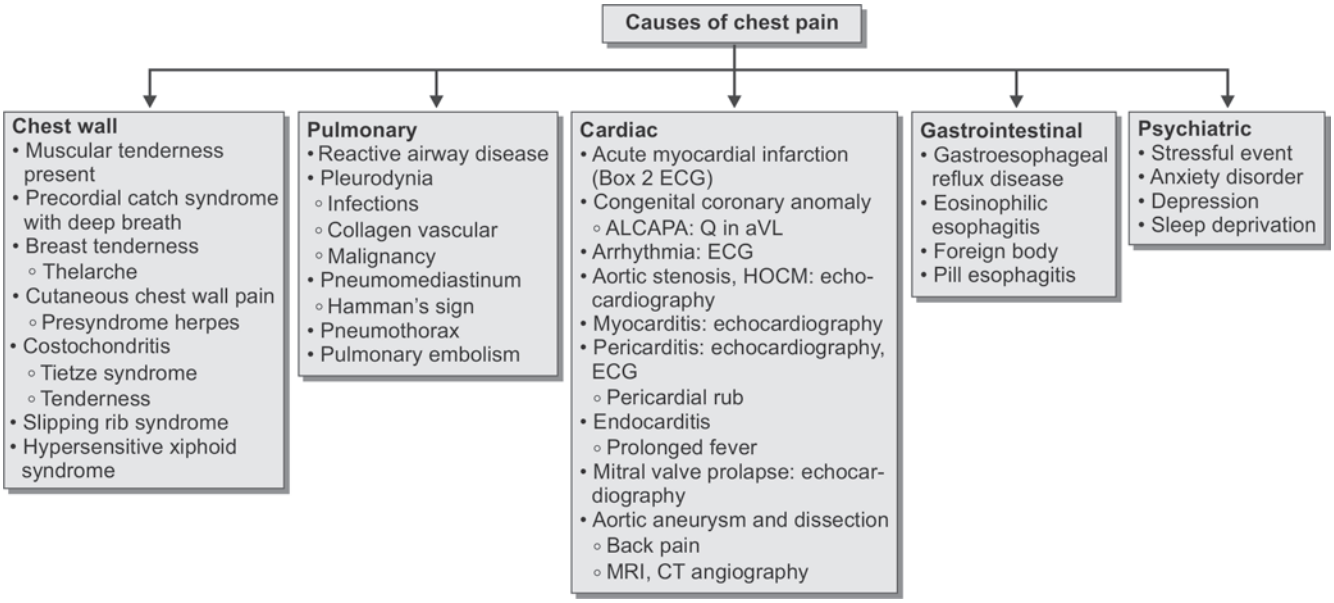
Laboratory investigations are rarely necessary, but may be useful when certain conditions are suspected. A complete blood count may be obtained for suspected infectious causes or in a patient with an underlying condition such as sickle cell disease. In a patient with suspected cardiac ischemia or myocarditis, cardiac enzymes may be useful; Holter monitor if arrhythmia is suspected, exercise stress test or PFT for unexplained exertional pain, and endoscopy for possible gastrointestinal sources of pain.

CONCLUSION

As the differential diagnosis of chest pain is exhaustive and many diagnoses are based on case reports rather than prospective studies, it is difficult to develop evidence-based guidelines for evaluation. The clinician should keep in mind the broad differential diagnosis and order further investigations when the history and physical examination are not conclusive.

ALGORITHM 1

Approach to chest pain



ECG, electrocardiography; ALCAPA, anomalous origin of the left coronary artery arising from the pulmonary artery; HOCM, hypertrophic obstructive cardiomyopathy; MRI, magnetic resonance imaging; CT, computed tomography.

KEY POINTS

- ☞ Chest pain in not usually cardiac in children
- ☞ If present during exercise it may be cardiac
- ☞ History of syncope or palpitation are red flags for cardiac chest pain
- ☞ Gastric etiology is most common
- ☞ History of traume or viral may help diagnose etiology
- ☞ R/o myocarditis with troponin I

SUGGESTED READINGS

1. Asnes RS, Santulli R, Bemporad JR. Psychogenic chest pain in children. Clin Pediatr (Phila). 1981;20(12):788-91.
2. Brenner JI, Ringel RE, Berman MA. Cardiologic perspectives of chest pain in childhood: A referral problem? To whom? Pediatr Clin North Am. 1984;31(6):1241-58.
3. Brown RT. Costochondritis in adolescents. J Adolesc Health Care. 1981;1(3): 198-201.
4. Coleman W. Recurrent chest pain in children. Pediatr Clin North Am. 1984;31(5):1007-26.
5. Driscoll DJ, Glicklich LB, Gallen WJ. Chest pain in children: a prospective study. Pediatrics. 1976;57(5):648-51.
6. Lane JR, Ben-Shachar G. Myocardial infarction in healthy adolescents. Pediatrics. 2007;120(4):e938-43.
7. Lin CH, Lin WC, Ho YJ, Chang JS. Children with chest pain visiting the emergency department. Pediatr Neonatol. 2008;49(2):26-9.
8. Mahle WT, Campbell RM, Favaloro-Sabatier J. Myocardial infarction in adolescents. J Pediatr. 2007;151(2):150-4.
9. Pantell RH, Goodman BW Jr. Adolescent chest pain: a prospective study. Pediatrics. 1983;71(6):881-7.
10. Rokicki W, Krzystolik-Ladzinska J, Goc B. Clinical characteristics of primary mitral valve prolapse syndrome in children. Acta Cardiol. 1995;50(2):147-53.
11. Rowe BH, Dulberg CS, Peterson RG, Vlad P, Li MM. Characteristics of children presenting with chest pain to a pediatric emergency department. CMAJ. 1990;143(5):388-94.
12. Rowland TW, Richards MM. The natural history of idiopathic chest pain in children. Clin Pediatr (Phila). 1986;25(12):612-4.
13. Said SA, el Gamal MI, van der Werf T. Coronary arteriovenous fistulas: collective review and management of six new cases-changing etiology, presentation, and treatment strategy. Clin Cardiol. 1997;20(9):748-52.
14. Selbst SM. Chest pain in children. Pediatrics. 1985;75(6):1068-70.
15. Selbst SM. Consultation with the specialist. Chest pain in children. Pediatr Rev. 1997;18(5):169-73.
16. Selbst SM. Evaluation of chest pain in children. Pediatr Rev. 1986;8(2):56-62.
17. Tsuji A, Nagashima M, Hasegawa S, Nagai N, Nishibata K, Goto M, et al. Long-term follow-up of idiopathic ventricular arrhythmias in otherwise normal children. Jpn Circ J. 1995;59(10):654-62.
18. Tunaoglu FS, Olgunturk R, Akcabay S, Oguz D, Gücüyener K, Demirsoy S. Chest pain in children referred to a cardiology clinic. Pediatr Cardiol. 1995;16(2):69-72.
19. Zav aras-Angelidou KA, Weinhouse E, Nelson DB. Review of 180 episodes of chest pain in 134 children. Pediatr Emerg Care. 1992;8(4):189-93.

CHAPTER 74

Systemic Hypertension

Nurul Islam

INTRODUCTION

Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is ≥95th percentile for gender, age, and height on more than or equal to three 3 occasions.

As with adults, adolescent with blood pressure levels ≥120/80 mmHg should be considered prehypertensive.

GRADATION

- Normotensive: both SBP and DBP less than 90th percentile
- Prehypertension: when SBP/DBP more than 90th percentile but less than 95th percentile
- Stage I hypertension: SBP or DBP more than 95th percentile but not 5 mmHg above the 99th percentile
- Stage II hypertension: SBP or DBP is more than 5 mmHg above the 99th percentile
- White coat hypertension: when hypertension is noted inside physicians office but not in normal surroundings
- Marked hypertension: when present in surroundings.

CAUSES

Primary

- Genetic influence
- Dietary habits
- Decreased physical activity
- Obesity
- Increased salt intake
- Stress
- Low birth weight
- Smoking.

Secondary

Childhood hypertension is mainly secondary. The most common cause is renal etiology, contributing almost 90%. Smaller group belongs to cardiac and endocrinal etiology.

- Renal:
  - Parenchymal lesions
  - Glomerulonephritis
  - Pyelonephritis
  - Reflux nephropathy
  - Hydronephrosis
  - Renal dysplasia
  - Polycystic kidney disease
  - Chronic renal failure
  - Renal tumor
  - Postrenal trauma
  - Systemic lupus erythematosus
- Renovascular:
  - Renal artery stenosis
  - Fibromuscular dysplasia
  - Renal vein thrombosis
  - Umbilical artery catheter-related thrombosis
  - Takayasu's arterirtis
  - Moyamoya disease
- Cardiac: coarctation of the aorta
- Endocrinal
  - Hyperthyroidism
  - Hyperparathyroidism
  - Congenital adrenal hyperplasia
  - Cushing syndrome
  - Pheochromocytoma
  - Catecholamine excess
  - Neuroblastoma
  - Iatrogenic steroid

- Central nervous system
  - Intracranial mass
  - Hemorrhage
  - Quadriplegia.

TRANSIENT HYPERTENSION

- Renal
  - Poststreptococcal glomerulonephritis
  - Henoch-Schönlein purpura
  - Acute tubular necrosis
  - Postrenal transplant
  - Postblood transfusion
  - Hypervolemia
  - Pyelonephritis
  - Trauma
  - Leukemic infiltration
- Central nervous system
  - Increased intracranial pressure
  - Guillain-Barré syndrome
  - Burn
  - Familial dysautonomia
  - Stevens-Johnson syndrome
  - Porphyria
  - Poliomyelitis
- Drugs
  - Cocaine
  - Oral contraceptive pills
  - Amphetamine
  - Cyclosporine
  - Tacrolimus
  - Vitamin D toxication.

CLINICAL PRESENTATION

The children are mostly asymptomatic.
Nonspecific symptoms are:

- Irritability
- Excessive sweating
- Feeding problem in small baby
- Failure to thrive.

Specific symptoms are:

- Features of cardiac failure
- Headache
- Vomiting
- Altered sensorium
- Convulsion
- Facial hemiparesis.

Sometimes, clinical symptoms may be on the basis of system involved or main problem.

INVESTIGATIONS

First Line

- Complete blood count
- Blood urea nitrogen
- Creatinine
- Electrolytes
- Urine—routine examination, culture and sensitivity
- Ultrasound—kidneys, ureters, bladder.

Second Line

- Antineutrophil antibodies
- C3, C4, antineutrophil cytoplasmic antibody
- Dimercaptosuccinic acid scan
- Doppler scan
- Urinary—vanillylmandelic acid, catecholamine.

Confirmatory Test

- Renal biopsy
- Micturating cystourethrogram
- Renal arteriography for renin angiotensin system
- Magnetic resonance angiography
- Computed tomography scan.

Special Tests for Endocrine Function

- Hormonal profile
- Serum cortisol
- Catecholamine
- Renin activity
- Aldosterone estimation.

When Primary Hypertension Suspected

- Take proper history
- Dietary habits
- Fasting blood sugar
- Lipid profile
- Uric acid.

Document Target Organ Damage

- 12-lead electrocardiogram
- Echocardiography evaluation
- Opthalmic evaluation
- Urinary microalbuminuria.

PRIMARY HYPERTENSION EVALUATION

Primary hypertension in childhood is usually characterized by mild or stage 1 hypertension and is often associated with positive family history of hypertension or cardiovascular disease.

- Rule out overweight
- Body mass index calculation
- Assessment of other cardiovascular risk factors
  - Low plasma high density lipoprotein cholesterol
  - Increased triglycerides
  - Abnormal glucose tolerance
  - Fasting plasma insulin concentration
  - Fasting lipid profile
- Fasting glucose level
- Rule out sleep disorder.

How Will You Approach a Child with Hypertension?

- Take good history
- Classify as
  - Transient (see table for causes) (Table 1)
  - Chronic
    - Renal
    - Endocrine, etc.
  - Other group of patients
    - With c/o urinary tract infection, hematuria, growth retardation, pain abdomen, swelling
- Take family history—rule out familial causes
- Sleep history—rule sleep associated problem (sleep apnea)
- Birth history—umbilical artery catheterization done or not
- Proper diet history
- Drug history
- General survey
  - Facies
  - Built
  - Growth
  - Pallor
  - Edema
  - Pulses
  - Four limb blood pressure
  - Head neck examination
  - Ophthalmic findings
  - Skin markers

TABLE 1: Clinical features giving a clue to the etiology of hypertension

Moon facies Elfin facies Webbing of neck	Cushing syndrome William syndrome Turner syndrome
Pallor, edema and growth retardation	Chronic renal failure
Webbing of neck, low hairline, widely spaced nipple	Turner syndrome
Moon facies, buffalo hump, hirsutism, truncal obesity	Cushing syndrome
Thin built	Hyperthyroidism, renal disease, pheochromocytoma
Presence of virilization	Congenital adrenal hyperplasia
Ophthalmic findings—proptosis	Hyperthyroidism
Café au lait spots, tubers, rashes, striae	Neurofibroma
Goiter	Thyroid
Asymmetric limb pulses, bruits	Arteritis
Weak lower limb pulses	Coarctation of aorta
Acute congestive heart failure	Acute nephritis
Adenotonsiller hypertrophy	Suggestive of sleep apnea

- Do systemic examinations
  - Cardiac
  - Respiratory
  - Abdomen
  - Central nervous system
- Plan for investigations on prority basis (as above).

Indications for Measurement of Blood Pressure in Children

- Children >3 years old seen in medical settings
- Children <3 years old
  - History of prematurity, very low birth weight, neonatal complications
  - Congenital heart disease
  - Recurrent urinary tract infection
  - Hematuria, proteinuria
  - Known renal disease
  - Family history of renal disease
  - Solid organ transplant
  - Malignancy or bone marrow transplant
  - Drugs known to raise blood pressure.

NONPHARMACOLOGICAL MANAGEMENT OF HYPERTENSION

Hypertension

Therapeutic Lifestyle Modification

- This is the first line of management of pediatric hypertension and can be the sole modality of therapy in patients diagnosed with pre-hypertension and stage I hypertension
- It focuses on dietary management, increased physical activity, stress reduction and avoidance of illicit drug and tobacco use
- Dietary management should include an age appropriate, salt restricted diet with emphasis on weight loss in the overweight or obese children
- To have a better chance of success, the entire family should adopt these lifestyle modifications.

Pharmacological Therapy

Please put in the table of guidelines of the international task force on hypertension

Other Forms of Therapy

- Bariatric surgery has a role in the treatment of hypertension in the morbidly obese adult and might become an option in the obese pediatric adolescent in the future. A recent study (demonstrated an improvement in metabolic syndrome including hypertension with up to 30% reduction in weight.

Renal nerve denervation is a therapeutic option in adults with resistant hypertension, which refers to uncontrolled hypertension despite therapy with 3 or more antihypertensives.

Indications for Antihypertensive Drug Therapy in Children

- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target organ damage
- Diabetes (type 1 and type 2)
- Persistent hypertension despite nonpharmacologic measures.

HYPERTENSIVE EMERGENCIES

Manifestations:

- Headache
- Vomiting
- Altered sensorium
- Convulsion
- Facial palsy
- Hemiparesis
- Left ventricular failure
- Renal failure
- Retinopathy.

Aim of treatment:

- Urgent reduction of blood pressure
- Reduction by 25% over the next 1 hour
- Gradual reduction to 95th percentile over the next 24 hours
- Below 95th percentile achieved by 48 hours.

Drugs of choice:

- Intravenous labetalol—bolus 1 mg/kg/dose, infusion 2 mg/kg/h, max 30 μg/kg/min
- Sodium nitroprusside—0.3–8 μg/kg/min
- Nifedipine—1–2 mg/kg/h
- Rapid acting diuretics
- Seizure control with intravenous diazepam—0.2 mg/kg.

TABLE 2: Classification of hypertension in children and adolescent and guidelines

Category	Frequency of blood pressure measurement	Therapeutic lifestyle changes	Pharmacologic therapy
Normal	Recheck at next schedule physical examination	Encourage healthy diet, sleep, and physical activity	No
Prehypertension	Recheck in 6 month	Weight management, physical activity, diet management	None unless compelling indications such as chronic kidney disease, diabetes mellitus, heart failure, or left ventricular hypertrophy
Stage 1 hypertension	Recheck in 1–2 week or early if symptomatic; if persistently elevated on two occasions, evaluate or refer to source of care within 1 month	Weight management, physical activity, diet management	Initiate treatment based on indications or if compelling indications
Stage 2 hypertension	Evaluate or refer to source of care within 1 week or immediately if the patient is symptomatic	Weight management, physical activity, diet management	Initiate therapy

ALGORITHM 1

Classification of hypertension, types, etiology, workup and treatment

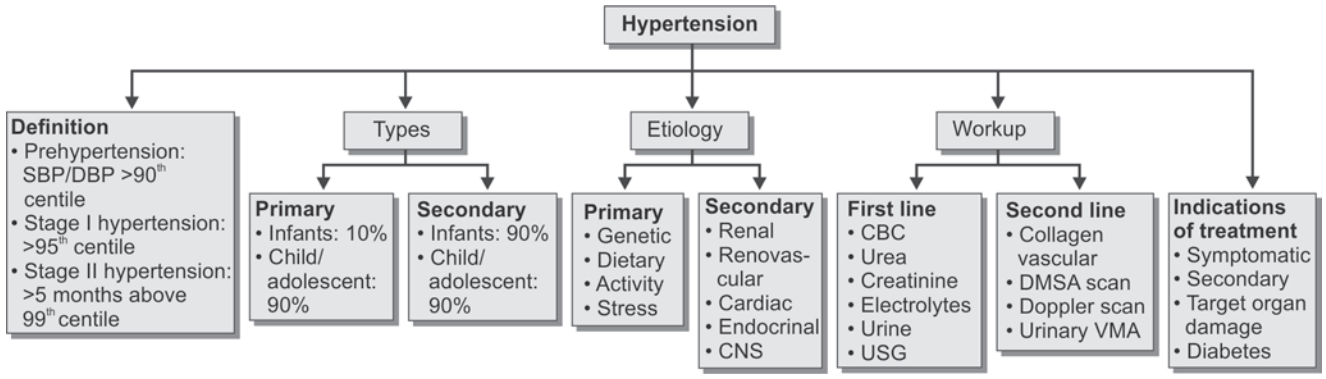


TABLE 3: Drug treatment of hypertension

Drug	Dose range	Frequency
Angiotensin II receptor blockers		
Losartan ≥6 years of age	0.7–1.4 mg/kg, up to 50–100 mg	Once daily
Valsartan ≥6 years of age	1.3–2.7 mg/kg, up to 40–160 mg	Once daily
Angiotensin-converting enzyme inhibitors		
Benazepril ≥6 years of age	0.2–0.6 mg/kg, up to 10–40 mg	Once daily
Enalapril	0.08–0.6 mg/kg, up to 5–40 mg	Once or twice daily
Fosinopril ≥6 years of age and weighing >50 kg	5–10 mg up to 40 mg	Once daily
Lisinopril ≥6 years of age	0.07–0.6 mg/kg, up to 5–40 mg	Once daily
Beta blockers		
Metoprolol, extended release, ≥6 years of age	1–2 mg/kg, up to 50–200 mg	Once daily
Propranolol	1–4 mg/kg, up to 20–40 mg	Two or three times daily
Vasodilator		
Hydralazine	0.75–7.5 mg/kg, up to 200 mg	Four times daily
Other		
Calcium channel blocker: amlodipine ≥6 years of age	2.5–5 mg, up to 5 mg	Once daily
Central α agonist: clonidine ≥12 years of age	0.2–2.4 mg, up to 2.4 mg	Twice daily
Diuretic: hydrochlorothiazide	1–3 mg/kg, up to 50 mg	Once daily

CHAPTER 75

Pediatrician's Perspective for Postoperative Follow-up of a Child

Vikas Kohli, Mridul Agarwal

INTRODUCTION

Once a child gets operated, the surgical issues dominate in the immediate post-operative. As the child recovers, the surgical issues decrease and the cardiology issues come to the forefront. Finally, as the child gets out of the ICU, the child's cardiology issues also become less dominating, the pediatric issues related to feeding and infection (prevention) become dominant.

Finally, on the long term, the pediatric issues like any normal child remain in the forefront. The pediatrician's though need to be sure that there is no special issue because of the cardiac surgery. So this chapter is devoted to this one special aspect related to Pediatricians in long term follow up of pediatric cardiac patients who have been operated.

Children after cardiac intervention procedure and cardiac surgery are under care of their pediatrician. Common concerns are discussed here.

GENERAL CARE

General Hygiene and Isolation

Parents are always counseled well regarding the hygienic handling of the child. The re-emphasis on hand washing and separation from other family members especially small children, ensures the adherence.

Fever and Cough

Persistent fever of more than 100°F always need evaluation. If cause of fever is obvious, like dehydration, upper respiratory tract infections, gastroenteritis etc., it can be treated accordingly or else further investigation in the form of white blood cell count, C-reactive protein, chest X-ray, or urine examination required localizing focus of infection.

Mild cough with clear expectoration is common after discharge for few days but cough with colored sputum, fever, crepitation, or increase rate and/or work of breathing need attention.

Feeding

Feeding and eating advice are no different from routine care.

WOUND CARE

Dressing

Children discharged after 5–7 days of surgery, do not have closed dressing over sternotomy or thoracotomy wound and do not requires active dressing.

Discharge

Any signs of redness, swelling, discharge, or opening of the wound need to be reported to the cardiac unit.

Sutures

The skin sutures used to close stenotomy and thoracotomy wound are dissolvable and do not need removal. The sutures used to close the drain sites need removal at first follow-up visit.

Scar

The nature of skin scar after surgery depends on personal propensity of scaring. The scar can be from thin white line to large with keloid. Some children have lot of itching and warmth over scar tissue; they can be advised calamine lotion or coconut oil along with cotton clothing to decrease friction and avoid direct sun exposure.

PAIN RELIEF

Most of the children at the time of discharge are on round-the-clock or SOS nonsteroidal anti-inflammatory drug (NSAID; mostly paracetamol). If the child complains of persistent pain or the infant cries excessively, the NSAID combination can be given.

Parents of infant and toddler are always counseled regarding handling for the first two weeks after surgery. They should avoid picking up baby under the arms, so that the stretching of the wound should not cause pain. Re-emphasis of the same is sometimes required.

INITIAL FOLLOW-UP

Most of the children are called for follow-up by 5–7 days. At this visit, the child assessed for any sign of infection, adequacy of oral intake, and the status of the wound. Stiches are removed, if any present, and analgesics are discontinued and cardiac medicines are adjusted.

FOLLOW-UPS

Corrective Surgeries

If no significant issues are noted during the initial follow-up, further follow-up are planned after 3–6 months depending on institutional policy. After that, usually annual follow-up is required unless indicated. After adolescence, the follow-up usually decreased to two yearly and then to five yearly thereafter.

Palliative Surgeries

These include children who have undergone Blalock-Taussig (BT) shunts or single ventricle palliation. These children require different plan and close follow-up along with oxygen saturation monitoring.

MEDICATIONS

Antibiotics

Children are rarely discharged on antibiotics for non-bloodstream infection.

Diuretics and Vasodilators

After cardiac surgeries, lots of time children have diuretics in their discharge medication. In absence of residual lesion, diuretics are usually stopped by 4–6 weeks. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers are given to some children for remodeling of ventricles, usually stopped by 3–6 months.

Aspirin and International Normalized Ratio Drugs

The patients of BT shunt and with the suture lines on side of systemic circulation are on aspirin at the time of discharge. While aspirin is stopped after 3–6 months, in the latter case, it is continued throughout the duration of BT shunt.

Patients with artificial conduit and prosthetic valve remain on anticoagulants (warfarin or nicoumalone) for lifetime. The international normalized ratio should be only monitored and adjusted by the cardiac unit, although bleeding complication may need immediate attention.

VACCINATIONS

Rearranging the Vaccination Schedule

Factors that should be considered prior to immunization before surgery:

- Diphtheria pertussis tetanus (DPT or DTaP) vaccine can cause fever within 2–3 days of administration
- Rash and fever can be caused by measles or MMR (measles, mumps, and rubella) vaccine as late as 2 weeks and by varicella vaccine as late as 4 weeks
- Blood product administration can interfere with the antibody response to live attenuated vaccine such as measles, rubella, and varicella vaccines; therefore, it should not be given within 2 weeks of cardiac surgery, else repeat dose will be required later
- Oral polio vaccine should be avoided in hospital inpatients.

Clinical Pearls

Vaccination plan before surgery

- No vaccine in the last week before surgery
- No measles, rubella, or varicella vaccine in previous 2–4 weeks.

Factors to be considered prior to immunization before surgery

- According to the Centers for Disease Control and Prevention's general recommendations on immunization, blood products can interfere with antibody response to measles, rubella, and varicella vaccine for 3–6 months; therefore, these vaccinations should be delayed at least by 3 months. Typhoid (Ty21a), yellow fever, live attenuated influenza vaccine, zoster, and rotavirus vaccines may be administered at any time before, concurrent with, or after administration of any blood or immune product
- The chance of a vaccine associated fever complicating postoperative management.

Clinical Pearls

Vaccination plan after surgery

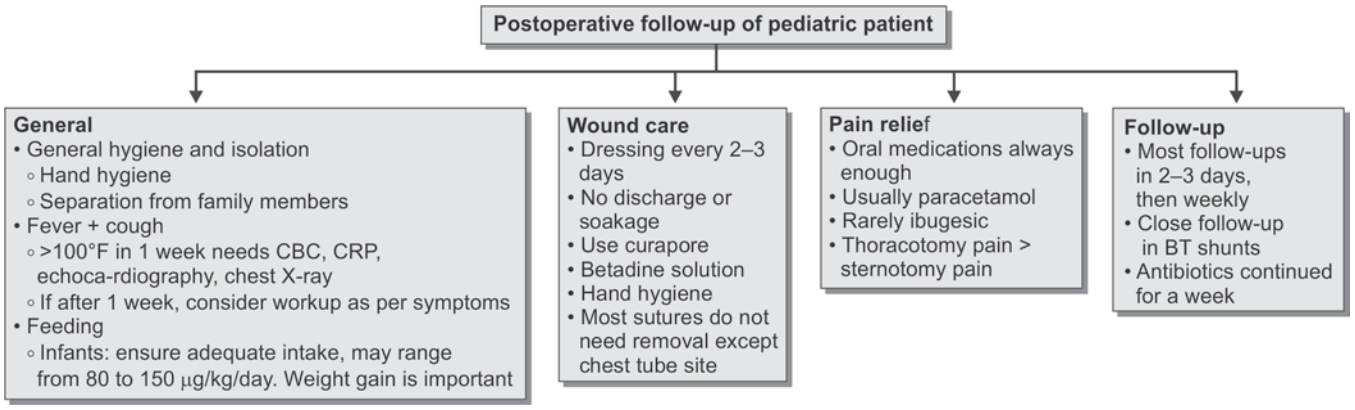
- No vaccine for the first 4–6 weeks
- No measles, rubella, or varicella vaccine for 3 months.

Additional Vaccine

Children with corrected or uncorrected congenital heart disease are at higher risk for lower respiratory tract infection, and should be considered for pneumococcal and influenza

ALGORITHM 1

General care of post of child



CBC, complete blood count;CRP,C-reactive protein;BT, Blalock-Taussig.

vaccine at appropriate time. Influenza vaccine is a must for all patients on aspirin.

DENTAL PROCEDURE

- No dental cleanings or scheduled surgeries for 3 months after heart surgery
- Between 3 and 6 months after surgery, antibiotics should be taken before any dental procedures.

ACTIVITY

Infants

- Babies can sleep on back and sides from the beginning and also prone after skin healing (2–3 weeks)
- Bath can be given without soiling wound during first week, and all over after, with soft soap

Children

- Should not be send to day care or school for the first 2–3 weeks
- Swimming can be allowed (if no other contraindication) to private pool after 4 weeks and to public pool and sea after 6 weeks
- Gym, games, or bike riding can be allowed after 6 weeks, although contact sports should be avoided for up to 3–6 months in most cases and forever when on anticoagulants
- Lifting weight, back pack, or items more than 10 pound should be avoided for 6 weeks.

Young Adults

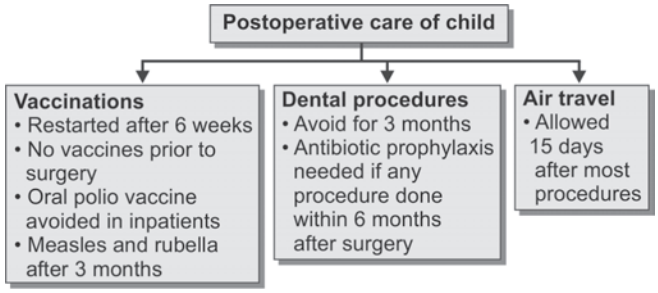
- Similar to children, except they can be given more leverage on weight up to 20 pounds.

AIR TRAVEL

- Air travel is usually safe after 2–3 weeks, except for few contraindications like severe pulmonary arterial hypertension, saturations less than 80%, and significant ventricle dysfunction. Children with pacemaker and implantable cardioverter defibrillator have different security check guidelines which need to be followed.

ALGORITHM 2

Long term follow up of post of child



INFECTIVE ENDOCARDITIS PROPHYLAXIS

- For palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization).

CARE OF SPECIAL CHILD

Children with genetic issues need multidisciplinary approach involving different pediatric specialties.

NEXT CHILD

- Counseling of genetic studies
- Fetal echocardiography should be done in all mothers if and when they conceive the next time, as there is an increased risk of heart disease in the next child.

KEY POINTS

- ☞ No vaccinations for 6 weeks
- ☞ If on aspirin, avoid chicken pox vaccination
- ☞ Isolation at home from other children to avoid infection especially respiratory
- ☞ Infective endocarditis prophylaxis is provided for procedures is provided for 6 months unless it is a palliative surgery like BT shunt
- ☞ Avoidance of school or day care for first 4–6 weeks

SUGGESTED READINGS

1. http://www.aboutkidshealth.ca/en/healthaz/testsandtreatments/procedures/pages/after-heart-surgery-caring-for-your-child.aspx
2. JOAO, Paulo Ramos David and FARIA JUNIOR, Fernando. Immediate post-operative care following cardiac surgery. J. Pediatr. (Rio J.) [online]. 2003, vol.79, suppl.2 [cited 2016-07-05], pp.S213-S222.
3. Pediatric home care for nurses: a family centred approach. By Wendy Votroubek, Aaron Tabacco. Chapter 8: Care of the child with altered ccardiac function pp217-244.

CHAPTER 76

Chronic Diarrhea in Children Less than 3 Years of Age

Moinak S Sarma, Surender K Yachha

INTRODUCTION

This topic will address only the relatively common causes of chronic diarrhea in children less than 3 years of age that are of practical importance to the physician and also the emerging entities that are often missed. Management of persistent diarrhea is beyond the scope of this chapter.

Chronic diarrheas may arise from intestinal diseases (small or large bowel), pancreatic, hepatobiliary, or systemic causes. Their differentiation is elaborated in the next chapter "Chronic Diarrhea in Children More than 3 Years of Age".

Gastrointestinal and systemic causes of chronic diarrhea in children less than 3 years of age are shown in boxes 1 and 2.

DEFINITIONS

Before embarking upon the details of this topic, a few clarifications regarding the terminologies used in diarrhea need to be understood.

While describing diarrhea of a fairly large duration, the terms "chronic", "persistent", "protracted", and "intractable" are loosely interchanged in literature and creates confusion in the minds of the pediatricians.

Chronic Diarrhea

Chronic diarrhea is defined as an insidious onset diarrhea of >2 weeks duration in children rarely leading to dehydration with

Box 1: Gastrointestinal causes of chronic diarrhea in children less than 3 years of age

Common causes

- Secondary lactose intolerance[%]
- Food protein allergy
  - Bovine/cow's milk intolerance (most common)
  - Concomitant soy allergy
- Celiac disease
- Parasitic infections: giardiasis and others
- Opportunistic infections in immunodeficiency states:
  - Human immunodeficiency virus
  - Primary immunodeficiency
- Intestinal lymphangiectasia
- Short bowel syndrome
- Acrodermatitis enteropathica
- Anatomical defects
  - Malrotation
  - Fistula (duodenocolic, small bowel)* bacterial overgrowth syndrome (secondary to blind loop syndrome)
- Nonspecific (Toddler's) diarrhea (diagnosis of exclusion)

Uncommon causes

- Intractable diarrhea of infancy (congenital diarrheas)
- Hirschsprung enterocolitis
- Infantile inflammatory bowel disease
- Pancreatic insufficiencies
  - Cystic fibrosis
  - Shwachman-Diamond syndrome
- Abetalipoproteinemia
- Glycogen storage disease type 1b*
- Congenital disorder of glycosylation type 1b[#]
- Progressive familial intrahepatic cholestasis type 1[$]
- Wolman disease (lysosomal acid lipase deficiency)

*Diarrhea in glycogen storage disease type 1b is due to opportunistic infections because of neutropenia and colitis due to inflammatory bowel disease

[#]Diarrhea in congenital disorder of glycosylation type 1b is due to protein-losing enteropathy

[$]Diarrhea in progressive familial intrahepatic cholestasis type 1 is due to bile acid malabsorption (deficiency of familial intrahepatic cholestasis 1 protein in small bowel)

[%]Secondary lactose intolerance in persistent diarrhea may often have a prolonged course and mimic chronic diarrhea.

Box 2: Systemic causes of chronic diarrhea in children less than 3 years of age

Common causes

- Urinary tract infection (most important)
- Nephrotic syndrome
- Septicemia
- Drugs: laxatives, antacids, antineoplastic

Uncommon causes

- Endocrinal causes, e.g., Addison's disease, hypoparathyroidism (autoimmune polyendocrinopathies)
- Neuroblastoma and ganglioneuroblastoma
- Constrictive pericarditis and restrictive cardiomyopathy

a wide range of underlying structural or chronic inflammatory causes (acquired or congenital) causing malabsorptive or maldigestive states.

Persistent Diarrhea

Persistent diarrhea is an episode of diarrhea of presumed infectious etiology, which starts acutely but lasts for >14 days commonly seen in children <2 years age resulting dehydration and dyselectrolytemia with or without gain in weight or loss in weight and not responding to usual therapy.

Protracted Diarrhea

Usually the term describes a prolonged diarrhea that resolves despite its initial severity. However, this term is often interchangeably used by several authors to encompass chronic and persistent diarrheas. Most authors, at present, restrict this term to those with prolonged diarrheas in infancy of postinfectious origin, allergy-related, or due to immunodeficiency.

Intractable Diarrhea

Prolonged diarrhea of more than 2 weeks occurring in infants less than 3 months of age. The term is used to describe a specific group of severe diarrheas of congenital nature that persist despite bowel rest and often require total parenteral nutrition for survival. This is a distinct entity and has been briefly discussed below.

Secretory Diarrhea

Secretory diarrhea refers to a diarrhea with profound losses of water and electrolytes in stools that persists despite bowel rest. It occurs due to sodium pump failures at the enterocyte as a result of toxins (e.g., *Vibrio cholera*).

Osmotic Diarrhea

Osmotic diarrhea is caused by damage to epithelium and loss of brush border enzymes resulting in poor tolerance and purging after an osmotic load and quiesence with bowel rest. (eg: secondary lactose intolerance due to lactase enzyme deficiency).

BOVINE OR COW'S MILK PROTEIN ALLERGY

Bovine or cow's milk protein allergy (CMPA) affects 2–5% of all children in the West, with the highest prevalence during the first year of life. In India, CMPA accounts for approximately 13% of all malabsorption cases in children less than 2 years of age. Temporal association with introduction to animal or formula milk (± products) is often noted. Wheeze, eczema, and atopy (20–30%) with similar history in family members (10%) may be associated. Nearly 50% children outgrow the allergy by 1 year and approximately 90% by 5 years of age. It is the most common food allergy in small children who are top fed.

There are two kinds of reactions to cow's milk:

1. Immediate [immunoglobulin E (IgE) mediated]: it occurs within minutes of milk intake and is characterized by anaphylaxis-like features: vomiting, pallor, shock-like state, urticaria, and swelling of lips seen in 10–20% cases
2. Delayed (T-cell, non-IgE mediated): it has an indolent course and presents mainly with gastrointestinal (GI) symptoms. This is more common in India seen in 80–90% cases.

Symptoms

The most common presentation is diarrhea with blood and mucus. Depending upon the site and extent of involvement, the child may have small bowel, large bowel, or mixed type diarrhea. Diarrhea and colitis is seen in 80% cases. They may have iron deficiency anemia and failure to thrive rarely as a clinical manifestation (especially those presenting as predominant small bowel diarrhea).

Diagnosis

Gold standard for diagnosis is double blind placebo controlled food challenge, but it is cumbersome to execute. A simpler yet conclusive way in India is to document the disease by the following methods:

- Flexible proctosigmoidoscopy: aphthous ulcers (80% cases)
- Rectal biopsy: more than 6 eosinophils per high power field + eosinophilic cryptitis (97% cases)
- Symptom resolution after withdrawal of animal milk or milk products (including formula feeds).

The new European Society of Pediatric Gastroenterology, Hepatology, and Nutrition, 2012 guidelines recommend the following:

1. Non-IgE mediated CMPA: a response to a trial of elimination diet for 2–4 weeks, followed by relapse of symptoms in next 2 weeks of oral challenge with cow's milk protein diagnoses the condition without any biopsy. Thereafter a therapeutic elimination diet is given
2. IgE mediated disease: CMP-specific IgE and skin prick tests. However these tests are not reliable in India due to lack of standarised laboratories.

The above recommendations reserve rectal biopsy and histopathology in scenarios of diagnostic dilemma, complicated disease and non-response to elimination diet

Treatment

All animal milk/milk products have to be eliminated from the diet. Breast milk should be continued. Calcium supplementation is mandatory as milk that has been withdrawn is a rich source of calcium. Explaining the natural history of the disease to parents, counseling, vigilance, and compliance are the cornerstones.

Child less than 4 Months of Age

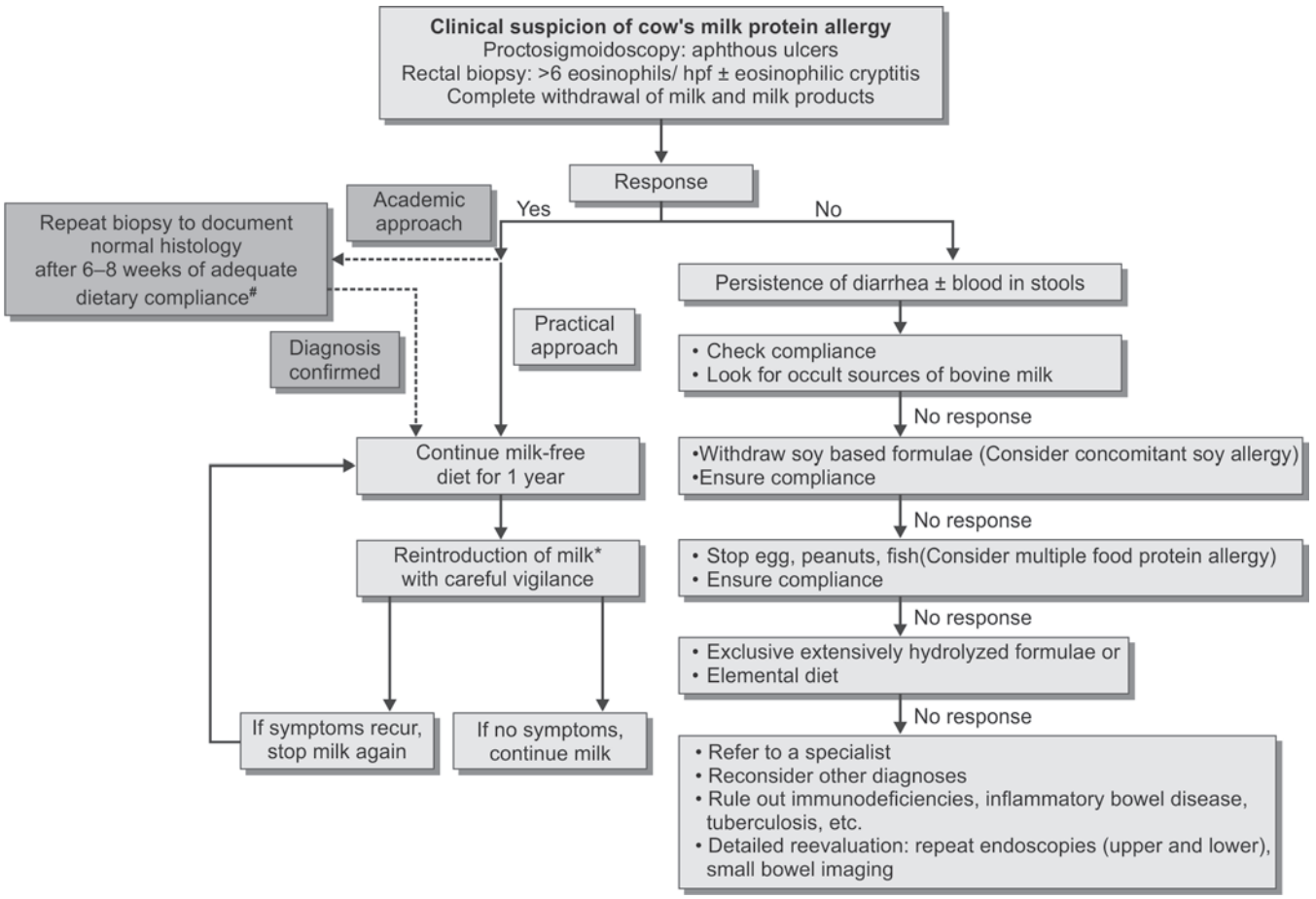
In Western countries, an exclusive extensively hydrolyzed formulation (EHF) is prescribed. In case of nonresponse to EHF, an elemental (amino acid formula) is used. Hypoallergenic formulae (EHF or elemental formulae) are not marketed in India. Hence, we are compelled to use soy formulae (not casein based). Soy formulations in infants less than 6 months of age are not recommended in the West (the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the American Academy of Pediatrics). Concomitant soy allergy is seen in 10–15% due to allergens (conglycinin and glycinin). Other problems with soy are high amounts of phytoestrogens that may interfere with neuroendocrine functions, high phytates that limit zinc, iodine, and iron absorption, and, manufacturing related aluminum contamination. Hence, there is a dire need to urge the marketing of hypoallergenic formulae in India.

Child more than 4 Months of Age

Formula feeds, animal milk, and milk products are stopped. Children more than 4 months of age are at an appropriate age for weaning and hence, dietary supplementation with cereals and pulses (region specific) is started. Rice gruel which is relatively hypoallergenic may be tried. If the child is more than 6 months of age, then, soy formulae can be permitted. Algorithm 1 outlines the for management of CMPA.

ALGORITHM 1

Approach and management of food protein allergy



#In an academic setting, biopsy is repeated twice after initial milk withdrawal. First assessment is at 6–8 weeks as shown above to confirm normalization of histology. Second assessment is at 48 hours of reintroduction of milk to decide wether it is safe to continue milk or not by (a) clinical symptoms and (b) histologic changes. Milk-free diet is continued if symptoms or histological changes reappear. If histology is normal and symptoms do not reappear, then, child can be continued on milk. However, in practical setting, both the repeat biopsies are not feasible due to the cumbersome process.

*Reintroduction of milk: child is given 10 mL/kg cow's milk (0.3 g/kg milk protein) initially and watched for 1 h. If there are no adverse events, then, 20 mL/kg cow's milk is given again watched for another 1 h. If there are no symptoms, such as diarrhea, vomiting, etc., then, normal milk feeding is continued.

SECONDARY LACTOSE INTOLERANCE

This condition is commonly seen as a cause of persistent diarrhea (secondary to viral gastroenteritis). However, it may be associated with underlying chronic diarrhea (celiac disease, Crohn's disease, giardiasis) due to villous atrophy and secondary deficiency of brush border enzymes (including lactase). It manifests as explosive (gaseous and noisy) stools and perianal excoriation that resolves on lactose-free diet. Persistent diarrhea causes damage to enterocyte and causes deficiency of the lactase enzyme located at the top of brush border epthelium. Hence lactose is not broken down to glucose and galactose. Unabsorbed dietary lactose delivered to colon is converted to hydrogen and lactic acid by colonic bacteria. Lactic acid results in decreased stool pH, hydrogen gives explosive stool and unabsorbed lactose gives positive reducing substances if tested. Lactose increased the osmolality (osmotic diarrhea). Fungal infection of the perineum in fungal diarrhea may mimic secondary lactose intolerance. In fungal infections, there are curdy white, satellite lesions and extension into the genitalia and groin flexures.

Confirmation is not required if stools are explosive and perianal area is excoriated. In doubtful cases, the diagnosis is confirmed by stool pH less than 6.0 and reducing substances more than 0.5%. Withdrawal of lactose containing milk for 3 weeks is the mainstay of treatment. Perianal area is managed by nursing on soft cloth, avoiding diapers, maintaining proper hygiene, and applying local emollients (coconut oil, liquid paraffin zinc oxide).

IMMUNODEFICIENCY STATES

Common presenting features and brief management of immunodeficiency has been discussed in detail in the next chapter. Additionally, there are few more immunodeficiency states with GI manifestations that are seen in younger children.

X-linked Agammaglobulinemia

- Onset after 6 months of age
- Chronic rotavirus infection
- Absent tonsils
- Panhypogammaglobulinemia + B cells less than 1%. Normal T cells.

Severe Combined Immunodeficiency

- Onset in first few months
- Cytomegalovirus colitis and mucocutaneous candidiasis
- Absent tonsils
- Leukopenia, hypogammaglobulinemia, absent T cells ± B cells

In both the groups, the children die by 1–2 years of age, if untreated. Treatment is specific; antimicrobials and intravenous immunoglobulin 400–600 mg/kg to tide over crisis. Allogenic bone marrow transplantation is curative.

NONSPECIFIC OR TODDLER'S DIARRHEA

This is a diagnosis of exclusion and contributes to 16% of all chronic diarrheas in preschool children. It is seen usually in thriving children of 6–20 months of age and spontaneously resolves by 3 years of age in majority. The diarrhea worsens with high osmolar feeds, e.g., juices, nectar fruits (grapes, melons, etc.). Occasionally, undigested food particles are seen in stool. No nocturnal symptoms or red flags are associated. Family history of irritable bowel syndrome may be present. Normal anthropometry and absence of anemia differentiate this condition from common conditions like celiac disease and CMPA. Treatment consists of reassurance, high fat (2 g/kg butter), and high fiber diet with reduced intake of juices. Antimotility agents should not be prescribed.

Celiac disease, and intestinal lymphangiectasia are discussed in detail in next chapter.

Box 3 shows brief clinical pointers and management of other pertinent causes of chronic diarrheas in children less than 3 years of age.

Box 3: Salient features and management of common causes of chronic diarrhea in children less than 3 years of age

- Short gut syndrome
  - History of intestinal resection for small bowel obstruction or necrotizing enterocolitis in infancy
  - Functional definition: massive small bowel resection >75% or dependence on parenteral nutrition for >6 weeks
  - Symptoms occur when >150 cm small bowel + no colon or <70 cm small bowel + intact colon (older children/adults)
  - Long-term total parenteral nutrition requirement
  - Treatment: small bowel lengthening surgeries or small bowel transplant)
- Anatomical defects
  - Duodenocolic fistula or small bowel fistulas:
    - May be idiopathic or secondary to inflammatory conditions, e.g., IBD, TB
    - Passage of undigested food particles soon after intake
    - Fistulous tract delineated by barium studies
    - Duodenocolic fistulous openings seen on UGIE ± colonoscopy
  - Malrotation: bacterial overgrowth, secondary lymphangiectasia
- Acrodermatitis enteropathica
  - May be primary (symptoms after weaning) or secondary to persistent diarrhea
  - Eczematous exfoliative rash in perioral, and perianal areas and extremities
  - Associated alopecia and sinopulmonary infections
  - Oral supplementation of 2–3 mg/kg or 50–150 mg zinc sulfate or gluconate daily
- Infantile inflammatory bowel disease
  - Less than 3% of all IBD in children
  - Emerging entity associated with rare immunodeficiency states such as interleukin-10 receptor defect or deficiency
  - Colitis in 100%, perianal disease in 80–90%, sepsis in >90%
  - May be associated with glycogen storage disease type 1b
  - Aggressive disease with poor prognosis and resistance to biological therapeutics (infliximab)
  - Hematopoietic stem cell transplant: promising therapeutic modality

Continued

Continued

- Shwachman-Diamond syndrome
  - Exocrine pancreatic insufficiency (steatorrhea) beginning in infancy
  - Cyclical neutropenia with risk of recurrent bacterial infections ± thrombocytopenia
  - Dental and skeletal abnormalities including short stature
  - Transient hepatomegaly ± transaminitis till 5 years of age
  - Diagnosis: abnormal pancreatic function tests, cyclical neutropenia, hypoplastic pancreas on computed tomography and genetic testing for abnormal Shwachman-Bodian-Diamond syndrome gene
  - Treatment: enzyme supplements, granulocyte colony stimulating factor, and regular skeletal monitoring
- Hirschsprung enterocolitis
  - Explosive diarrhea or colitis in a background history of constipation from birth or after pull through surgery for Hirschsprung disease
  - History of delayed passage of meconium. Distension, tenderness, fever, and shock
  - Erect X-ray abdomen: intestinal cutoff sign
  - In the setting of enterocolitis, barium enema is also contraindicated for the risk of perforation
  - Treatment: intravenous antibiotics, rectal irrigation (saline washes). Colonic decompression (diversion colostomy) in severe cases
- Wolman disease
  - Stormy neonatal course in first 2 weeks of life, rapid deterioration and death within 6 months
  - Associated with hepatosplenomegaly, liver failure, and intractable ascites
  - Consanguinity and sibling death
  - Bilateral adrenal calcification on abdominal imaging and foamy histiocytes on bone marrow studies
  - Enzymatic studies: deficient lysosomal acid lipase in white blood cells and fibroblasts
  - Corticosteroids for adrenal insufficiency
  - Bone marrow transplant may not be useful in all cases
- Abetalipoproteinemia
  - Diarrhea begins within first year of life, worsens with high fat diet, and some improvement is noted when patient learns dietary aversion
  - Neurologic symptoms (ataxia, areflexia, loss of vibration and position) appear after first decade
  - Retinitis pigmentosa seen in adulthood
  - Absence of chylomicron, low density lipoprotein and very low density lipoprotein in plasma (fasting lipid profile)
  - Hemolytic anemia and acanthocytosis in peripheral smear
  - UGIE (fat loading): white duodenal mucosa
  - Small bowel histology: lipid droplet filled enterocytes at villus tips
  - Treatment: restricted fat intake with supplementation of all fat soluble vitamins. High dose vitamin E (1000–2000 mg/day)

UGIE, upper gastrointestinal endoscopy; TB, tuberculosis; IBD, inflammatory bowel disease

INTRACTABLE DIARRHEA OF INFANCY

These are very rare causes of chronic diarrhea that are of congenital nature, severe in their course, often dependent on parenteral nutrition and most requiring small bowel transplant.

Setting to Suspect Intractable Diarrhea of Infancy

- Dehydrating diarrhea in an infant beginning in neonatal period or less than 3 months of age and
- Prolongation of diarrhea beyond 2 weeks despite extensive hospital therapy with one or more of the following:
  - At least 3 negative stool cultures for bacterial pathogen
  - Family history of consanguinity, sibling death, or polyhydramnios
  - Associated dysmorphism or systemic features
  - Common conditions like food protein allergy, intestinal lymphangiectasia, antibiotic associated diarrhea ruled out
  - No response to empirical elemental diet.

Common causes of intractable diarrhea of infancy (IDI) with their salient features are shown in table 1. Brief approach to IDI is shown in algorithm 2.

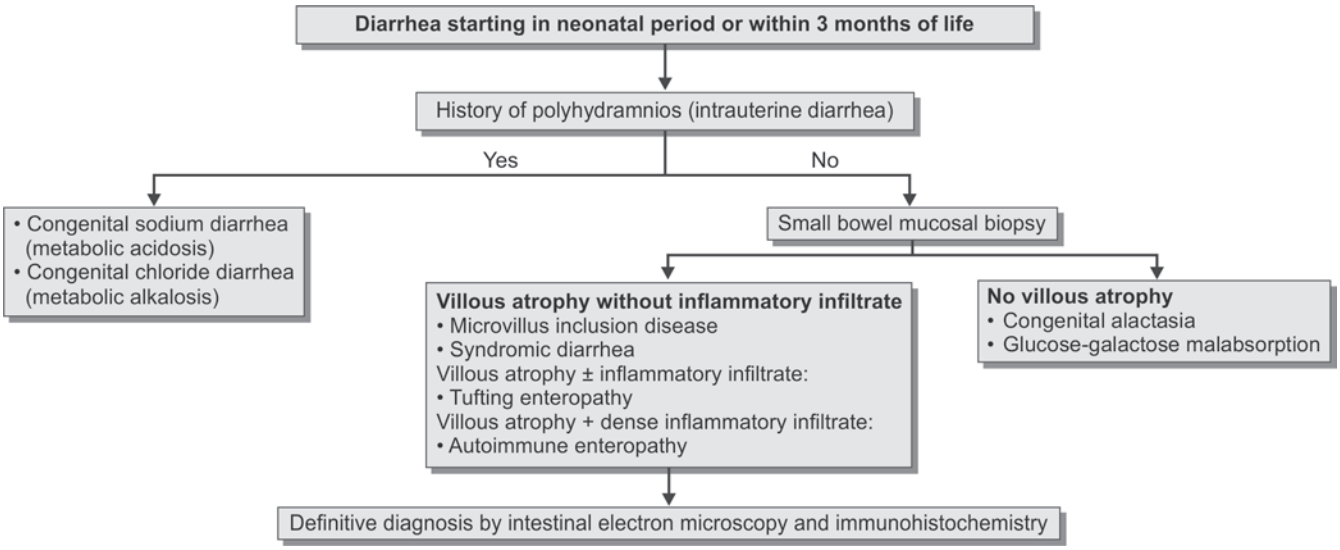
Except congenital alactasia which has favorable prognosis with absolute restriction of lactose in diet, the rest of the disorders have no definitive treatment; often require life-long parenteral nutrition or small bowel transplant. Intractable diarrhea of infancy patients patients have very high mortality.

TABLE 1: Common causes of intractable diarrhea of infancy and their characteristic features

Condition	Characteristic features
Congenital sodium diarrhea	• Elevated levels of fecal Na^+ and HCO_3^- • Antenatal polyhydramnios
Congenital chloride diarrhea	• Elevated levels of fecal Cl^- (>90 mmol/L) • Antenatal polyhydramnios
Microvillus inclusion disease	• Absent microvilli with inclusions in enterocytes
Tufting enteropathy	• Epithelium of villi arranged in "tufts" • Associated with choanal, esophageal, or anal atresia
Autoimmune enteropathy Part of IPEX syndrome (Immune dysregulation-polyendocrinopathy-enteropathy-X linked disease)	• Eczema, type I diabetes mellitus, and polyendocrinopathy • High serum immunoglobulin E and anti-enterocyte antibody positive
Syndromic diarrhea	• Facial dysmorphism, trichorrhexis nodosa (wooly hair), immunodeficiency, and cirrhosis of liver
Congenital alactasia (primary lactase deficiency)	• Improvement on lactose-free diet • Deficient lactase activity in a duodenal or jejunal biopsy when the other disaccharidases are normal
Glucose-galactose malabsorption	• Elimination of glucose and galactose (and lactose) from the diet results in the complete resolution of diarrhea • Diagnosis of exclusion

ALGORITHM 2

Approach to intractable diarrhea of infancy



Clinical Pearls

- Relatively thriving child with colitis: think of bovine (cow's) milk protein allergy
- Severe colitis with failure to thrive not responding to milk-free, soy-free, hydrolysed or elemental diet: think of infantile inflammatory bowel disease
- Small bowel diarrhea + perianal erythema + explosive stool: think of secondary lactose intolerance
- Severe intractable diarrhea beginning just after neonatal period: think of congenital diarrheas
- Diarrhea + fever: think of urinary tract infections and sepsis
- Chronic diarrhea with recurrent systemic infections: think of immunodeficiency states.

*Diarrhea in an underlying surgical setting are short gut syndrome, hirschprung enterocolitis, duodenocolic fistula, bacterial overgrowth syndrome (due to malrotation, blind-loop syndrome)

KEY POINTS

- ☞ Cow's milk protein allergy (CMPA) is the most common cause of colitis in children less than 3 years of age
- ☞ Algorithm approach of management of CMPA is to be followed
- ☞ Secondary lactose intolerance, celiac disease, and intestinal lymphangiectasia are common causes of small bowel diarrhea in children less than 3 years of age
- ☞ Urinary tract infections and sepsis are important systemic causes.

SUGGESTED READINGS

1. Avery GB, Villacivencio O, Lilly JR, Randolph JG. Intractable diarrhea in early infancy. Pediatrics. 1968;41:712-22.
2. Bhatia J, Greer F. American Academy of Pediatrics Committee on Nutrition. Use of soy protein based formulas in infant feeding. Pediatrics. 2008;121(5):1062-8.
3. ESPGHAN Committee on Nutrition, Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, et al. Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2006;42(4):352-61.
4. Goldman AS, Anderson DW, Sellers WA, Saperstein S, Kniker WT, Halpern SR. Oral challenge with milk and isolated milk proteins in allergic children. Pediatrics. 1963;32:425-43.
5. Goulet O, Philips AD. Congenital enteropathy involving intestinal mucosa development. In: Walker AW, Goulet O, Kleiman RE, Sherman PM, Shneider BL, Sanderson RI (Eds). Pediatric Gastointestinal Diseases, 4th edition. BC Decker; 2004. pp. 922-31.
6. Guarino A, Spangnuolo MI, Russo S, Albano F, Guandalini S, Capano G, et al. Etiology and risk factors of severe and protracted diarrhea. J Pediatr Gastroenterol Nutr. 1995;20:173-8.
7. Høst A, Halken S, Jacobsen SP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. Ped Allergy Immunol. 2002:13 (Suppl 15):23-8.
8. Høst A. Frequency of cow's milk allergy in childhood. Ann Allergy Asthma Immunol. 2002;89(6 Suppl. 1):33-7.
9. Kneepkens CM, Hoekstra JH. Chronic nonspecific diarrhea of childhood: pathophysiology and management. Pediatr Clin North Am. 1996;43:375-90.
10. Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. Gastroenterology. 2012;143:347-55.
11. Matthai J. Yachha SK. Pediatric Gastroenterology Chapter, Indian Academy of Pediatrics. Chronic and Persistent Diarrhea in Infants and Young Children: Status Statement. Ind Pediatr. 2011;48:37-42.
12. Poddar U, Agarwal J, Yachha SK, Srivastava A. Toddler's diarrhea: is it an under recognized entity in developing countries? J Trop Pediatr. 2013;59:470-5.
13. Poddar U, Yachha SK, Krishnani N, Srivastava A. Cow's milk protein allergy (CMPA): an entity for recognition in children in developing countries. J Gastroenterol Hepatol. 2010;25:178-82.
14. Wales PW, Christison-Lagay ER. Short bowel syndrome: epidemiology and etiology. Semin Pediatr Surg. 2010;19:3-9.
15. Yachha SK, Misra S, Malik A, Nagi B, Mehta S. Spectrum of malabsorption syndrome in North Indian children. Indian J Gastroenterol. 1993;12:120-5.

CHAPTER 77

Chronic Diarrhea in Children More than 3 Years of Age

Surender K Yachha, Moinak S Sarma

INTRODUCTION

Chronic diarrhea is defined as an insidious onset diarrhea of more than 2–3 weeks duration in children. Causes of chronic diarrhea in older children (>3 years) and adolescents are distinctly different from those in younger age.

APPROACH TO CHRONIC DIARRHEA

Approach to chronic diarrhea should be considered with the following points in mind:

- Small or large bowel type of diarrhea: features in history and examination that help in differentiating small from large bowel diarrhea shown in table 1. To summarize, large volume diarrhea without blood and mucus suggests "small bowel type" and small volume stools with blood and mucus suggests "large bowel type" of diarrhea.
- Gastrointestinal (GI) versus systemic causes: commonly, diarrhea is of intestinal origin and sometimes due to pancreatic etiology, and rarely, hepatobiliary causes. Cholestasis due to biliary obstruction or intrahepatic cause can cause diarrhea due to fat malabsorption as a result of deficiency of bile. Diarrhea may be caused due to liver diseases having genetic or metabolic defects mostly prevalent among young children. Pruritus, fat soluble vitamins (A, D, E, and K), and calcium malabsorption is commonly associated with hepatobiliary diseases. Maldigestion due to deficiency of pancreatic enzymes results in clinical steatorrhea in cystic fibrosis, Shwachman-Diamond syndrome (cyclical neutropenia and skeletal dysplasia), or chronic pancreatitis. Diarrhea may also be a systemic manifestation of other conditions like nephrotic syndrome, sepsis, or collagen vascular disorders. Box 1 enumerates the common and uncommon causes of diarrhea in children more than 3 years of age.

TABLE 1: Differentiating small versus large bowel diarrhea

Features	Small bowel diarrhea	Large bowel diarrhea*
Stool volume	Large	Small
Blood in stool	No	Usually present
Rectal symptoms (urgency, tenesmus)	No	Yes
Carbohydrate malabsorption	Yes, explosive	No
Protein malabsorption	Yes	No
Pain (if any)	Periumbilical, no reduction after passage of stool	Hypogastric, reduced after passage of stool
Color of stool	Pale	Normal
Smell of stool	Unusually offensive	Normal
Nutrient deficiency (iron, calcium, mutivitamins)	Frequent	Can occur due to blood loss

*Large bowel diarrhea in exceptional cases may not necessarily have blood in stools or rectal symptoms.

Box 1: Causes according to age of onset (in order of priority)

- Common causes
  - Celiac disease
  - Parasites: giardiasis and others
  - Lymphangiectasia
  - Gastrointestinal tuberculosis
  - Inflammatory bowel disease (Crohn's disease; ulcerative colitis* unclassified IBD)
  - Immunodeficiency syndromes
  - Pancreatic insufficiency
  - Bacterial overgrowth syndrome (diagnosis of exclusion) in a non-surgical setting
- Uncommon causes
  - Tropical sprue
  - Immune proliferative small intestinal disease (IPSID)
  - Anatomical causes (malrotation of gut)
  - Intestinal fistulae (duodenocolic commonest)
  - Late-lactose intolerance (very rare)
  - Autoimmune enteropathy
  - Systemic causes:
    - Nephrotic syndrome[#]
    - Constrictive pericarditis[$]
  - Endocrine causes:
    - Hyperthyroidism
    - Addison's disease

*Ulcerative colitis presents as bloody diarrhea. Crohn's disease may present either as colitis or small bowel diarrhea or both.
[#]Diarrhea in nephrotic syndrome is presumed to be due to bowel wall edema (hypoalbuminemia).
[$]Secondary lymphangiectasia due to chronic back pressure is the cause of diarrhea in constrictive pericarditis, can also occur due to other causes.

WHAT SHOULD YOU LOOK FOR IN HISTORY?

- Details of duration of symptoms, nature, frequency and consistency of stools, and presence of blood/mucus/clinical steatorrhea (stool floating in water, greasy oily droplets)
- Age of onset, dietary details, i.e., introduction of wheat/wheat products and their relationship with onset of diarrhea. Relationship with milk intake and quantity
- Family history of atopy (food allergy, asthma, or allergic rhinitis), celiac disease, inflammatory bowel disease (IBD) or cystic fibrosis
- History of abdominal surgery, systemic disease, features of intestinal obstruction, pedal edema, anasarca, recurrent infections at multiple sites, previous blood transfusion, and coexisting medical problems which predispose the child to diarrhea like congenital immunodeficiency, diabetes mellitus, hyperthyroidism, cystic fibrosis, etc.

WHAT SHOULD YOU LOOK FOR IN PHYSICAL EXAMINATION?

- Growth parameters
- Volume status and rarely, presence of dehydration
- Signs of vitamin and mineral deficiencies anemia, tetany, (conjunctival xerosis, bitot's spots, angular stomatitis, glossitis, cheilitis, rickets, phrynoderma)
- Edema: symmetric and pitting (hypoalbuminemia) or asymmetric and nonpitting (lymphedema)
- Fever and other signs of toxicity
- Extra-gastrointestinal manifestations in eye, skin, joints, oral cavity (particularly aphthous ulcers) in IBD
- Inspection of perianal area for fissures, anal tags, and fistulae in IBD
- Oral thrush and scars of recurrent skin infections in immunodeficiency
- Abdominal examination: abdominal distention, localized or generalized tenderness, masses, hepatosplenomegaly, and ascites.

The common etiologies are elaborated below. Algorithm 1 shows an approach to chronic diarrhea more than 3 years of age (major etiologies).

CELIAC DISEASE

It is an enteropathy caused by permanent sensitivity to gluten in genetically susceptible subjects. It is the most common cause of chronic diarrhea in children over 2 years of age in North India. Boxes 2 and 3 summarize the diagnosis and management of the same.

INTESTINAL LYMPHANGIECTASIA

It is characterized by ectasia of the bowel lymphatic system, which on rupture causes leakage of lymph in the bowel. Box 4 summarizes the diagnosis and management of the same.

IMMUNODEFICIENCY

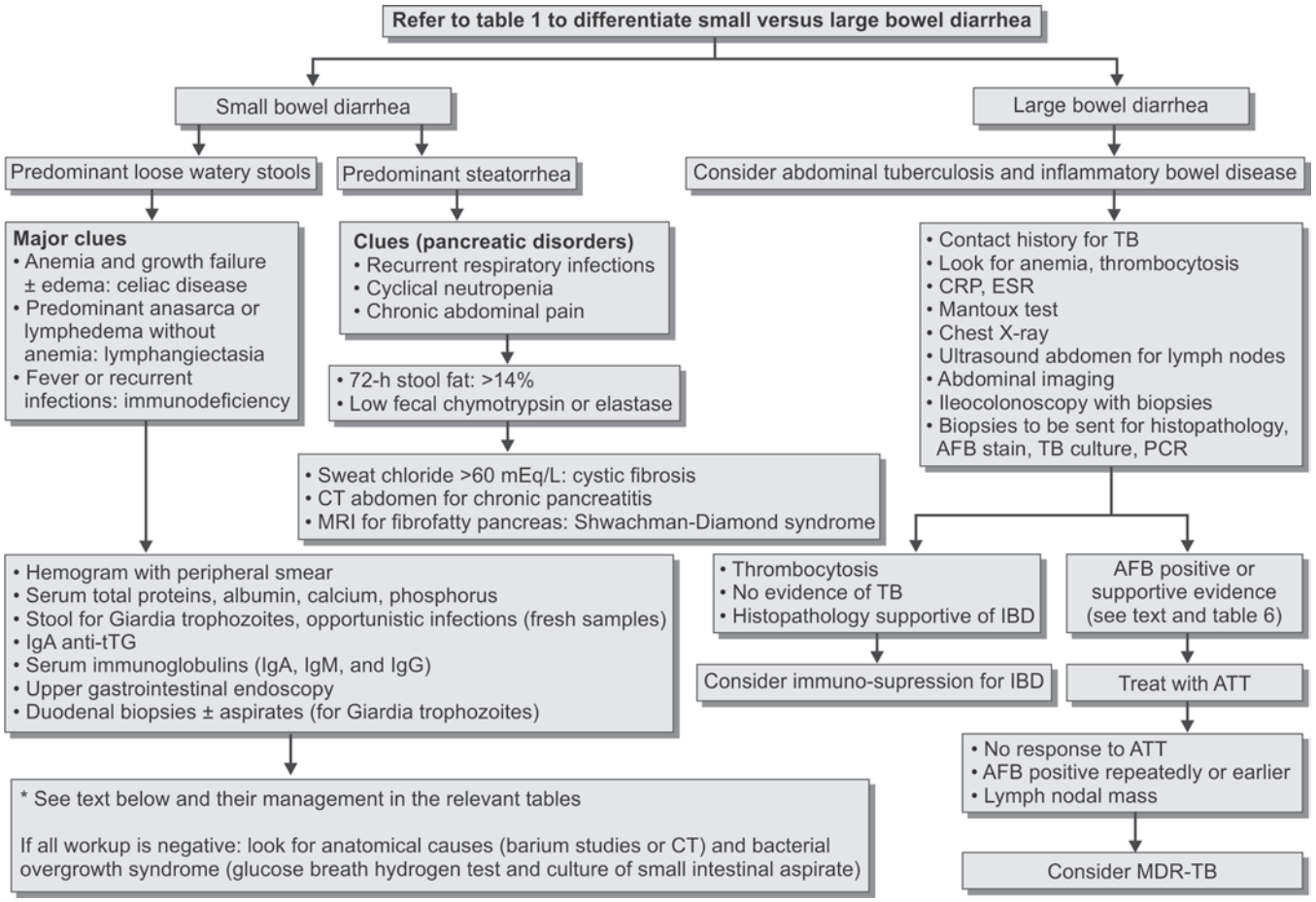
Both congenital and acquired immunodeficiency can cause chronic diarrhea. It should be suspected if there is history of recurrent infections at multiple sites (chest/GI/skin) and wasting. The common immunodeficiency conditions in children more than 3 years of age presenting with diarrhea are human immunodeficiency virus (HIV) infection, selective immunoglobulin A deficiency, common variable immunodeficiency, and chronic granulomatous disease. Boxes 5 and 6 summarize the diagnosis and management of the same. Diarrhea is either due to opportunistic enteric infections or due to bacterial overgrowth.

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the GI tract and is of two main types: (1) Crohn's disease (CD) and (2) ulcerative colitis (UC). In approximately 10% cases, the findings are nonspecific and subjects cannot

ALGORITHM 1

Approach to management of chronic diarrhea in children more than 3 years of age: major etiologies



CT, computed tomography; MRI, magnetic resonance imaging; AFB, acid fast bacilli; TB, tuberculosis; ATT, antitubercular therapy; MDR-TB, multidrug resistance tuberculosis; anti-tTG, anti-tissue transglutaminase; IBD, inflammatory bowel disease; IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction.

*Note:**

- Selective IgA deficiency: recurrent giardiasis
- IgA anti-tTG positive + villous atropy + other biopsy changes (Box 2): celiac disease
- IgA anti-tTG negative + low IgA level + villous atropy + other biopsy changes (Box 2): celiac disease
- Dilated lacteals on duodenal biopsies: intestinal lymphangiectasia (Box 4 for other supportive features)
- Low IgA, IgM, and IgG ± villous atropy ± paucity of plasma cells on duodenal biopsies: immunodeficieny workup as shown in Box 5.

be classified into one of the above two groups. These cases are labeled as IBD unclassified. Nearly 25% of all IBD patients present in the pediatric age group. Worldwide, the incidence of IBD is increasing in children with increase in recent reports of both UC and CD from India. The average age of presentation in children is nearly 10–11 years. Genetics is a very important risk factor for IBD and up to 30% patients may have an affected family member with IBD. Box 7 summarizes the disease distribution of UC and CD.

Clinical Features

Children with CD present with abdominal pain, diarrhea (with or without blood), and constitutional symptoms (fever, anorexia, growth failure). In contrast, children with UC present with only recurrent or prolonged episodes of bloody diarrhea, commonly without constitutional symptoms. Table 2 summarizes the clinical, histologic, and endoscopic differences between UC and CD.

Extraintestinal manifestations are seen in 25–30% children with IBD. They can precede, follow, or occur concurrently with the intestinal disease and may be related or unrelated to the activity of the intestinal disease. Arthralgia/arthritis is the most common manifestation seen in 15–17% cases. Uveitis, erythema nodosum and sclerosing cholangitis are the other manifestations.

Diagnosis

The initial evaluation of a child with suspected IBD includes a detailed clinical, family, and treatment history. Also, a complete examination with growth charting, perianal and

Box 2: Classical clinical features and workup of celiac disease

- Presentation
  - Onset after weaning when gluten is introduced
  - Small bowel diarrhea, failure to thrive, short stature, and gaseous abdominal distension
  - Anemia, rickets, and multivitamin deficiencies
- Workup: mandatory in India
  - Positive serology: IgA anti-tTG (preferred) or IgA anti-EMA
  - Upper gastrointestinal endoscopy: scalloping ± reduced number of duodenal folds, mosaic pattern, cobblestoning of duodenal mucosa (not specific)
  - Endoscopic duodenal biopsy:*
    - Partial to total villous atrophy
    - Hyperplastic crypts
    - Increased intraepithelial lymphocytes (>30/100 enterocytes)
    - Lymphoplasmacytic infiltrates
- Workup: supportive
  - HLA-DQ2 or 8 positive (not done routinely). Only in exceptional cases where diagnosis is doubtful
  - Serum IgA levels:
    - Suspect if serology is negative and clinical suspicion is high
    - Levels <5 mg/dL suggests IgA deficiency
  - Serum IgG anti-DGP
    - Children <2 years of age if tTG or EMA is negative
    - Concomitant IgA deficiency

IgA, immunoglobulin A; tTG, tissue transglutaminase antibody; EMA, endomysial antibody; DGP, deamidated gliadin peptide; HLA, human leukocyte antigen.

*Between 4–6 biopsies should be obtained (at least 4 from second part of duodenum and one from first part). Biopsies should be directly immersed in formalin solution for best orientation under microscope.

Box 3: Diagnosis and treatment of celiac disease

Diagnosis of celiac disease based on the modified ESPGHAN 1990 criteria:

- Clinical picture consistent with celiac disease
- Changes in intestinal biopsy as described above (+ serology*)
- Unequivocal response to GFD within 12 weeks of initiation of GFD

New ESPGHAN 2012 guidelines for diagnosis:

- Small bowel biopsy may be omitted when all three following tests are fulfilled: anti-tTG ≥10 times upper limit, anti-EMA positive and HLA DQ 2/8 positive (details in original article)
- However, due to certain limitations in India (cost, unreliability of laboratory reports, and overlap with other chronic diarrheal diseases), the above guideline is difficult to implement currently. Hence, small bowel biopsy is still recommended for diagnosis (personal view).

Treatment:

- GFD (wheat and barley) should never be started without a positive histology
- Lifelong GFD, vigilance, and counseling. Region-specific dietary chart
- Hematinics, folic acid, and multivitamin supplementation for 3 months
- Response to GFD should be assessed at 8–12 weeks to label the patient having celiac disease as per diagnostic criteria
- At follow-up: compliance with repeated reinforcement of GFD, symptomatic, anthropometric, and laboratory (hemoglobin, albumin, and transaminases) normalization to be assessed

ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; GFD, gluten-free diet; EMA, endomysial antibody; tTG, tissue transglutaminase; HLA, human leukocyte antigen; IgA, immunoglobulin A.

*In India positive serology (IgA-tTG) should be demonstrated as there are other conditions that may result in villous atrophy mimicking celiac disease

rectal examination for fistulae, tags, and fissures to be done. Laboratory tests may reveal anemia and thrombocytosis (67%), low albumin, high erythrocyte sedimentation rate (ESR) and C-reactive protein in 40–60% cases. Hence, IBD must be suspected in any child presenting with constitutional symptoms, chronic large bowel diarrhea (± blood), and thrombocytosis. Table 3 summarizes the diagnostic modalities available for IBD.

Treatment

The goal of treatment is to control inflammation, mucosal healing, improve growth, and ensure a good quality of life with the least toxic therapeutic regimen. Ensuring proper nutrition with caloric supplementation (~120% of recommended dietary allowances) is a necessity for children with IBD. Calcium and vitamin D supplementation should be given as these children are at an increased risk of osteoporosis. As IBD is a chronic disease with remissions and exacerbations, proper counseling of both, patient and family, at diagnosis is essential. The main drugs used for IBD are listed in the tables 4 and 5. Additionally, for perianal fistulizing CD, antibiotics (ciprofloxacin 20 mg/kg, metronidazole 10–20 mg/kg, azithromycin 10 mg/kg, or rifaximin 10–30 mg/kg) for 4–6 weeks have shown good short-term response.

Box 4: Features and management of intestinal lymphangiectasia

Presentation:

- Small bowel diarrhea with anasarca ± lymphedema of peripheries
- Abdominal or thoracic chylous effusions may be associated
- Usually, absence of anemia and rickets (in contrast to celiac disease)
- Hypocalcemic tetany

Diagnosis:

- Panhypoproteinemia, low immunoglobulins, hypocalcemia, and lymphopenia
- Upper gastrointestinal endoscopy: white patches in duodenum (snow-flake appearance), better appreciated after overnight fat (butter) loading 2 g/kg
- Small bowel biopsy: dilated lacteals in the villi

Treatment:

- Diet: low fat, high medium chain triglyceride with high protein (2–4 g/kg)
- Medium chain triglycerides should be 85% of total fat intake
- Calcium supplementation
- Intravenous albumin (1 g/kg) during acute exacerbations
- In refractory cases: subcutaneous octreotide 15–20 µg daily twice or 10–20 µg depot preparation once in 4 weeks
- Resection if localized segment of small bowel is involved by identifying the segment by 99Tc albumin scintigraphy

Box 5: Clinical features of common immunodeficiency states (above 3 years of age)

Common features
- Positive family history, affected sib, or sib death
- Associated systemic infections (sinopulmonary, skin, urinary, meningeal, etc.)
- Small bowel, large bowel, or mixed diarrhea depending on the opportunistic pathogen
- Recurrent GI infections: Cryptosporidia, Isospora, Giardia, Cytomegalovirus, fungal

Human immunodeficiency virus infection
- Hepatosplenomegaly, lymphadenopathy, thrombocytopenia, hypergammaglobulinemia
- Enzyme-linked immunosorbent assay and Western blot tests positive
- Opportunistic infections depending upon the level of CD4 count

Selective IgA deficiency
- Recurrent giardiasis
- Serum IgA <5 mg/dL

Common variable immunodeficiency
- Age of onset variable usually after 2 years of age
- Low serum IgG ± low IgA or M with variable B-cell numbers

Chronic granulomatous disease
- Multifocal abscess (skin, liver), colitis
- Blood nitro-blue tetrazolium reduction test positive

IgA, immunoglobulin A; IgG, immunoglobulin G.

Box 6: Common infections and management of immunodeficiency states

- Common infections include:
  - Viral: Cytomegalovirus, Herpes simplex, Adenovirus
  - Bacterial: Salmonella, Shigella, Mycobacterium avium complex (MAC), *Campylobacter jejuni, Clostridium difficile*
  - Fungal: candidiasis, histoplasmosis, cryptococcosis
  - Protozoa: Microsporidium, *Isospora belli*, Cryptosporidium, *Entamoeba histolytica, Giardia lamblia*, Cyclospora, *Blastocystis hominis*
  - Parasites: strongyloides
- Diagnosis:
  - Serum immunoglobulin, B-cell and T-cell assays
  - Colonic biopsies, duodenal fluid examination and multiple stool samples for opportunistic infections (special stains, polymerase chain reaction and fungus
- Treatment:
  - Specific antimicrobials for the isolated organisms
  - Acquired immunodeficiency syndrome: highly active antiretroviral therapy (HAART)
  - Common variable immunodeficiency: intravenous immunoglobulin therapy 400–600 mg/kg every 3–4 weeks to maintain serum immunoglobulin G levels >500–700 mg/dL

Surgery is indicated in UC patients with severe acute colitis refractory to medical disease. Uncontrolled hemorrhage, perforation, toxic megacolon, abscesses, and obstruction are the other indications for surgery. Nearly 40% pediatric patients with UC require total colectomy within 5–10 years of diagnosis.

Box 7: Disease distribution

- Ulcerative colitis
  - Distal colitis (proctitis/proctosigmoiditis): 5–20%
  - Left side colitis (up to splenic flexure): 10–40%
  - Pancolitis: 50–90%
- Crohn's disease
  - Ileocolonic disease: 50–70%
  - Isolated colonic involvement: 10–20%
  - Small bowel: 10–15%
  - Associated:
    - Upper gastrointestinal involvement: 30–40%
    - Perianal disease: 20–25%

Note: Crohn's disease is also classified as predominantly inflammatory, fistulizing, or stricturing disease based on the clinical features.

TABLE 2: Differentiation between Crohn's disease and ulcerative colitis

Parameters	Crohn's disease	Ulcerative colitis
Distribution	Entire GI tract	Colon only
	Transmural inflammation	Mucosal disease
	Discontinuous (skip) lesions	Continuous involvement
Bloody diarrhea	Less common	Common
Abdominal pain	Common	Less common
Growth failure	Common	Less common
Perianal disease (abscess/fistulae)	Present	Absent
Histopathology	Noncaseating granuloma (any part of GI tract)	Widespread crypt architectural distortion
	Transmural involvement	Diffuse inflammatory infiltrate
	Focal discontinuous crypt architectural distortion	Basal plasmacytosis
	Focal discontinuous chronic inflammation	Goblet cell depletion
	Focally enhancing gastritis (stomach)	Crypt abscess
	Pyloric gland metaplasia (terminal ileum)	Paneth cell metaplasia
Endoscopy	Deep irregular serpiginous or aphthous ulcers	Diffuse superficial ulceration
	Normal intervening mucosa (skip lesion)	Granularity, loss of vascular pattern, friability
	Ileal involvement, rectal sparing (60%)	Rectal involvement and ileal sparing (unless back-wash ileitis)

TABLE 3: Diagnostic modalities available for inflammatory bowel disease

Diagnostic modality	Importance
Colonoscopy with ileal intubation Multiple biopsies from disease sites	Most important to differentiate ulcerative colitis vs. Crohn's disease
Upper gastrointestinal endoscopy with biopsies	To look for granulomas (40%)
Small bowel imaging	For small bowel strictures fistula
Barium enteroclysis, CT or magnetic resonance enteroclysis	Extramural complications may be seen in CT/MRI
MRI pelvis	Fistula, pelvic and genitourinary abscess
Capsule endoscopy	Ideal to evaluate small bowel involvement after excluding intestinal stricture that may result in retention of capsule. Disadvantage: biopsies cannot be taken
Enteroscopy	Limitation of not able to pass bigger diameter enteroscopes in younger children

CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 4: Drugs used in inflammatory bowel disease (first line therapy)

Drug	Dosage and route	Indication	Main side effects
• Sulfasalazine or • 5-aminosalicylic acid or mesalamine (active moiety of sulfasalazine)	• 40–60 mg/kg/day oral • 50–100 mg/kg/day oral • Enema	• Anti-inflammatory (local action) in mild ulcerative colitis and maintenance • Enema in mild-to-moderate left-sided colonic disease	• Folate deficiency • Pancreatitis • Steven-Johnson syndrome • Hepatotoxicity • Oligospermia (with sulfasalazine)
• Prednisolone	• 1–2 mg/kg oral	• Induction therapy (first line) in all types of inflammatory bowel disease	• Cushingoid facies • Hypertension • Glaucoma • Cataract • Fractures • Hyperglycemia • Growth impairment
Thiopurines:			
• Azathioprine • 6-Mercaptopurine (active moiety of azathioprine)	• 2–3 mg/kg/day oral • 1–2 mg/kg/day oral	• Frequent relapses* • Steroid dependence# • Steroid resistance† • Maintenance in moderate-to-severe disease	• Myelosuppression • Hepatotoxicity • Pancreatitis

*Frequent relapses: 2–3 relapses per year.

#Steroid dependency: initial remission but recurrence while tapering or inability to stop steroids in 14–16 weeks of initiation.

†Steroid resistance: nonresponse to optimal doses of oral steroids within 7–14 days of initiation and good compliance.

Risk of adenocarcinoma colon is 8% after 20 years of disease in pediatric UC.

ABDOMINAL TUBERCULOSIS

High index of suspicion for abdominal tuberculosis is to be considered in any child with:

- Constitutional symptoms (prolonged fever, anorexia, and weight loss) + any of the features in table 6
- Contact with open case of tuberculosis (adult)
- Mantoux test positivity (≥5 mm in HIV and ≥10 mm in non-HIV patients irrespective of age at 48–72 hours of tuberculin injection)
- Contributory laboratory features: high ESR, lymphocytosis.

Diagnosis

- Definitive: demonstration of acid fast bacilli (fine needle aspiration cytology from lymph nodes, ascitic fluid, endoscopic biopsies) on Ziehl-Neelson (ZN) staining or culture (BACTEC or Lowenstein-Jensen media). If adequate tissue is sampled and processed, a definitive diagnosis is achievable in up to 64% of pediatric cases
- Supportive: tubercular granuloma with caseation in the biopsies (endoscopic/peritoneal/liver)
- In the absence of above features, a probable diagnosis of abdominal tuberculosis is made when suggestive clinical features and response to antitubercular therapy (ATT) without relapse after completion of therapy is observed

TABLE 5: Drugs used in inflammatory bowel disease (second line therapy)

Drug	Dosage and route	Indications	Main side effects
• Methotrexate	• 15 mg/m^2 IM weekly	• Steroid sparing • Refractory disease and/or intolerant to thiopurines	• Hepatotoxicity • Myelosuppression • Folate deficiency
• Cyclosporine	• 2–4 mg/kg/day IV infusion followed by 5–8 mg/kg/day oral	• Rescue therapy for maximum 4 weeks in severe refractory ulcerative colitis	• Nephrotoxicity • Hypertrichosis • Gum hyperplasia • Hypertension • Paraesthesia
• Tacrolimus	• 0.1 mg/kg oral		
• Biological agents (infliximab, adalumimab)	• 5 mg/kg IV at 0, 2, 6 weeks and thereafter need based	• Fistuling CD • Severe disease not responding to immunomodulators	• Autoimmunity • Demyelination • Psychiatric problems • Flare infections (espc. tuberculosis) • Hepatosplenic T-cell lymphoma (in combination with azathioprine)
• Thalidomide	• 1.5–2.5 mg/kg oral	• Refractory CD and intolerant to biological agents (very selective group)	• Irreversible peripheral neuropathy • Agitation • Hallucination

CD, Crohn's disease; IM, intramuscular; IV, intravenous.

TABLE 6: Presentation and specific workup in abdominal tuberculosis

Involvement	Features	Tissue sampling and specific workup (laboratory and abdominal imaging)
Peritoneum	• Dry: adhesive intestinal obstruction lump (cocoon abdomen) • Wet: exudative ± loculated ascites • "Doughy" feel of abdomen	• Peritoneoscopy/laparoscopy: peritoneal tubercules • Ascitic fluid: lymphocytosis with high adenosine deaminase
Lymph nodes	• Lump (lymph nodal mass)	• Fine needle aspiration from necrotic, enlarged (>10 mm) and/or calcified, conglomerate lymph nodes
Gastrointestinal tract (luminal)	• Ulcerative: abdominal pain, GI bleed, anemia • Hypertrophic: Intestinal obstruction • Ulcerohypertrophic: Combination of above 18–64% present as chronic diarrhea or colitis	• Features on colonoscopy* • Colonic and ileal biopsies by endoscopy# • Laparotomy and surgical biopsy of small bowel
Hepatic	• Systemic symptoms with hepatomegaly • Non-resolving liver abscess	• Raised serum alkaline phosphatase • Multiple hypodense ± calcified foci in liver
Combination	• Nodal ± peritoneal ± GI	• Tissue sampling and workup as above
Disseminated	• Abdominal + other organs (lungs, peripheral LN, bone marrow)	

*Ab.TB is a close differential of Crohn's disease. Some major endoscopic features (though not discriminatory) may favor Ab.TB:

- Segmental involvement (as compared to skip areas in CD)
- Deep circular transverse ulcers (as compared to deep linear serpiginous ulcers in CD)
- Short colonic strictures (as compared to multiple long strictures in CD).

#Due to significant overlap between the two diseases, all biopsy specimens should be simultaneously sent for histopathology, ZN staining, TB culture and TB-PCR (polymerase chain reaction). Culture positivity may be seen despite initial ZN stain negativity. Tissue TB-PCR (nested or real time) has high specificity (98%) but lower sensitivity (68–75%).

- Due to emergence of multidrug resistance tuberculosis (MDR-TB) and delay in obtaining culture sensitivity, World Health Organization recommends "Line Probe Assay" from all acid fast bacilli positive tissue samples (ZN stain or culture). Line probe assay provides drug sensitivity within 6 hours and differentiates Mycobacterium tuberculosis from nontubercular Mycobacteria.

Treatment

Antitubercular drugs are the mainstay of treatment of abdominal tuberculosis as per the current pediatric guidelines in India. Surgery is indicated if there is bowel perforation, obstruction, or massive hemorrhage. It is important to differentiate intestinal tuberculosis from Crohn's disease

as they mimic each other in clinical presentation but have different treatment. One should also suspect MDR-TB in patients with a definite diagnosis of abdominal tuberculosis but a poor response to standard ATT. Multidrug resistance tuberculosis presents mostly as refractory lymph nodal masses in the abdomen with close differential diagnosis of non-Hodgkin's lymphoma.

Clinical Pearls

- Small bowel diarrhea
  - Small bowel diarrhea + anemia and rickets: think of celiac disease
  - Small bowel diarrhea + predominant edema without anemia: think of intestinal lymphangiectasia
  - Small bowel diarrhea + recurrent infections: think of immunodeficiency
  - Abdominal tuberculosis rarely presents as small bowel diarrhea
  - In celiac disease, do not start gluten-free diet without confirmation of diagnosis (serology + histopathology)
- Large bowel diarrhea
  - Large bowel diarrhea in an older child: think of inflammatory bowel disease and tuberculosis
  - Workup for both should be sent together as they may mimic each other
  - Necrotic or calcified lymph node in chest or abdomen and exudative ascites is specific for tuberculosis
  - Attempt to obtain tissue diagnosis in abdominal tuberculosis before starting antitubercular therapy.

KEY POINTS

- ☞ Differentiating small from large bowel diarrhea, malabsorption from maldigestion clinically provides a clue to diagnosis
- ☞ Common causes of chronic small bowel diarrhea in children above 3 years of age are celiac disease (in North India), giardiasis, intestinal lymphangiectasia, and immunodeficiency
- ☞ Celiac disease and lymphangiectasia require life-time therapy whereas giardiasis and opportunistic infections in immunodeficiency states require antimicrobials. Immunodeficiency needs to be treated as per cause
- ☞ Common causes of small bowel diarrhea in children above 3 years of age are abdominal tuberculosis and inflammatory bowel disease (IBD)
- ☞ Antitubercular therapy is the mainstay of therapy in abdominal tuberculosis. Multidrug resistance tuberculosis (MDR-TB) should be considered if there is nonresponse and acid fast bacilli is positive in tissue. Usually, abdominal MDR-TB presents as large abdominal lymph nodal masses
- ☞ Immunosuppression is the mainstay of treatment in IBD. Only a small proportion requires surgeries in select situations.

SUGGESTED READINGS

1. Al Sinani S, Rawahi YA, Abdoon H. Octreotide in Hennekam syndrome-associated intestinal lymphangiectasia. World J Gastroenterol. 2012;18:6333-7.
2. Baldassano RN, Piccoli DA. Inflammatory bowel disease in pediatric and adolescent patients. Gastroenterol Clin North Am. 1999;28:445-58.
3. Husby S. For ESPGHAN Working Group on Coeliac Disease. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-60.
4. Kumar A, Gupta D, Nagaraja SB, Singh V, Sethi GR, Prasad J, et al. Updated National Guidelines for Pediatric Tuberculosis in India, 2012. Indian Pediatr. 2013;50:301-6.
5. Lee HS, Park KU, Park JO, Chang HE, Song J, Choe G, et al. Rapid, sensitive, and specific detection of M. tuberculosis complex by real-time PCR on paraffin-embedded human tissues. J Mol Diagn. 2011;13:390-4.
6. Magro F, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, et al. European Consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis. 2013;7:827-51.
7. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8(10):1179-207.
8. Sabery N, Bass D. Use of serologic markers as a screening tool in inflammatory bowel disease compared with elevated erythrocyte sedimentation rate and anemia. Pediatrics. 2007;119:e193-9.
9. Sandhu BK, Fell JM, Beattie RM, Mitton SG, Wilson DC, Jenkins H; on Behalf of the IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition. Guidelines for the Management of Inflammatory Bowel Disease in Children in the United Kingdom. J Pediatr Gastroenterol Nutr. 2010;50:S1-13.
10. Sari S, Baris Z, Dalgic B. Primary intestinal lymphangiectasia in children: Is octreotide an effective and safe option in the treatment? J Pediatr Gastroenterol Nutr. 2010;51:454-7.
11. Sauer CG, Kugathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. Med Clin North Am. 2010;94:35-52.
12. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child. 2003;88:995-1000.
13. Thapa BR, Yachha SK, Mehta S. Abdominal tuberculosis. Indian Pediatr. 1991;28:1093-100.
14. Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55:340-61.
15. Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135:1114-22.
16. Walker Smith JA. For working group of European Society of Pediatric Gastroenterology and Nutrition. Revised criteria for diagnosis of celiac disease. Report of Working group of ESPGHAN. Arch Dis Child. 1990;65:909-11.
17. Malik R, Srivastava A, Yachha SK, Poddar U, Lal R. Childhood abdominal tuberculosis: Disease patterns, diagnosis, and drug resistance. Indian J Gastroenterol. 2015 Nov;34(6):418-25
18. Yachha SK, Poddar U. Celiac disease in India. Indian J Gastroenterol. 2007; 26:230-7.

CHAPTER 78

Approach to Upper Gastrointestinal Bleed in Children

Anshu Srivastava

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a commonly encountered problem in children that usually manifests as hematemesis or melena. The incidence in pediatric intensive care unit (ICU) is reported to vary from 6 to 25% and approximately 5% of UGI endoscopies in children are done for UGIB. Although less than 1% of UGIB is life threatening, medical attention is sought early in majority due to its alarming nature and this helps in prompt diagnosis and management. Children tolerate UGIB better than adults due to absence of systemic comorbidities but are at greater risk of developing shock due to their smaller blood volumes. Approach to a child with UGIB is discussed in this chapter.

DEFINITIONS

Upper gastrointestinal bleeding: this denotes bleeding from a site in the gastrointestinal tract above the ligament of Trietz (esophagus to duodenojejunal flexure).

The common terms used to describe UGIB are as follows:

- Hematemesis is presence of bright red or altered coffee-ground blood in vomiting
- Melena is passage of black, tarry, sticky stools with an offensive smell and suggests an UGI or small bowel site of bleeding
- Hematochezia is passage of bright red blood in stools and is usually seen with bleeding in colon but very brisk UGIB with fast gut transit may also present with hematochezia
- Hemobilia refers to bleeding from the biliary tree and *hemosuccus pancreaticus* to bleeding from the pancreas. In both these conditions, blood enters the duodenum from the common bile duct or pancreatic duct through the ampulla of vater.

Obscure gastrointestinal bleeding (OGIB): bleeding from gastrointestinal tract that persists or recurs without any obvious etiology after a diagnostic esophagogastroduodenoscopy and colonoscopy. It accounts for ~5% of all gastrointestinal bleeds and is classified into two types:

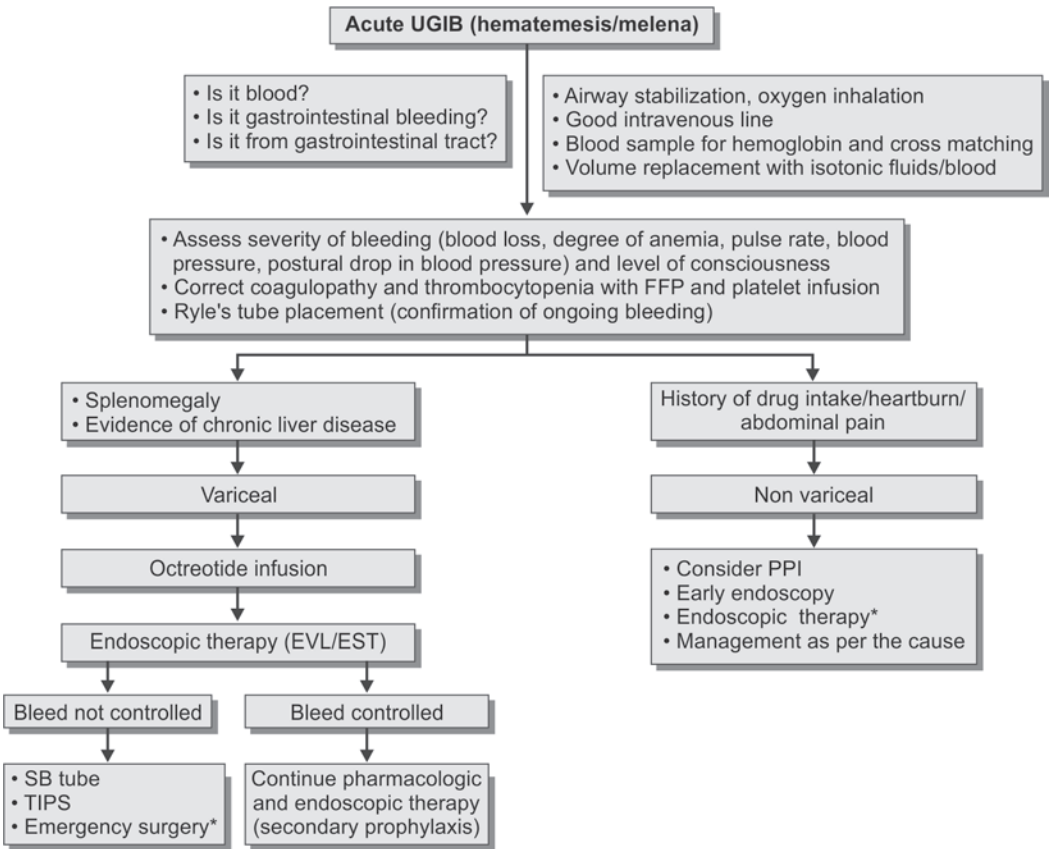
1. Occult OGIB: presents as stool occult blood positivity and iron deficiency anemia
2. Overt OGIB: presents as visible blood in stool and/or vomitus.

Approach: a detailed history, followed by physical examination, is helpful in determining the most probable cause of UGIB. Management includes simultaneous stabilization of child and determination of etiology of UGIB, followed by definitive therapy (Algorithm 1).

- The first question is if the hematemesis and/or melena is due to blood or not, especially in an otherwise healthy child
  - The food items looking like blood in vomitus are shown in box 1
  - An Apt-Downey test is used to differentiate the swallowed maternal blood from hematemesis in a neonate
  - Box 2 shows ingested items which may present as melena. The differentiation is made by performing a guaiac (detects "heme" component of hemoglobin) or fecal immunochemical testing (detects "globin" component of hemoglobin) in stool
- The next step is to differentiate UGIB from epistaxis, oropharyngeal bleeding, and hemoptysis:
  - History of chronic cough and passage of bright red blood associated with sputum indicates toward hemoptysis
  - Nose and oropharynx should be examined to rule out other sites of bleed
  - It is important not to confuse onset of menarche with melena
  - History of bleeding from multiple sites points toward systemic causes like thrombocytopenia and coagulopathy.

ALGORITHM 1

Approach to a patient with acute upper gastrointestinal bleeding



*As per discussion in the text.

EVL, endoscopic variceal ligation; EST, endoscopic sclerotherapy; SB, Sangstaken Blakemore; TIPS, transjugular intrahepatic portosystemic shunt; PPI, proton pump inhibitors.

Box 1: Causes of red colored vomitus (other than upper gastrointestinal bleeding)

- Food items containing red food coloring (jelly, candies, Kool aid, juices)
- Tomatoes, strawberries, beetroot, cranberries
- Ingestion of maternal blood (in neonates)

Box 2: Causes of melena like stools (other than upper gastrointestinal bleeding)

- Food items: ingestion of spinach, licorice, grape juice
- Drugs: peptobismol (contain bismuth), Iron
- Ingestion of maternal blood (in neonates)

The important causes of UGIB in children are given in table 1 and clues in history and physical examination toward the likely cause are shown in table 2.

Clinical Pearl

- Tests for occult blood are required to distinguish blood from other similar appearing substances in vomitus and stool.

TABLE 1: Causes of upper gastrointestinal bleeding

Neonate/infant	Child and adolescent
Swallowed maternal blood	Esophagitis—reflux, infections, pill
Esophagitis	Mallory–Weiss tear
Gastritis, gastroduodenal ulcer/erosion	Caustic ingestion
Foreign body ingestion	Foreign body
Sepsis/coagulopathy/stress erosions	Portal hypertension—esophageal/ gastric varices; congestive gastropathy; gastric antral vascular ectasia
Cow's milk protein allergy	Gastritis, peptic ulcer (duodenal/ gastric)
Hemorrhagic disease of newborn	Arteriovenous malformation
Vascular malformation Esophageal varices	Henoch–Schönlein purpura, Crohn's disease, stress/sepsis/ coagulopathy related erosions
Upper gut duplication	Tumors—leiomyoma, lymphoma
Uncommon: trauma (nasogastric tube), gastric cardia prolapse, heterotopic pancreatic tissue	Rare: gastrointestinal duplication, hemobilia, radiation gastritis, Munchausen's syndrome by proxy

TABLE 2: Clues in history and examination toward etiology of upper gastrointestinal bleeding

Likely diagnosis	Clinical signs/symptoms
Variceal bleeding	• Painless significant bleed, similar episode in the past, splenomegaly, jaundice, ascites
Esophagitis	• Presence of heart burn/regurgitation/dysphagia/odynophagia, placement of Ryle's tube, corrosive intake
Mallory–Weiss tear	• Repeated retching and vomiting followed by hematemesis
Gastritis/erosions/ulcer	• History of drug ingestion like aspirin/non-steroidal anti-inflammatory drugs/steroids • Epigastric pain • Intensive care unit patient on mechanical ventilation • Family history of peptic ulcer disease
Vascular malformation	• Painless bleed, presence of hemangiomas at other sites
Cow's milk protein allergy	• Introduction of animal milk, presence of diarrhea/eczema, family history of atopy
Munchausen's syndrome by proxy	• Complaints disproportionate to examination findings, absence of anemia, negative stool occult blood during active bleeding

MANAGEMENT

The management approach is as shown in algorithm 1. Assessment of severity of bleed and hemodynamic status should be done by measurement and monitoring of heart rate, blood pressure, postural change in blood pressure and heart rate, pulse volume, capillary refill time, oxygen saturation (pulse oxymetry), and urine output.

Minor bleed has no effect on heart rate and blood pressure, moderate bleed is associated with postural hypotension and tachycardia whereas massive bleed is associated with shock (defined in children as tachycardia with signs of decreased organ or peripheral perfusion).

Presence of blood on nasogastric (NG) tube aspiration confirms an UGI source of bleeding. However, absence of blood on NG aspiration does not rule out an UGIB (duodenal source or intermittent bleeding from stomach/esophagus). A serum urea nitrogen to creatinine ratio above 30 also points toward an upper gastrointestinal source of bleeding.

INVESTIGATIONS

Investigations are aimed at establishing the site, severity, and cause of bleeding. Hematocrit (Hct) should be monitored frequently to assess severity of blood loss as the hemoglobin falls only after a few hours, after hemodilution. A complete hemogram including platelet count, coagulation profile (PT/APTT), liver function tests, urea, creatinine, electrolytes, and cross matching should be done in all patients at admission.

Upper gastrointestinal endoscopy is the investigation of choice both for diagnosing the cause and providing therapy. It should preferably be done under general anesthesia or conscious sedation with airway protection to avoid aspiration and only after the patient is hemodynamically stable. The yield of UGI endoscopy is best if it is done within 24 hours of onset of UGIB. A complete examination of esophagus, stomach, and duodenum with retroflexion to inspect the fundus and gastroesophageal junction is essential (Figs 1–3). Biopsy should always be taken to look for helicobacter pylori in patients with gastric/duodenal ulcers.

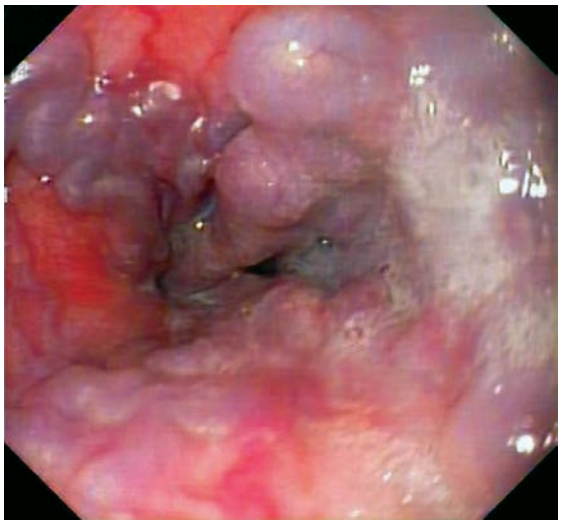


Fig. 1: Upper gastrointestinal endoscopy showing large esophageal varices

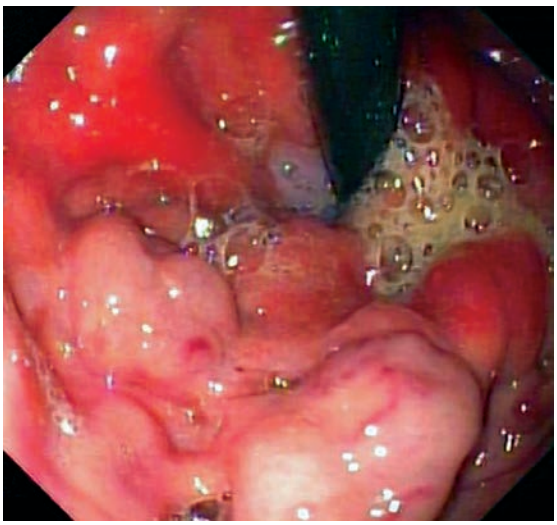


Fig. 2: Upper gastrointestinal endoscopy showing gastric varices with red color signs on retroversion

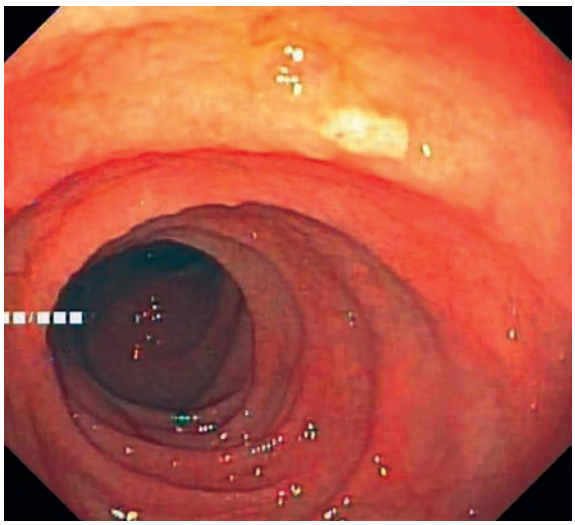


Fig. 3: Upper gastrointestinal endoscopy showing duodenal ulcer without signs of active bleeding

The other investigations which help in reaching a diagnosis are discussed below.

Ultrasonography with Doppler provides information about portal vein, hepatic veins, inferior vena cava, presence of collaterals, etc. and helps in diagnosis of portal hypertension [extra hepatic portal venous obstruction (EHPVO) and chronic liver disease].

Contrast enhanced computed tomography scan: this is useful in evaluation of patients with mass lesions, suspected hemobilia or hemosuccus pancreaticus. Selective angiography of celiac trunk is required in patients where a vascular lesion like pseudoaneurysm is suspected. Therapy with coil/gel embolization can be done at the time of angiography.

Nuclear scintigraphy (technetium 99m labeled pertechnetate scan) is helpful in children suspected to have duplication cyst of proximal gastrointestinal tract.

Enteroscopy (single/double balloon) is required in some cases for evaluation of lesions in distal duodenum (third and fourth part) if the etiology cannot be determined on standard UGI endoscopy.

Clinical Pearls

- Hematocrit should be monitored to assess severity of bleeding as hemoglobin falls later, after hemodilution.
- The yield of upper gastrointestinal endoscopy in patients with upper gastrointestinal endoscopy is maximum if done within 24 hours of onset of bleed.

TREATMENT

The treatment of a child with UGIB depends on the severity of bleeding and has two main arms.

General supportive measures: a good venous access, intake output monitoring, oxygen supplementation (if required), and charting of vitals are mandatory. Blood transfusion should be given to achieve hemoglobin of 7–8 g/dL. Coagulopathy and thrombocytopenia are corrected by appropriate component therapy (plasma, platelets, etc.) if required. Short-term antibiotic prophylaxis (third generation cephalosporin for 7 days), should be given to children with cirrhosis and variceal bleed as it reduces bacterial infection, variceal rebleeding and death.

Specific treatment: the choice of treatment depends upon the patient's condition, available facilities, and expertise of the personnel. Specific treatment can be broadly divided into management of variceal and nonvariceal bleed.

Variceal Bleeding

In a child with portal hypertension, esophageal varices are the most common cause of UGIB (Fig. 1). Gastric varices, congestive gastropathy and gastric antral vascular ectasia can also present with hematemesis.

Somatostatin and octreotide: these drugs decrease the splanchnic and azygous blood flow, thus reducing the portal pressure. Somatostatin and octreotide both are equally effective. Limited studies in children have shown control of bleeding in 64–71% children. Overall, this therapy is well tolerated with mild side effects like hyperglycemia, abdominal discomfort, nausea, and diarrhea which often resolve spontaneously. Infusion should be given for at least 24–48 hours after the bleeding has stopped to prevent recurrence and infusion should not be stopped abruptly. The doses are shown in table 3. Vasopressin, terlipressin, and nitroglycerine are other drugs useful in management of variceal bleed but data are largely limited to adults.

Clinical Pearls

- In patients with upper gastrointestinal endoscopy, transfusion should be given to achieve a hemoglobin of 7–8 g/dL
- Antibiotic should be given to all patients with chronic liver disease and variceal bleeding.

Endoscopic Therapy

Esophageal varices: endoscopic variceal ligation (EVL) and endoscopic sclerotherapy (EST) are the two main methods. The varices are inspected and their location, size, and extent are documented with a fiber-optic endoscope. In EST, 2–3 mL of sclerosant (1% ethoxysclerol) is injected into each variceal column. Endoscopic variceal ligation is done with a device called multiple band ligator. The variceal column is sucked into a cylinder attached at the tip of the endoscope and the band is deployed by pulling the trip wire around the varix. Both EST and EVL have a 90–100% efficacy in controlling acute bleeding. The major complications include esophageal ulceration, stricture esophagus and rarely perforation.

TABLE 3: Drugs used to control upper gastrointestinal bleeding

Drugs for acid suppression	
Antacids	• 0.5–1.0 mL/kg q 4 h PO, titrate to keep gastric pH >4
Ranitidine	• PO 2–4 mg/kg/day q 8–12 h, max 10 mg/kg/d (300 mg) • IV 2–4 mg/kg/day q 8–12 h
Sucralfate	• 0.5–1.0 g PO q 6 h
Proton pump inhibitors	• Omeprazole 0.7–3.3 mg/kg/day single or two divided doses • Lansoprazole 15 mg/day if weight less than 30 kg; 30 mg if weight more than 30 kg • Esomeprazole 10 mg/day if weight <20 kg; 20 mg if weight >20 kg • Proton pump inhibitors infusion for ulcer bleed-intravenous pantoprazole 2 mg/kg (max 80 mg) loading followed by 0.2 mg/kg/h infusion (max 8 mg/h)
Drugs for variceal bleeding	
Vasopressin	• Start at 0.002–0.005 U/kg/min, increase to a max dose of 0.01/U/kg/min
Octreotide	• 1 µg/kg bolus and then 1 µg/kg/h infusion, max 5 µg/kg/h
Somatostatin*	• 250 µg bolus and then 250 µg/h infusion in adults
Terlipressin*	• 2 mg every 4 h IV for 24–48 h, then 1 mg every 4 h in adults

PO, per os; IV, intravenous.

Endoscopic variceal ligation is preferred over EST due to lesser side effects and quicker eradication with less number of sessions. However, EVL cannot be done in children less than 2–3 years due to technical reasons and in them EST is the only option.

Gastric varices: endoscopic injection of tissue adhesive glue, i.e., N-butyl-2-cyanoacrylate or isobutyl-2-cyanoacrylate is used for gastric varices (Fig. 2). These agents harden within 20 seconds of contact with blood, and lead to a more rapid control of active bleeding. Only a small volume (0.5–1 mL) of glue is injected at a time and multiple injections can be done in a single session. Appropriate care must be taken to avoid damage to the endoscope during glue injection. The role of Balloon-occluded retrograde transvenous obliteration in the management of acute gastric varices bleeding is promising but merits further evaluation.

Tamponade of varices: this is required only when the endoscopic and pharmacologic measures have failed. Sangstaken-Blakemore tube (SBT) is a triple lumen tube with connection to an esophageal balloon, a gastric balloon and one perforated distal end which helps in aspiration of the stomach contents. The SBT is relatively cheap, requires little skill vis-à-vis EST and has efficacy of above 75% in controlling acute variceal bleeding. Both pediatric and adult size SBTs are available. The tube is passed through the nose and allowed to reach the stomach. Thereafter, the gastric balloon is inflated with 75–150 mL of air depending on the size of the patient (stomach) and the tube is gently pulled outward so that it sits snugly against the fundus and gastroesophageal junction. A plain X-ray of the abdomen is done to check the proper placement of gastric balloon in the stomach. If the bleeding continues after inflation of gastric balloon then the esophageal balloon is inflated. Esophageal necrosis and perforation, pulmonary aspiration and rebleeding on deflation of balloon are important complications. The esophageal balloon should be deflated after 12–24 hours, and in case of continued bleeding it can be reinflated. However, it should be remembered that SBT is a temporary treatment and efforts should be done to arrange for endoscopic therapy at the earliest.

Transjugular intrahepatic portosystemic shunt (TIPS): it is indicated in patients where the variceal bleeding cannot be controlled by medical and endoscopic measures. The TIPS can be done in cirrhotic patients with a patent splenoportal axis. It is not feasible in patients with EHPVO due to thrombosed portal vein. It involves insertion of a multipurpose catheter through the jugular vein and superior vena cava. The catheter is thereafter passed via hepatic vein into a branch of portal vein through the hepatic parenchyma. The passage is dilated by a balloon and an expansile metallic mesh prosthesis is placed to maintain the communication directly between the portal vein and hepatic vein. This procedure results in bypassing liver resistance and consequently decreases the portal pressure. Experience in children is limited with an overall success rate is approximately 75–85%.

Surgical Management

Emergency surgery is required when all the other therapeutic measures have failed or when bleeding is from ectopic varices that cannot be effectively controlled by endoscopic procedures. Surgery can be done either in the form of portocaval shunt (selective or nonselective) or devascularization with esophageal staple transection.

Acute variceal bleeding (AVB) is a serious and life-threatening complication of patients with portal hypertension. Standard of care mandates early administration of vasoactive drugs followed by endoscopic therapy preferably within 12 hours of bleed. Balloon tamponade followed by TIPS or surgery may be done in patients who fail endoscopic and drug therapy. All patients surviving an episode of AVB should undergo further secondary prophylaxis with EST/EVL to prevent rebleeding.

Nonvariceal Bleeding

The etiology of nonvariceal UGIB is diverse and management largely depends on the cause.

Pharmacological Therapy

Proton pump inhibitors (PPI) promote clot stability and facilitate hemostasis by raising the intragastric pH. Proton pump inhibitors infusion should be initiated in any patient suspected to have nonvariceal bleeding from the upper gastrointestinal tract as it reduces both the incidence of high-risk stigmata of hemorrhage on endoscopy [37.2 vs. 46.5%;

odds ratio (OR) 0.67, 95% confidence interval (CI) 0.54–0.84) and the need for endoscopic hemostasis (8.6 vs. 11.7%; OR 0.68, 0.50–0.93).

Drugs like NSAID/aspirin/anticoagulants should be stopped as far as possible in patients with UGIB.

Specific therapy: antifungal (fluconazole) in esophageal candidiasis and specific antiviral therapy (acyclovir/gancylovir) in esophagitis due to herpes/cytomegalovirus infection is essential.

Helicobacter pylori infection should be looked for and treated in all patients with bleeding peptic ulcers. The high false-negative rate for *H. pylori* testing in the setting of acute UGIB should be remembered. Triple therapy [PPI plus two of the three antibiotics (amoxicillin, clarithromycin, and metronidazole)] for 7–10 days is the treatment of choice.

Dietary changes: stoppage of milk and milk products is required for infants with UGIB due to cow's milk allergy.

Endoscopic Therapy

An early (within 12–24 h) and meticulous UGI endoscopy done after resuscitation of the patient is essential both for finding the cause of NVB and offering therapy. Blood coming from papilla at endoscopy suggests hemobilia or hemosuccus pancreaticus. Pre-endoscopy administration of prokinetic is beneficial in patients at risk of having blood obscuring endoscopic visualization.

Endoscopic biopsies are taken to diagnose *H. pylori* infection in patients with ulcer disease and in those with esophagitis/gastritis. Endoscopic treatment is effective in patients with focal sites of bleeding and involves injection (adrenaline or hypertonic saline), electrocoagulation, heater probes, and hemoclips application.

Peptic ulcer bleeding: endoscopic hemostasis using thermal or mechanical therapies alone or in combination with injection should be done in all patients with high-risk ulcers [Forrest Ia (active spurting bleeding), Ib (active oozing bleeding), IIa (nonbleeding visible vessel), and IIb (adherent clot)].

The intravenous PPI infusion should be continued for 72 hours as it has been shown to decrease rebleeding, need for surgery and also mortality. Patients who have hemodynamic instability, active bleeding at endoscopy, ulcer size over 2 cm, ulcer located in high lesser gastric curvature or posterior duodenum, hemoglobin level less than 10 g/dL, and need for transfusion are at a higher risk of having rebleeding after endoscopic hemostasis. The therapeutic options for patients with postendotherapy rebleeding include repeat endoscopic hemostasis, transcatheter arterial embolization of the bleeding vessel and surgery.

Clinical Pearls

- Intravenous octreotide and proton pump inhibitors infusion should be given to all patients with upper gastrointestinal bleeding due to varices and peptic ulcer, respectively
- Endotherapy (endoscopic variceal ligation/endoscopic sclerotherapy) is the main stay for management of variceal bleeding.

PREVENTION

- Stress ulcers, erosions of the stomach and duodenum are well-known complications of critical illness in children admitted to the pediatric intensive care unit (Fig. 3). Nearly 10% of PICU subjects have UGIB but it is clinically significant only in less than 2% cases. Children with coagulopathy, respiratory failure, and high pediatric risk of mortality score >10 are at an increased risk of bleeding. Although literature is limited, pooled data from two randomized controlled trials shows that prophylactic acid neutralizing treatment was significantly more effective in preventing UGIB compared with no treatment (two studies = 300 participants; relative risk, 0.41; 95% CI 0.19–0.91)
- Secondary prophylaxis for variceal bleeding by EST/EVL as discussed above
- *H. pylori* eradication therapy to prevent recurrence of peptic ulcer. Eradication should be ensured by repeat testing.

CONCLUSION

Acute UGIB is a potentially serious problem in children and presents with hematemesis or melena. As the causes of UGIB vary with age, it is important to evaluate children for the age specific etiologies. Esophagitis, gastritis, and varices are the most common causes of UGIB in Indian children with peptic ulcer disease being uncommon. The approach to diagnosis is largely dictated by the child's condition. Prompt hemodynamic stabilization is of utmost importance and physical examination and blood investigations are done simultaneously. Upper gastrointestinal endoscopy is the most useful diagnostic and therapeutic tool for children presenting with UGIB. Medications like octreotide and PPI are useful in variceal and ulcer bleed respectively with surgery being reserved for cases with continued bleed and failure of endoscopic therapy.

KEY POINTS

- ☞ Upper gastrointestinal bleeding (UGIB) is a common emergency in children and presents as hematemesis or melena
- ☞ Urgent upper gastrointestinal endoscopy should be done after hemodynamic resuscitation to evaluate the cause of bleeding and provide endoscopic therapy
- ☞ In patients with variceal bleeding (esophageal or gastric):
  - Octreotide infusion should be started at admission
  - Blood transfusion should be given to target a hemoglobin of ~8 g/dL
  - Antibiotic should be given in patients with chronic liver disease and variceal bleeding
- ☞ Proton pump inhibitor infusion followed by oral therapy should be given in patients with UGIB due to peptic ulcer disease
- ☞ Specific therapy according to the etiology of UGIB is essential to improve patient outcome
- ☞ Surgery is recommended for children with UGIB and failed medical and endoscopic therapy.

SUGGESTED READINGS

1. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatology. 2005;43:167-76.
2. Eroglu Y, Emerick KM, Whitington PF, Alonso EM. Octreotide therapy for control of acute gastrointestinal bleeding in children. J Pediatr Gastroenterol Nutr. 2004;38:41-7.
3. Franciosi JP, Fiorino K, Ruchelli E. Changing indications for upper endoscopy in children during a 20-year period. J Peadiatr Gastroenterol Nutr. 2010;51:443-7.
4. GarciaPag n JC, Barrufet M, Cardenas A, Escorsell A. Management of gastric varices. Clin Gastroenterol Hepatol. 2014;12:919-28.
5. Hegade VS, Sood R, Mohammed N, Moreea S. Modern management of acute non-variceal upper gastrointestinal bleeding. Postgrad Med J. 2013;89:591-8.
6. Jorge L. Herrera. Management of acute variceal bleeding. Clinics Liver Disease. 2014;18:347-57.
7. Khamaysi I, Gralnek IM. Acute upper gastrointestinal bleeding (UGIB) initial evaluation and management. Best Pract Res Clin Gastroenterol. 2013;27:633-8.
8. Kim SJ, Kim KM. Recent trends in the endoscopic management of variceal bleeding in children. Pediatr Gastroenterol Hepatol Nutr. 2013;16:1-9.
9. Molleston JP. Variceal bleeding in children. J Pediatr Gastroenterol Nutr. 2003;37:538-45.
10. Reveiz L, Guerrero-Lozano R, Camacho A, Yara L, Mosquera PA. Stress ulcer, gastritis, and gastrointestinal bleeding prophylaxis in critically ill pediatric patients: a systematic review. Pediatr Crit Care Med. 2010;11:124-32.
11. The Harriet Lane Handbook, 6th edition. Mosby (An Imprint of Elsevier); 2002.
12. Yachha SK, Khanduri A, Sharma BC, Kumar M. Gastrointestinal bleeding in children. J Gastroenterol Hepatol. 1996;11:903-7.

CHAPTER 79

Management of Lower Gastrointestinal Bleed

Malathi Sathiyasekaran

DEFINITION

Lower gastrointestinal bleed (LGIB) indicates bleeding from sites distal to the ligament of Trietz presenting as bleeding per rectum (PR).

The introduction of capsule endoscopy and double balloon enteroscopy in the diagnostic armamentarium of LGIB has given rise to a new term midgastrointestinal bleeding (MGIB) for a bleed occurring anywhere distal to the ampulla of Vater and up to the ileocecal valve. In this article, both small bowel bleed (MGIB) and colonic bleed have been included in the discussion.

TYPES OF BLEED

Lower gastrointestinal bleed may be overt or occult. Overt bleeding can be acute massive or chronic intermittent and can present as hematochezia (passage of frank blood per rectum), melena or streaks of blood. Occult bleeding is not clinically apparent but becomes manifest by laboratory evidence of iron deficiency or chemical evidence of blood in the stool. Obscure gastrointestinal bleeding refers to a bleed where the bleeding site is not obvious even after evaluation by upper gastrointestinal endoscopy, an ileocolonoscopy, or a contrast radiological study of the small intestine.

INCIDENCE

Lower gastrointestinal bleeding in infants and children is common in clinical practice yet its epidemiology has not been well studied. In an emergency department in Boston, United States, rectal bleeding was the prime complaint in 0.3% of more than 40,000 patients with life-threatening bleed occurring in 4.2%, three of whom had ileocolic intussusception and one Meckel's diverticulum.

ETIOLOGY

The common causes of LGIB in children depend on the age of presentation. In this article, the neonatal causes of LGIB have not been included. The causes of LGIB are:

1. Gastrointestinal (Table 1)
2. Hematological: bleeding disorders, coagulation defects, DIC, thrombocytopenia (dengue, idiopathic thrombocytopenia purpura)
3. Vasculitic disorders: Henoch-Schönlein purpura
4. Connective tissue disorders: Ehlers-Danlos syndrome and Cutis laxa
5. Factitious: various coloring agents, jelly, beetroot, and drugs such as phenolphthalein or rifampicin can color the stool.

TABLE 1: Gastrointestinal causes

1 month to 2 years	2 to 12 years	12–18 years
Anal fissure	Anal fissure	Anal fissure
Cow's milk protein allergy	Juvenile polyp	Infection colitis
Infectious/Allergic colitis	Infectious colitis	Inflammatory bowel disease
Lymphonodular hyperplasia	Inflammatory bowel disease	Solitary rectal ulcer
Meckel's diverticulum	Solitary rectal ulcer	Colonic polyp
Intussusception	Intussusception	Hemorrhoids
Volvulus	Intestinal duplication	Intestinal duplication
Segmental enteritis	Segmental enteritis	Segmental enteritis
Vascular malformations	Vascular malformations	Vascular malformations

MANAGEMENT OF LOWER GASTROINTESTINAL BLEED

Clinical Evaluation

A focused yet detailed history and physical examination are essential in the evaluation of all children with LGIB.

History

A meticulous history including details such as whether bleed is major or minor, chronic recurrent or acute massive, treatment, and associated symptoms. Details of the bleed such as duration, number of episodes, frequency, volume, color, presence of clots, mucus, frank bleed, or mixed with feces should be obtained. History will help in establishing the site and probable etiology.

Site of bleed: 10% of UGIB may present with bleeding PR. Hematemesis is suggestive of UGIB. Similarly, melena is more often seen in UGIB, whereas hematochezia is usually from small bowel or colon. Specks or streaks of bright red blood indicate bleed from anorectal region.

Etiology: acute massive bleed may be due to Meckel's diverticulum, intestinal duplication, or arteriovenous malformation. Eliciting certain associated symptoms in the history help in determining the etiology of LGIB:

- Crampy abdominal pain and frequent loose stools mixed with mucus and blood suggest an infectious, inflammatory, or ischemic pathology
- Painless bleeding is more typical of a colonic polyp, Meckel's diverticulum, ulcerated duplication, or vascular malformation
- Painful defecation with streaks of blood suggests anal fissure
- Colicky abdominal pain, vomiting, red currant jelly stool, and mass abdomen are suggestive of intussusception
- Constipation, mucorrhea, small rectal bleed, with or without digital evacuation, and rectal prolapse may suggest solitary rectal ulcer syndrome (SRUS)
- Recent antibiotic administration followed by passage of blood and mucus in stools would indicate antibiotic associated colitis or pseudomembranous colitis
- An infant with stools mixed with blood following introduction of bovine milk protein one should suspect Cow's milk protein allergy
- An infant of normal weight on breast milk with blood in the stool may have benign allergic proctocolitis due to transfer of allergen through breast milk
- Passage of large volume, maroon or bright red blood requiring blood transfusions suspect Meckel's diverticulum, intestinal duplication, or arteriovenous malformation
- Mass prolapsing per rectum with bleeding could be due to a prolapsing polyp, prolapse rectum, or an intussusceptum vascular. A polyp is globular and prolapses soon after defecation, a prolapse is circumferential with a central lumen whereas in intussusception severe pain is a characteristic feature
- A family history of bleeding PR requiring surgical intervention polyposis coli may be a possibility
- Failure to thrive, recurrent infections with bleeding PR may point to immune deficiencies either congenital or human immunodeficiency virus related
- History of ingestion of beet or coloring agents suggests factitious bleed
- History of recurrent petechiae, ecchymosis, or epistaxis in addition to bleeding PR may suggest a hematological disorder
- Abdominal pain, diarrhea, loss of weight, pedal edema, and fever suggests inflammatory bowel disease (IBD)
- History of abdominal pain, bleeding PR with rash on legs and gluteal region suggests Henoch-Schönlein purpura
- History of fever, rash, features of third spacing, and bleeding PR consider dengue fever
- Cutaneous hemangioma and bleeding PR suspect blue rubber bleb nevus syndrome (Fig. 1)
- Family history of bleeding PR, buccal pigmentation consider Peutz Jegher's syndrome (Fig. 2)
- Telengiectasia on fingers and lips with bleeding PR consider hereditary hemorrhagic telangiectasia

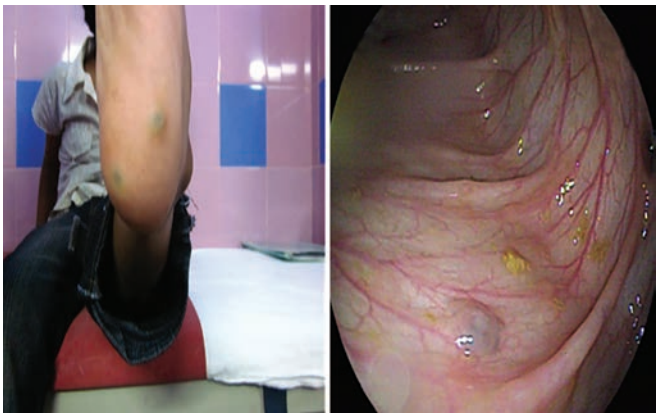


Fig. 1: Bluish black hemangiomas on the sole and hemangiomas on colonoscopy (blue rubber bleb nevus syndrome)

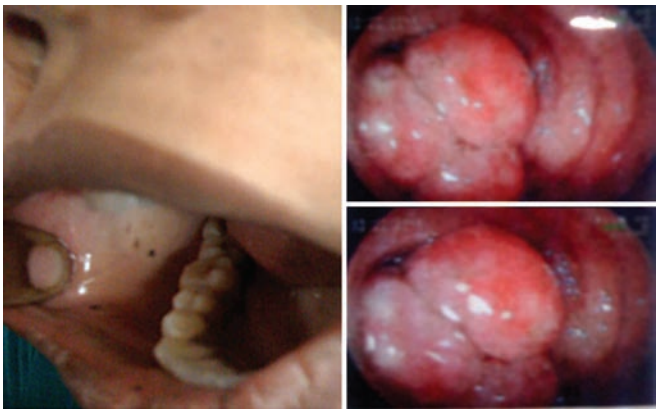


Fig. 2: Oral buccal mucosal pigmentation and colonic polyps (Peutz Jegher's syndrome)

Examination

General: in children with acute lower gastrointestinal bleed whether major or minor a complete examination including vital signs is necessary.

Skin: examination of the skin for petechia, ecchymosis, palpable purpura (Figs 3 and 4) and hemangiomas, buccal pigmentation, and café au lait spots to exclude familial syndromes.

Abdomen: Splenomegaly may indicate portal hypertension. Right upper quadrant mass may indicate intussusception. Distended abdomen with dilated bowel loops suggests intestinal obstruction, volvulus, gangrene, or segmental enteritis.

Perianal examination: the presence of skin tags, perianal fistula or fissure may be markers of IBD.

Investigations

Laboratory studies: basic investigations such as hemoglobin, total and differential white blood cell count, platelet, bleeding time, clotting time, and prothrombin time are included in the investigative panel. Refractory iron deficiency anemia is an important manifestation of occult gastrointestinal bleed and should be evaluated diligently.

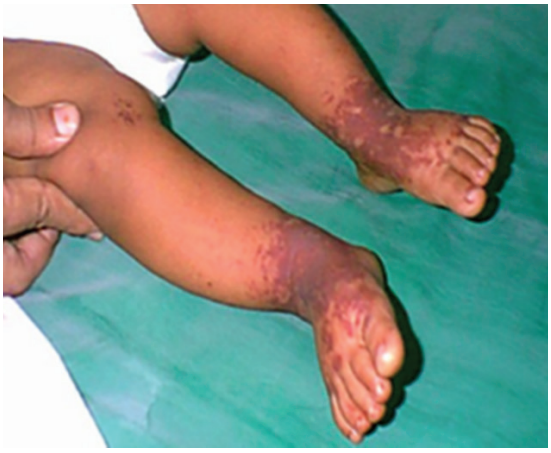


Fig. 3: Infant with dengue and thrombocytopenia with ecchymosis both ankles

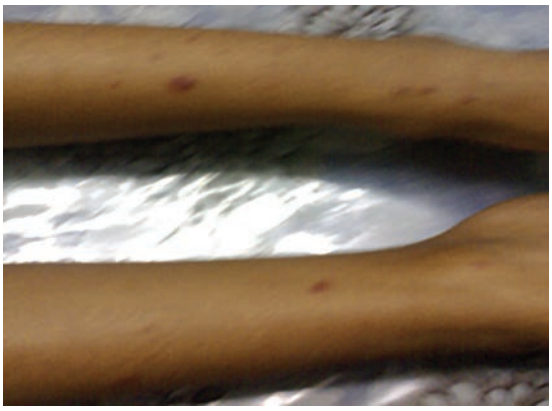


Fig. 4: Palpable Henoch-Schonlein purpura

Stool examination: a simple macroscopic examination of the stool is essential before considering sophisticated investigations.

Microscopic examination: if the stools show more than 10 pus cells/HPF it may indicate an invasive form of colitis. Presence of numerous eosinophils would suggest an allergic colitis or cow's milk protein allergy. The presence of trophozoites with hemophagocytosis would be diagnostic of *Entamoeba histolytica* infection. If the clinical setting is suggestive of infectious colitis then stool culture for *Shigella*, *Salmonella*, and *Campylobacter jejuni* may be helpful. Occult bleeding is identified by testing stool for occult blood.

Radiology: plain X-ray abdomen is done when there is pain, bilious vomiting, or features of intermittent intestinal obstruction. Ultrasonography can detect bowel wall thickening pseudokidney appearance or identify characteristic features of intussusception such as target sign (Fig. 5). Air contrast or saline contrast enema helps not only to confirm but also treat ileocolonic intussusception. Computerized tomography or magnetic resonance angiography is generally reserved for evaluation of mass lesions or complex vascular anomalies. Endosonography helps in the visualization of submucosal lesions and arteriovenous malformations.

Radionuclide studies: scintigraphy is useful in the evaluation of children with obscure but active LGI bleed of at least 0.1 mL/minute. In young children with acute massive bleed if Meckel's diverticulum or duplication cyst is suspected radionuclide studies may be done even prior to endoscopy. Radionuclide study using technetium-99m (Tc99m) pertechnetate helps to identify ectopic gastric mucosa within a Meckel's diverticulum or a duplication cyst with a sensitivity of 85%, specificity 95%. Technetium-labeled red blood cells identifies arteriovenous malformations and bleeding ulcers.

Endoscopy: when the bleed is chronic and intermittent ileocolonoscopy is preferred as the first line of investigation. Upper gastrointestinal endoscopy should always be done along with ileocolonoscopy since 10% of upper gastrointestinal bleed can present as bleeding per rectum.

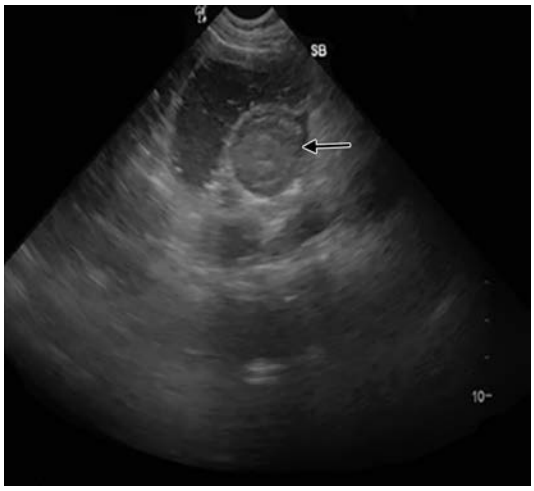


Fig. 5: Abdominal ultrasound showing target sign "intussusception"

Ileocolonoscopy: early colonoscopy helps both in diagnosis and therapy of mucosal lesions of the colon. The overall yield ranges from 69 to 80%. Bowel preparation is safely achieved in children using a standard oral polyethylene-glycol electrolyte solution. Ileocolonoscopy helps both in the diagnosis and therapy of LGIB. The majority of mucosal lesions, such as allergic colitis, polyps, solitary rectal ulcer, IBD, vascular malformations, rectal varices, portal colopathy (Figs 6–12), can be diagnosed. Biopsy of the mucosal lesions will help in confirming the etiology.

Additional Procedures

The above investigations will suffice to identify the source of bleeding in the majority of children with LGIB. However, in a small percentage (3–5%), the source will remain obscure necessitating small bowel examination, either with triple vessel arteriography, small bowel enema, magnetic resonance enteroclysis, enteroscopy, or intraoperative enteroscopy.

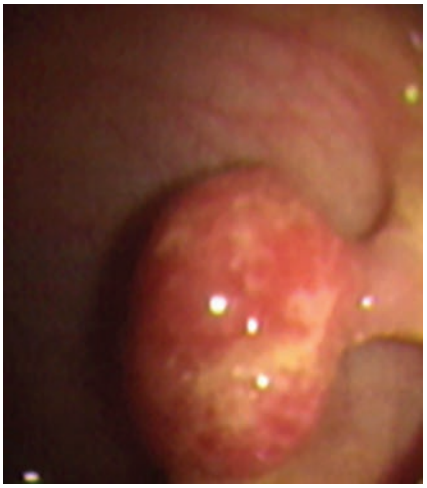


Fig. 8: Colonic polyp

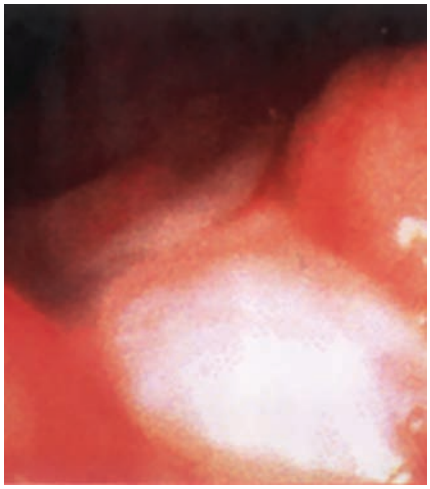


Fig. 6: Solitary rectal ulcer

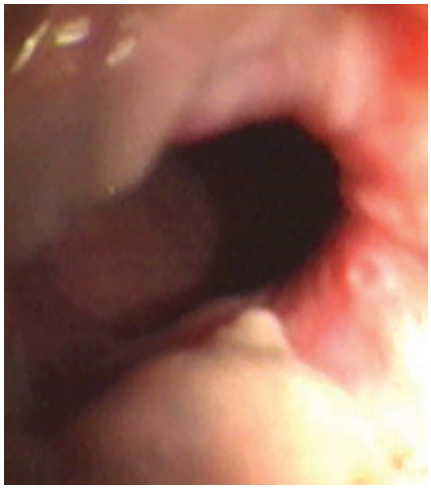


Fig. 9: Ano fissure

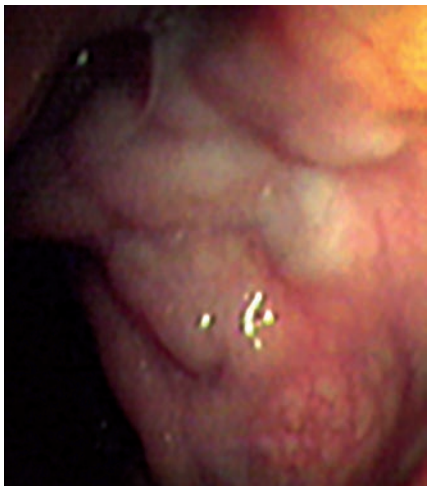


Fig. 7: Rectal varices

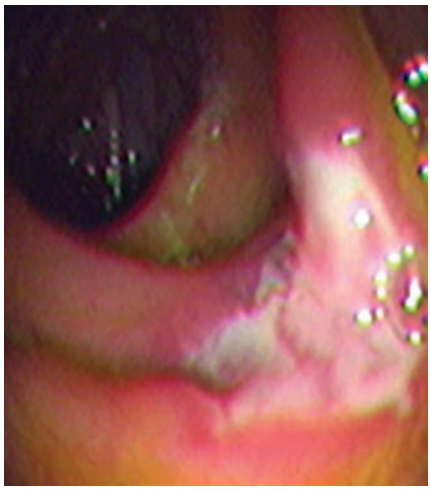


Fig. 10: Irregular colonic ulcer: Crohn's disease

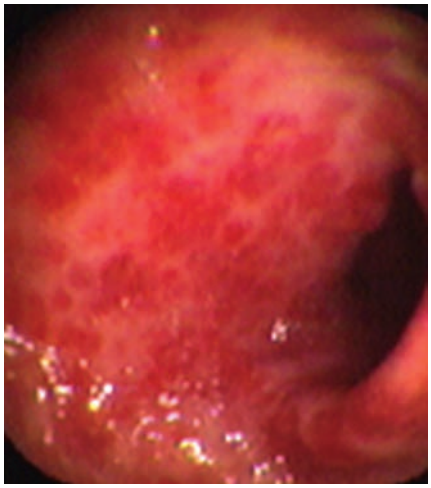


Fig. 11: Severe ulcerative colitis

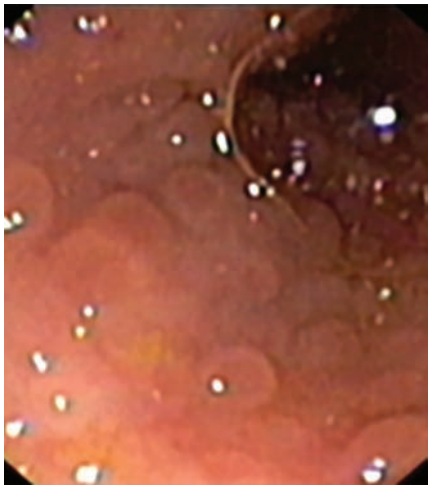


Fig. 12: Nodular lymphoid hyperplasia cow's-milk protein allergy

Triple Arteriography

This is rarely necessary in children with LGIB. It is, however, useful in obscure small bowel bleed if there is active bleeding of at least 0.5 mL/minute. The advantage of arteriography is that it helps both in localization and embolization of the lesion.

Double Balloon Enteroscopy

This procedure helps in visualizing the entire small bowel up to the ileocecal valve. It is not regularly used in pediatrics but may be warranted in older children and adolescents with obscure LGIB.

Capsule Endoscopy

Children more than 5 years of age can swallow the capsule but in younger children, it can be introduced endoscopically. Capsule endoscopy is an excellent modality for identifying obscure gastrointestinal bleed. The detection rate is higher (87–92%) if the procedure is done during active bleed. Impaction of the capsule may occur if there is an underlying stricture

Intraoperative Enteroscopy

In this procedure, both surgeon and endoscopist work as a team in the evaluation of a child with LGIB. A pediatric colonoscope or enteroscope can be negotiated through an operative enterotomy and the small bowel visualized. It helps in detecting the majority more than 85% of obscure small bowel bleeding lesions. The surgeon guides the intestine over the scope and examines the outer serosa by palpation and transillumination while the endoscopist examines the inner mucosa.

Diagnostic Laparoscopy/Laparotomy

In children with recurrent gastrointestinal bleed, and if investigations are futile, it may be worthwhile performing a diagnostic laparoscopy to identify lesions such as enteric duplication cyst.

Management

The management of lower GI bleed includes prompt resuscitative measures and treatment of the specific condition by five distinct modalities such as diet modification, medications, endotherapy, radiological intervention, and surgery.

Diet

- Cow's-milk protein allergy (CMPA): avoidance of bovine milk protein and milk products till the age of 9 months to 1 year is recommended for all infants diagnosed as having significant CMPA. Majority will be able to tolerate cow's milk protein by the age of 3–5 years
- Fissure in ano and solitary rectal ulcer syndrome (SRUS): introduction of fruits and vegetables to increase bulk and fiber will benefit children with LGIB due to fissure in ano or SRUS.

Medications

- Bacillary dysentery: in India, the recommendation is to consider infectious colitis as *Shigella colitis* and treat with oral cefixime 10 mg/kg/day for 7 days if child is ambulant and with intravenous ceftriaxone 100 mg/kg for those hospitalized
- Amoebic colitis: routine antiamebic medication should not be prescribed for children with acute colitis. Metronidazole 10 mg/kg/day thrice a day for 5 days is given only if trophozoite with hemophagocytosis suggestive of *Entamoeba histolytica* is identified or in spite of two antibiotics which are known to be sensitive for *Shigella* in that region have been administered and the child has persistence of symptoms
- Ulcer bleeds: proton pump inhibitors like omeprazole at a dose of 0.7 to 1 mg/kg/day or H2 blockers, such as ranitidine at a dose of 4–6 mg/kg/day, can be administered or orally if the bleed is secondary to duodenal ulcer, gastric ulcer, or nonsteroidal anti-inflammatory drugs induced gastrointestinal injury. Proton pump inhibitors score over

ranitidine in controlling ulcer bleeds and is recommended at a dose of 1 mg/kg and given slow intravenous followed by infusion

- Coagulopathy: injection of vitamin K (1 mg/year of age, maximum 10 mg) intravenous/intramuscular is given when the bleed occurs in individuals with colopathy and hepatocellular dysfunction. Fresh frozen plasma (FFP) may be necessary in children with prolonged international normalized ratio not responding to injection of vitamin K
- Thrombocytopenia and coagulopathy: in children with LGIB secondary to thrombocytopenia as in dengue fever or dengue shock syndrome platelet transfusion, FFP and rarely recombinant factor V may be required
- Variceal bleed: the role of octreotide and somatostatin is well established in acute variceal bleed. When the bleed is nonvariceal, somatostatin and its analog octreotide (1–2 μg/kg bolus followed by 1 μg/kg/hour continuous intravenous or 1 μg/kg every 8–12 hours subcutaneously for 24–48 hours) may reduce the risk of continued or recurrent bleeding. These vasoactives act by reducing the splanchnic flow and may help in tiding over the crisis till active intervention is available
- Inflammatory bowel disease: in IBD, the bleeding stops once the activity of the disease is controlled. Inflammatory bowel disease is managed according to the severity of disease. Five amino salicylic acid 40–50 mg/kg/day is initiated in children with mild ulcerative colitis (UC) and mild Crohn's disease (CD). Steroids at a dose of 1 mg/kg/day is given for induction of remission and tapered over a period of 12 weeks in moderate UC or CD. Immunomodulators such as azathioprine 6 mercaptopurine are excellent steroid sparing agents and used in the phase of maintenance
- Anal fissure can be managed with stool softeners and high fiber diet
- Solitary rectal ulcer syndrome is managed by encouraging the child to increase fiber in the diet and thus avoiding constipation and straining during defecation. The child is trained to acquire a proper and regular bowel habit. In some situations, several sittings of biofeed back therapy may be required. Various modalities of topical therapy have been tried such as 5 amino salicylic acid suppository and sucralfate enema. When the bleed is severe and not responding to dietary modifications Argon plasma coagulation and surgery may be recommended.

Endotherapy

- If SRUS does not respond to medications, endoscopic laserization with argon plasma can be attempted
- Colonic polyps are managed by endoscopic polypectomy

Interventional Radiology

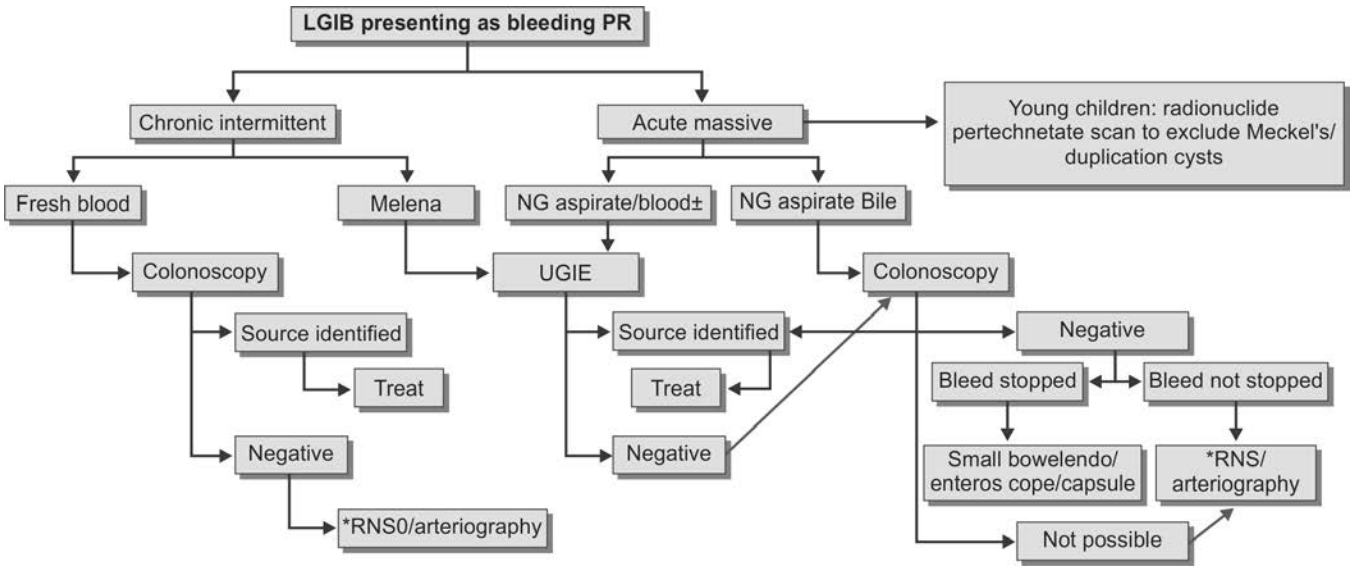
- Intussusception in infants less than 2 years can be reduced either with air or saline enema
- When the bleed occurs due to an arteriovascular malformation or a bleeding, aneurysm embolization using coils is an excellent method to arrest the bleed.

Surgery

- Children with familial polyposis coli are advised total colectomy to prevent malignancy
- Intussusception which has not been reduced by pneumatic reduction should be tackled surgically
- Meckel's diverticulum, volvulus, and duplication are all managed surgically.

ALGORITHM 1

Management of lower gastrointestinal bleeding after stabilization of child



*Radionuclide studies RBC tagged/pertechnetate.

LGIB, lower gastrointestinal bleeding; RNS, radio nuclide studies; UGIE, upper gastrointestinal endocospy.

CONCLUSION

Lower gastrointestinal bleed presenting as bleeding per rectum is a common problem in children and may be due to several causes. The bleed may be very insignificant or sinister. A careful detailed history and clinical examination will help in diagnosis. Since acute massive bleed in young children is usually due to Meckel's diverticulum or duplication cysts, radio nuclide scan using Tc99m pertechnetate may be done as a precedent to ileocolonoscopy. The given algorithm 1 for LGIB should be modified according to the age of the child, clinical presentation, and feasibility of investigation.

Clinical Pearls

- Lower gastrointestinal bleed may be insignificant or sinister in presentation
- Detailed history and simple macroscopic examination of stool is the most important tool in evaluation
- Meckel's scan should be included in the initial diagnostic workup of infants with acute massive bleed
- Ileocolonoscopy is a safe procedure for both diagnosis and therapy of lower gastrointestinal bleeding.

KEY POINTS

- ☞ Lower gastrointestinal (GI) bleeding may be due to GI and non-GI causes
- ☞ Lower gastrointestinal bleeding (LGIB) may be chronic intermittent or acute massive
- ☞ Essential to evaluate and identify the etiology
- ☞ In acute massive GI bleed, radio nuclide scan may be done prior to endoscopy
- ☞ Ileocolonoscopy should be included in the protocol
- ☞ Surgery is indicated in some select conditions of LGIB.

SUGGESTED READINGS

1. Abraldes JG, Bosch K. Somatostatin and analogues in portal hypertension. Hepatology. 2002;35:1305-12.
2. Arguelles-Arias F, Caunedo A, Romero J, S nchez A, Rodrguez-T llez M, Pellicer FJ, et al. The value of capsule endoscopy in pediatric patients with a suspicion of Crohns disease. Endoscopy. 2004;36:869-73.
3. Chaudhary V, Hyser MJ, Gracias VH, Gau FC. Colonoscopy: the initial test for acute lower gastrointestinal bleeding. Am Surg. 1998;64:723-8.
4. Ell C, May A. Mid-gastrointestinal bleeding: capsule endoscopy and push-and-pull enteroscopy give rise to a new medical term. Endoscopy. 2006;38(1):73-5.
5. Fox VL. Gastrointestinal bleeding in infancy and childhood. Gastroenterol. Clin N Amer. 2000;29:36-64.
6. Khurana AK, Saraya A, Jain N, Chandra M, Kulshreshta R. Profile of lower gastrointestinal bleeding in children from a tropical country. Tropical Gastroenterol. 1998;19:70-1.
7. Lacroix J, Nadeau D, Laberge S, Gauthier M, Lapierre G, Farrell CA. Frequency of upper gastrointestinal bleeding in a pediatric intensive care unit. Crit Care Med. 1992;20:35-42.
8. Leung Alexander KC, Wong AL. Lower gastrointestinal bleeding in children. Pediatr Emeg Care. 2002:18:319-23.
9. Pandey S, Srivastava A, Lal R, Yachha SK, Poddar U. Enteric duplication cysts in children: A target in algorithm for evaluation of lower gastrointestinal bleeding. Indian J Gastroenterol. 2014;33:285-8.
10. Poddar U, Thapa BR, Vaiphei K, Singh K. Colonic polyps: experience of 236 children. Am J Gastroenterol. 1998;93:619-22.
11. Siafakas C, Fox VL, Nurko S. Use of octreotide for the treatment of severe gastrointestinal bleeding in children. J Pediatr Gastroentrol Nutr. 1998;26:356-9.
12. Strate LL. Lower GI bleeding:epidemiology and diagnosis. Gastroenterol Clin N Am. 2005:34:643-64.
13. Vinton NE. Gastrointestinal bleeding in infancy and childhood. Gastroent Clin N Amer. 1994;93-188.

CHAPTER 80

Acute Liver Failure

Vidyut Bhatia, Anupam Sibal, Akshay Kapoor

INTRODUCTION

Acute liver failure (ALF) is a devastating illness associated with high mortality mainly due to rapid death or injury to a large proportion of hepatocytes, leaving insufficient functional hepatocytes to sustain life. Acute liver failure is a multisystem disorder wherein liver cell function dysfunction and coagulopathy exist with or without the presence of encephalopathy. Recently, the gastroenterology chapter of Indian Academy of Pediatrics (IAP) has published guidelines for the management of ALF. The management of ALF described in this chapter is largely based on the IAP guidelines.

DEFINITION AND DIAGNOSIS

Earlier classification of ALF was based on the time interval between jaundice and onset of encephalopathy. However, this definition failed to capture the complexities associated with ALF in infants and children. Since in most young children and infants it is difficult to define and classify encephalopathy, the current definition relies more on coagulopathy as an index of liver function.

The consensus report of the gastroenterology subspeciality chapter of IAP has defined ALF as "Severe hepatocellular injury presenting with biochemical evidence of liver injury and uncorrectable coagulopathy 6–8 hours after one dose of parenteral Vitamin K. Uncorrectable coagulopathy is defined as INR >1.5 in patients with HE or INR >2.0 in patients without HE, with no previous evidence of CLD".

As noted above, staging of hepatic encephalopathy in infants and young children is difficult as compared to adults. The grading as recommended by the guidelines is as follows. Grades I and II are indistinguishable with clinical features of inconsolable cry and poor attention to tasks, inappropriate behavior, and hyperreflexia. In grade III, somnolence, stupor, combativeness, and hyperreflexia are present. In grade IV, the child is comatose, arousable with painful stimuli (IVa) or no response (IVb). Reflexes are absent and neurological manifestations like decerebration or decortication are seen.

Clinical Pearl

- Encephalopathy is not essential to make a diagnosis of acute liver failure in children.

ETIOLOGY OF ACUTE LIVER FAILURE IN INDIA

Acute viral hepatitis is the most common cause of ALF either alone or in combination with other etiologies. The other underlying causes of ALF are given in table 1.

DIAGNOSTIC WORK-UP

Table 2 summarizes the diagnostic work-up necessary to establish the etiology of ALF. An approach to a child presenting with features of acute liver diseases is presented in algorithm 1.

TRANSPORT AND INITIAL MANAGEMENT

The main objective of transporting a child with ALF is to ensure safe and timely transfer to a tertiary center with liver transplant facilities. It is important to act early because the risks involved with patient transport may increase or even preclude transfer once deeper stages of encephalopathy are reached. Any child who develops grade III encephalopathy should be intubated and the airway secured before transport. A continuous monitoring of vital parameters should be available during transport.

TABLE 1: Underlying etiology of acute liver failure in children

Infections	Acute viral hepatitis (A, E, B)
Drugs	Valproate, isoniazid, paracetamol
Toxins	Iron, herbal medicines, mushroom
Metabolic	Wilson's disease, galactosemia, tyrosinemia type 1, fructosemia
Vascular	Budd-Chiari, veno-occlusive disease
Autoimmune	Autoimmune liver disease
Idiopathic	–

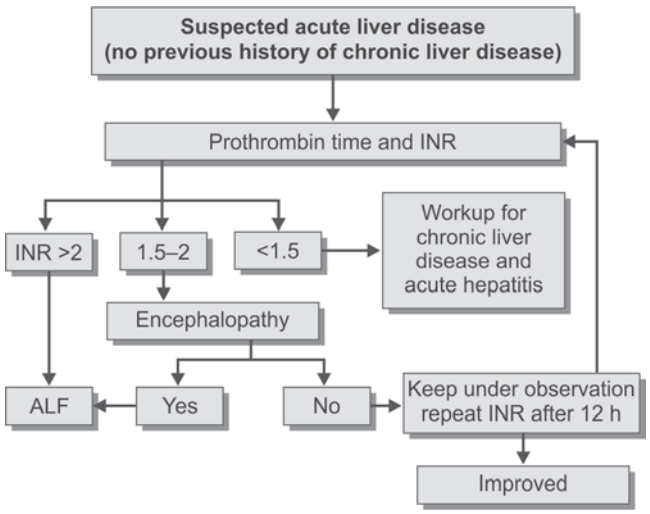
TABLE 2: Diagnostic workup for acute liver failure in children

General workup	Total and conjugated bilirubin, AST, ALT, GGTP, alkaline phosphatase, prothrombin time (INR), PTTK, hemogram, serum electrolytes, blood urea, creatinine, blood and urine cultures, blood group, chest X-ray, serum α-fetoprotein, lactate, lactate dehydrogenase, blood ammonia, ABG, urine for reducing substances, G6PD levels
Specific workup	
Infectious	IgM anti-HAV, IgM anti-HEV, HBsAg, IgM anti-hepatitis B core antigen, CMV PCR, IgM varicella zoster virus, IgM Epstein-Barr virus, HIV 1,2
Wilson's disease	Serum ceruloplasmin, 24 urinary copper estimation, KF ring
Autoimmune	Coombs test, antinuclear antibody (>1:40), liver kidney microsomal antibody, smooth muscle antibody (>1:20), IgG levels
Hemophago-cytosis	Serum triglyceride, cholesterol, ferritin, and bone marrow biopsy
Drug overdose	Acetaminophen, valproate drug levels

AST, aspartate transaminase; ALT, alanine transaminase; GGTP, gamma-glutamyl transpeptidase; INR, international normalized ratio; PTTK, partial thromboplastin time activated with Kaolin; G6PD, glucose-6-phosphate dehydrogenase deficiency; ABG, arterial blood gas; Ig, immunoglobulin; HAV, hepatitis A virus; HEV, hepatitis E virus; HBsAg, hepatitis B surface antigen; CMV, cytomegalovirus; PCR, polymerase chain reaction KF, Kayser-Fleischer.

ALGORITHM 1

Approch to a child with acute liver disease



INR, international normalized ratio; ALF, acute liver failure.

The management of child with ALF should always be done in the intensive care unit of the hospital. Initial management includes placement of a central venous catheter line, volume resuscitation as per protocol, glucose given at least 4–6 mg/kg/min, so as to keep the blood glucose level between 120–200 mg/dL, and use of vasoactive drugs if required. All such medications that decrease the level of consciousness should be avoided to prevent worsening of encephalopathy. If sedation is mandatory (e.g., for intubation) a short acting agent like propofol can be given.

Clinical Pearl

- Sedation should be given to a child only when support for intubation and ventilation is available.

SUPPORTIVE MANAGEMENT

Medications or devices that may support a failing liver is the holy grail of current hepatology research on the management of ALF. Most of the drugs currently being used have not undergone vigorous clinical trials before being used in the management of ALF. N-acetyl cysteine (NAC) has been used in the management of ALF secondary to acetaminophen poisoning. There is increasing evidence for its use in non-acetaminophen causes of ALF. NAC can be used in the dose of 100 mg/kg/24 hours. Its role has been questioned by a recent multicentric study, wherein it was seen as no better than placebo. However, most patients in this study were not infectious hepatitis related (only 10%), and a large proportion of the (50%) patients were found to be ineligible for the study (50% of these are recorded as "reasons unknown"). Moreover, the study was conducted over a period of 9 years leading to heterogeneity in treatment received over the years as treatment modalities do change with time.

Ammonia is an accepted triggering factor in cerebral edema; however, agents that decrease blood ammonia levels (L-ornithine L-aspartate, lactulose and other non-absorbable antibiotics) have not been found to be beneficial. Protein restriction in children with hepatic encephalopathy is no longer recommended. Energy intakes should be increased appropriately to counter catabolic stat. Prophylactic administration of proton pump inhibitors in ALF is found to be useful as it is helpful in prevention of gastrointestinal hemorrhage.

Specific therapy should be administered if the underlying cause of ALF has been determined (Box 1).

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE

Raised intracranial pressure more than 20 mmHg occurring as a consequence of cerebral edema is one of the leading causes of mortality in ALF. Sustained severe hypertension, bradycardia, pupillary changes, reflexes (brisk—sluggish), muscle tone changes, and decerebrate posturing are clinical indicators of presence of cerebral edema.

Children with lower grade encephalopathy (I–II) should be managed in a quiet environment and general measures such as treating fever, infection, and seizures must be implemented. However, if encephalopathy progresses to a higher grade, endotracheal intubation must be done.

Prophylactic administration of 3% saline to maintain sodium at 145–155 mmol/L in patients with severe encephalopathy is recommended over mannitol. However, once obvious neurological signs develop, a bolus of intravenous mannitol (0.25–1 g/kg, 20% mannitol) over 15 minutes must be given. This can be repeated if serum osmolality is less than 320 mOsmol/L.

Box 1: Specific therapy of common causes of pediatric acute liver failure

Neonatal hemochromatosis
- High-dose of intravenous immunoglobulin in combination with exchange transfusion
- Liver transplantation if no improvement is seen

Herpes simplex
- High dose acyclovir 60 mg/kg/day for 21 days, continued till polymerase chain reaction is negative

Type 1 tyrosinemia
- Nitisinone 1 mg/kg/day per os divided bid
- Dietary restrictions of phenylalanine and tyrosine
- Liver transplantation if no improvement is seen

Galactosemia
- Lactose-free diet, avoid galactose containing dietary items

Hereditary fructose intolerance
- Fructose-free diets, avoid fructose and sorbitol infusions

Acetaminophen poisoning
- N-acetyl cysteine

Mitochondrial cytopathies
- Electron acceptors and cofactors: coenzyme Q10: 3–5 mg/kg
- Antioxidants: vitamin E: 25 IU/kg
- Carnitine: 50–100 mg/kg

Wilson's disease (therapy based on scoring system)
- D-penicillamine/trientine (20 mg/kg/day) may be administered
- Liver transplantation

Clinical Pearl

- Three percent saline is preferred to 20% mannitol for decreasing raised ICP in children with acute liver failure.

COAGULOPATHY

Patients with ALF develop failure of synthesis of clotting factors, altered platelet number and function, intravascular coagulation, and altered blood vessel wall integrity. Routine correction of coagulopathy or thrombocytopenia is not recommended. Prophylactic fresh frozen plasma (FFP) is not recommended, as it does not reduce the risk of significant bleeding nor transfusion requirements and obscures the trend of international normalized ratio (INR) as a prognostic marker. However, replacement with FFP is recommended in patients with clinically significant bleeding, while performing invasive procedures or in situations where INR >7. Single dose of vitamin K1 (5–10 mg, slowly not more than 1 mg/min) is recommended empirically in all patients with ALF. According to the consensus statement, platelet transfusion is not recommended unless a threshold platelet count of 10,000–20,000/mm^3 is reached or there is significant bleeding and thrombocytopenia less than 50,000 per cubic millimeter. A platelet count of 50–70,000/mm^3 is usually considered adequate when an invasive procedure is to be performed.

Clinical Pearl

- Prophylactic fresh frozen plasma is only recommended when any invasive procedure is attempted.

SEPSIS

Infection remains one of the major causes of death in patients with ALF. The reasons for increased sepsis in these children are management in intensive care with invasive modalities, neutropenia (secondary to bone marrow suppression), deranged neutrophil function (due to defective sodium pump) and defective opsonization (due to decreased plasma complement).

The most commonly isolated organisms are Gram-positive cocci (*Staphylococci, Streptococci*), enteric Gram-negative bacilli, and *Candida albicans*. Prophylactic antibiotics or antifungals have not been shown to improve outcome or survival in patients with ALF. However, as suggested in the recommendations, "empirical administration of antibiotics is recommended when

- Infection or the likelihood of impending sepsis is high, e.g., surveillance cultures reveal significant isolates
- Progression of, or advanced stage (III/IV) HE
- Refractory hypotension
- Renal failure
- Presence of systemic inflammatory response syndrome components (temperature >38 or <36°C, white blood count >12,000 or <4,000/mm^3, tachycardia)
- Empirical antibiotics are also recommended for patients listed for liver transplantation, since infection often results in delisting or delay and immunosuppression postliver transplantation is imminent."

Broad-spectrum coverage with a third-generation cephalosporin and an antifungal have been recommended.

LIVER ASSIST DEVICES

The high cost of liver transplantation, lifetime immunosuppression, limited availability of donors, and risk of death while awaiting liver transplantation have stimulated the development of liver assist devices (LAD) and other modalities like plasmapheresis, exchange transfusions, extracorporal blood cleansing, devices containing cultured hepatocytes, cross-circulation with animals, and molecular adsorbent recirculating system. Experience on the use of LAD in children is limited and restricted to case reports or small series.

HEPATOCYTE TRANSPLANTATION

Hepatocyte transplantation has been performed in patients with ALF as a potential alternative to liver transplantation. Cryopreserved hepatocytes are usually infused into the intrahepatic portal vein with many cells rapidly cleared by the innate immune system, which needs to be prevented. Newer methods that utilize encapsulation of hepatocytes are being used through the intraperitoneal route in ALF with the advantage of avoiding immunosuppression.

CRITERIA FOR LIVER TRANSPLANTATION

Liver transplantation is the only definite treatment available for ALF. Several prognostic scores have been used to identify children who may benefit from an early liver transplantation. These include King's College Hospital criteria, pediatric end-stage liver disease score, Acute Physiology and Chronic Health Evaluation II, and Clichy criteria. However, an INR >4 or factor V concentration of less than 25%, as recommended in

the consensus statement, are by far the best available criteria for listing for liver transplantation. Acute fulminant Wilson's disease has a high mortality necessitating liver transplantation in most cases. Special prognostic score is now available for these children and a score of 11 or more indicates mortality, with 93% sensitivity and 98% specificity.

Recently, the authors performed a survey of seven major transplant centers across India. Out of approximately 355 pediatric liver transplantation performed at these centers, ALF constituted about 19% of all cases. In India, majority of liver transplants are living related, as cadaveric donation is a rarity. A welcome development has been the increasing numbers of fathers willing to come forward as donors. Another positive aspect has been the involvement of community in arranging for funds for those who cannot afford liver transplantation. The availability of generic immunosuppressant drugs and consumables has greatly aided in bringing doing costs. The average cost of transplant in India is 12–15 lakhs. This is only about $1/5^{th}$ to $1/10^{th}$ the cost in the West.

The paucity of facilities for liver transplantation in several regions of the world has prompted many foreign nationals to come to India for liver transplants. India has now become a major center for liver transplantation for international patients because of the high quality—low cost value proposition. Children from over 20 countries have now received a liver transplantation in India (personal communication).

Clinical Pearl

- International normalized ratio >4 is the best available parameter for listing for transplant.

PROGNOSIS AND OUTCOME

In more than 50% of children with ALF, there is poor survival unless liver transplantation is offered at the appropriate time. Prognostic factors that have been found to predict poor outcome in ALF include unknown etiology, high grade (III/IV) of encephalopathy, time to onset of encephalopathy more than 7 days, higher bilirubin (>17.5 mg/dL), lower ALT (≤2384 IU/L), uncorrected prothrombin time more than 55s and clinical signs of cerebral edema. Children with encephalopathy and coagulopathy have a poorer outcome than those with coagulopathy alone.

KEY POINTS

- ☞ Hepatitis A and E infections are responsible for the majority of cases of acute liver failure, with death rates of more than 50% reported from the developing world
- ☞ Early restoration of intravascular volume and maintenance of systemic perfusion mitigates the severity of organ failure
- ☞ Acetylcysteine may benefit patients with non-acetaminophen-related acute liver failure
- ☞ For children who progress to stage 3 encephalopathy endotracheal intubation and sedation for airway control is recommended
- ☞ Serial evaluation of laboratory coagulation variables (prothrombin time) is central to prognostic evaluation
- ☞ Administration of coagulation factors should be avoided, except when needed to treat bleeding or before invasive procedures.

SUGGESTED READINGS

1. Acharya SK, Bhatia V, Sreenivas V, Khanal S, Panda SK. Efficacy of L-ornithine L-aspartate in acute liver failure: a double-blind, randomized, placebo-controlled study. Gastroenterology. 2009;136:2159-68.
2. Alagille D, Habib EC, Thomassin N. L'atresie des voies biliaires extrahepatiques permeables chez l'enfant. J Par Pediatr. 1969:26(1):51-71.
3. Arora NK, Nanda SK, Gulati S, Ansari IH, Chawla MK, Gupta SD, et al. Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India. J Med Virol. 1996;48:215-21.
4. Bernal W, Auzinger G, Sizer E, Wendon J. Intensive care management of acute liver failure. Semin Liver Dis. 2008;28:188-200.
5. Bhatia V, Sibal A. Are fathers catching up with mothers in liver donation? Indian Pediatr. 2013;50:158.
6. Bucuvalas J, Yazigi N, Squires RH, Jr. Acute liver failure in children. Clin Liver Dis. 2006;10:149-68.
7. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-Year experience and revised King's score for liver transplantation. Liver Transplantation. 2005;11:441-8.
8. Kamath BM, Spinner NB, Piccoli DA. Alagille syndrome. In: Suchy F, Sokol RJ, Balistreri WF, editors. Liver disease in children. 3rd ed. New York: Cambridge University Press; 2007. pp. 326-45.
9. Kapoor A, Bhatia V, Jerath N, et al. Expanding indications for pediatric liver transplantation. Apollo Medicine. 2012;9:55-61.
10. Kaur S, Wadhwa N, Sibal A, Jerath N, Sasturkar S. Outcome of live donor liver transplantation in Indian children with bodyweight 7.5 kg. Indian Pediatr. 2011;48:51-4.
11. Kortsalioudaki C, Taylor RM, Cheeseman P, Bansal S, Mieli-Vergani G, Dhawan A. Safety and efficacy of N-acetylcysteine in children with non-acetaminophen-induced acute liver failure. Liver Transpl. 2008;14:25-30.
12. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009;137:856-64, 864.e1.
13. Raghunathan A. An abdominal affair 2012 [19-07-2013]. Available from: http://week.manoramaonline.com/cgi-bin/MMOnline.dll/portal/ep/theWeekContent.do?programId=1073755753&contentId=13007946&tabId=13.
14. Sales I, Dzierba AL, Smithburger PL, Rowe D, Kane-Gill SL. Use of acetylcysteine for non-acetaminophen-induced acute liver failure. Ann Hepatol. 2013;12:6-10.
15. Schweizer P. Treatment of extrahepatic bile duct atresia: results and long-term prognosis after hepatic portoenterostomy. Pediatric Surgery International. 1986; 1:30-6.
16. Sgroi A, Serre-Beinier V, Morel P, Bühler L. What clinical alternatives to whole liver transplantation? Current status of artificial devices and hepatocyte transplantation. Transplantation. 2009;87:457-66.
17. Sibal A, Gupta S, Bhatia V, et al. Liver transplant for children: Indian scenario. Indian Journal of Transplantation. 2011;5:53-5.
18. Soin A, Kumaran V, Mohanka R, Mehta N, Mohan N, Nundy S. Bridge venoplasty: a new technique to simplify venous outflow reconstruction in living donor domino liver transplantation. Surgery. 2010;148:155-7.
19. Sperl J, Prochazkova J, Martasek P, Subhanová I, Franková S, Trunecka P, et al. N-acetyl cysteine averted liver transplantation in a patient with liver failure caused by erythropoietic protoporphyria. Liver Transpl. 2009;15:352-4.
20. Squires RH, Dhawan A, Alonso E, Narkewicz MR, Shneider BL, Rodriguez-Baez N, et al. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. Hepatology. 2013;57:1542-9.
21. Zhu JJ, Xia Q, Zhang JJ, Xue F, Chen XS, Li QG, et al. Living donor liver transplantation in 43 children with biliary atresia: a single-center experience from the mainland of China. Hepatobiliary Pancreat Dis Int. 2012;11:250-5.

CHAPTER 81

Corrosive Injury in Children

Barath Jagadisan

INTRODUCTION

In a pediatric emergency room, ingestion of corrosive substances by children and adolescents is not an uncommon cause of visit. Children beyond 1 year of age and less than 6 years, who are ambulant and inquisitive and who can drink from bottles are the ones who commonly come with accidental ingestion. The common practice of storing acid toilet cleaners in bottles meant for beverages and water is one of the reasons for accidental ingestion. Corrosive ingestion for self-harm, similar to that seen in adults, is usually seen in adolescent age group. Based on the data available from the American Association of Poison Control Centers, children under the age of 6 years account for 51% of individuals who ingest corrosives. Such data are not available in developing countries due to under-reporting of cases resulting from the absence of effectively functioning poison control centers or systematic data collection.

TYPES OF CORROSIVES

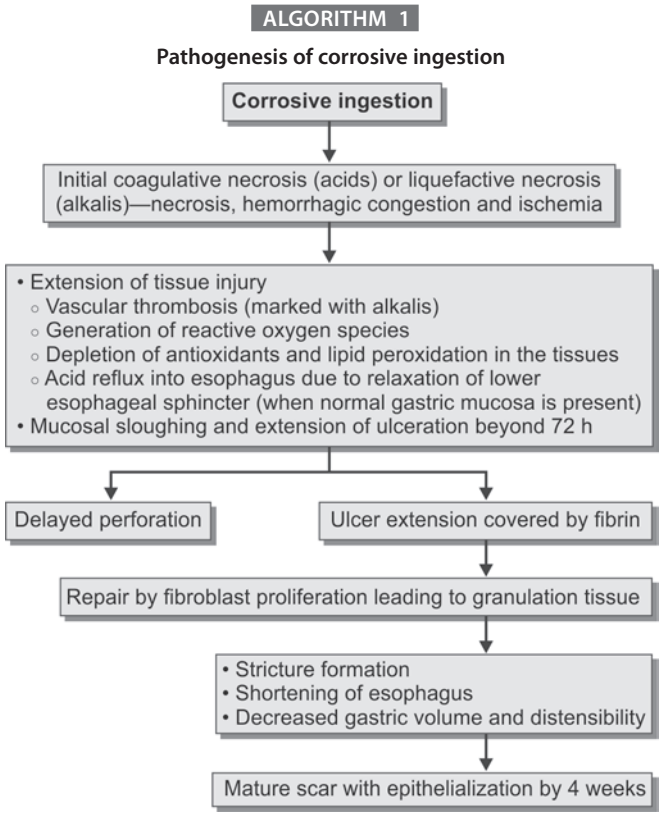
The corrosives ingested may be common household solutions like toilet cleaners, household bleach, laundry detergents, drain cleaners and oven cleaners or they may be farm and industrial chemicals stored in the house. Thus, parental occupation also seems to have an influence on corrosive injury in children. A popular herbicide, paraquat, which is widely stored in agrarian rural households is corrosive in nature and is available in containers that are not child proof. Children from households of goldsmiths come with accidental ingestion of aqua regia, a combination of hydrochloric and nitric acid. Broadly, these corrosives are classified as acids and alkalis. Unlike in the west, acid ingestion is more common in developing countries like India because of the free availability of acids.

PATHOGENESIS OF CORROSIVE INJURY

The nature and severity of corrosive injury is a function of the type of corrosive (acid/alkali; table 1), amount ingested, concentration of the corrosive and the physical state of the corrosive (solid/liquid). Acids cause coagulative necrosis of the mucosa. This results in the formation of eschar on the surface of the esophagus. If the amount of acid consumed is less, the eschar might prevent further penetration of the acid into deeper tissue. In contrast, alkalis produce liquefactive necrosis, saponification and thrombosis of underlying vessels and thereby have the potential to penetrate deep into the tissue causing transmural injury and perforation. This distinction is not absolute since acids cause deep injuries and perforation when ingested in higher amounts. The volume of ingestion is more in self-harm rather than in accidental ingestion. Hence, the proportion of severe injury is less in children compared to that in adolescents. Also, because of their higher viscosity and longer time for clearance from the esophagus, alkalis can potentially cause predominant damage to the esophagus while acids are rapidly cleared into the stomach causing predominant

TABLE 1: Difference between injury from alkalis and acids

Injury	Acids	Alkalis
Type of necrosis	Coagulative	Liquefactive
Formation of eschar/coagulum	Yes	No
Depth of injury	Limited by coagulum formation	Deep, transmural
Risk of perforation	Lower	Higher
Location of injury	Predominantly esophagus due to viscous nature and slow esophageal clearance	Predominantly stomach due to rapid esophageal clearance



gastric injury. Again, this distinction is more theoretical rather than a reality as acid ingestion causing deep esophageal injury is not uncommon. The concentration of the corrosive determines the depth of injury and time taken for clinical deterioration. Solid corrosives have a prolonged contact with the mouth and esophagus while liquids are rapidly cleared into the stomach. The antrum and pylorus are the areas that receive the corrosive first from the esophagus and thus perforation and strictures are seen more in these areas. Apart from the local effects, corrosives like acids have significant systemic complications including disseminated intravascular coagulation and organ (renal, hepatic) dysfunctions. A common cause of death in paraquat ingestion is acute lung injury.

The sequence of events following a corrosive ingestion is depicted in algorithm 1. Before 4 weeks, the tensile strength of the tissue is less and hence late endoscopies beyond 96 hours carry a risk of perforation. For the same reason, stricture dilatation is usually not attempted before 3 weeks after corrosive injury. The process of fibrosis progresses even after epithelialization and hence the stricture continues to worsen. Therefore, a much delayed follow-up endoscopy will detect mature tight strictures where, even visualization of a lumen for cannulation and dilatation becomes difficult.

CLINICAL MANIFESTATIONS

The manifestations of corrosive injury include:

- Airway injury in the form of stridor and dyspnea
- Refusal of feeds
- Drooling of saliva
- Dysphagia
- Odynophagia
- Retrosternal pain
- Abdominal pain
- Vomiting
- Hematemesis. Large volume hematemesis is seen with extensive gastric injury
- Oral cavity may show erythema, edema, bleeding and ulceration
- Systemic involvement in the form of acute lung injury, renal and hepatic failure and disseminated intravascular coagulation
- Perforation and mediastinitis leading to death.

The clinical presentation in a tertiary care center is not necessarily an exact representation of the spectrum of injury and clinical manifestations of CI, as children with extensive injury and rapid deterioration are unlikely to reach the hospital.

In an attempt to find a noninvasive indicator of injury or its severity, the presence of symptoms and oral cavity injury have been compared with endoscopic findings in the esophagus and stomach. Among 378 children with corrosive injury, symptoms were shown to have no correlation with esophageal injury. Eighty two percent of the symptomatic children had no esophageal injury while 12% of asymptomatic children were shown to have severe esophageal injury. Even though increasing number of symptoms may correlate with a greater likelihood of significant injury, deep mucosal injuries can occur without symptoms. The presence of airway injury in the form of stridor is frequently associated with esophageal injury, but most studies indicate that no single symptom or group of symptoms can reliably predict esophageal or gastric injury. Similarly, the absence of oral lesions does not rule out esophageal injury. Esophageal injury can be found in up to 61% children in the absence of oral lesions. The reverse is also true where significant oral cavity lesions may not have any distal injury. These observations are the basis of recommending endoscopic assessment in all children with corrosive injury irrespective of their symptoms or their oral cavity manifestations.

This does not undermine the importance of clinical examination. The presence of respiratory symptoms points to the need for early management of airway or pulmonary problems. Careful clinical examination together with computed tomography (CT) is more relevant in diagnosing perforation rather than endoscopy alone. Since perforation can occur at any time in the first 2 weeks, any clinical worsening or new symptoms should be carefully evaluated.

INVESTIGATIONS IN THE ACUTE PHASE

Chest and Abdominal Radiographs

Radiographs of the chest and abdomen may show evidence of mediastinal air or subdiaphragmatic air in the case of esophageal or gastric perforation. In the case of esophageal perforation, there is evidence of mediastinitis and pleural effusion.

Laboratory Investigations

Investigations to look for acidosis, dyselectrolytemia, disseminated intravascular coagulation and multiple organ dysfunctions are relevant in a sick child prior to surgery and as part of monitoring during the course of management.

Early Endoscopic Evaluation

Endoscopic evaluation provides an evaluation of the extent of mucosal injury and an estimate of its severity in terms of the possible transmural extent of the injury and thereby, guides management and helps in prognostication.

The selection of time for endoscopic evaluation has varied in the past. Since ongoing mucosal necrosis and sloughing increases the friability of tissues, endoscopy is done before 96 hours. The practice of delaying endoscopy with the idea of visualizing a more mature state of necrosis is not preferred nowadays. Most endoscopists prefer early endoscopy within 72 hours because of the lower risk of perforation. Endoscopic assessment, in the hands of an expert, is a safe procedure when done with care.

Endoscopic assessment is contraindicated in the case of severe hypopharyngeal injury and in the case of perforation. It is best done under sedation. Deep sedation without intubation is required in children. Routine anesthesia and intubation is not preferred unless there is stridor and respiratory problems. Caution is to be exercised in the case of epiglottic or laryngeal inlet edema where respiratory problems are anticipated and intubation is advisable. The principles of endoscopy in corrosive ingestion include gentle scope maneuvering and minimal air insufflation. It is recommended that the scope is not negotiated beyond severe mucosal injuries of grade 3 especially if it is circumferential. Some endoscopists do not follow this rule and consider it safe to negotiate beyond these severe injuries also.

The purpose of endoscopy is to grade the mucosal injury. Injury is graded as in table 2. Presence of perforation may be referred to as grade 4 injury where endoscopy is contraindicated.

Many cases of corrosive injury may not have any gastrointestinal injury, more so in the cases of accidental ingestion. These patients identified by endoscopy can be discharged early. The injury grading correlates well with morbidity and mortality. Children with grades 1 and 2A injury do not usually develop strictures. Stricture frequency in grade 3 injury may approach up to 75%. Mortality is more in grade 3 injuries. Endoscopic grading can guide the need for feeding jejunostomy. Extensive grade 3b injuries may necessitate emergency surgical procedures.

TABLE 2: Endoscopic grading of mucosal injury during endoscopy

Grade of injury	Endoscopic findings
0	Normal appearance
1	Edematous and hyperemic mucosa
2A	Superficial injury—friability, hemorrhagic areas, erosions with whitish exudates and membranes, superficial ulceration
2B	Grade 2A with deep discrete ulcers or circumferential involvement
3A	Multiple scattered areas of ulceration and necrosis seen as brown/black/gray areas
3B	Extensive areas of necrosis

A grade 3 injury may not always indicate a definite transmural involvement. Emergency resective surgery guided by endoscopic mucosal injury grading alone may result in unnecessary gastrectomy and esophagectomy in 12–15% cases, thus necessitating a better mode of identifying transmural injury.

Endoscopic ultrasound with miniprobes has been used in corrosive injury to predict the risk of stricture in follow-up. In patients who have developed stricture, endoscopic ultrasound with a radial probe has been used to predict the response to dilatation.

Computed Tomography

Unlike endoscopy which assesses only the mucosal aspect of the injury, CT provides information on the extent of transmural injury. In situations where clinical assessment suggests a high possibility of perforation even in the absence of obvious evidence of perforation in chest and abdominal radiographs, a CT rather than an endoscopy should be the first investigation to be performed to look for perforation. Computed tomography grading of the injury has also been used as a modality to predict the risk of stricture formation but is not routinely done for this purpose alone.

MANAGEMENT (ALGORITHM 2)

Management in the Acute Phase

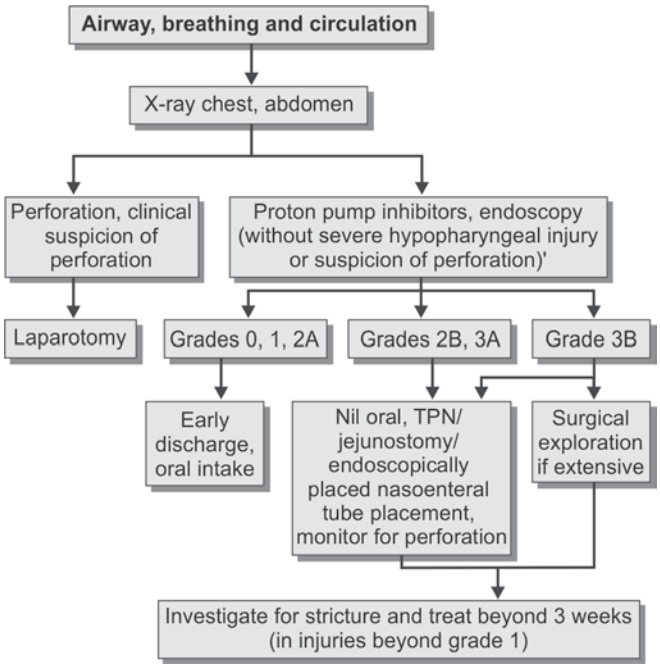
Adherence to the basic tenets of emergency care is essential in the management of patients with corrosive injury. The patient is assessed for respiratory distress and airway intubation or tracheostomy may be required in cases with airway problems. Epiglottic and supraglottic edema are harbingers for airway compromise even in the absence of symptoms at presentation. The patient's ventilation and hemodynamic status may require support in cases with perforation.

There is no role for gastric lavage or inducing emesis to remove the corrosive. Inducing emesis will only lead to repeat exposure of proximal mucosa to the corrosive and lead to aspiration of the corrosive. Similarly, attempts at neutralization of the corrosive by weak acids or weak bases will prove counter productive. Milk and activated charcoal should be avoided.

Blind placement of nasogastric tube should be avoided. This might lead to perforation. Some centers prefer placing a endoscopically guided nasojejunal tube to assist feeding and to use it as a stent that might maintain at least a narrow lumen that can be used for cannulation during stricture dilatation. This is controversial and is discouraged by others as the tube increases reflux and might lead to the development of long strictures. The latter view is contested as one study shows equivalence of nasojejunal feeding with jejunostomy feeding

ALGORITHM 2

Management of corrosive ingestion in children



in maintaining nutrition in patients with corrosive injury without increasing the frequency of strictures.

Based on the data suggesting the presence of lower esophageal sphincter relaxation, high frequency of acid reflux into the esophagus and the preliminary data showing impressive healing of corrosive injury with infusion of proton pump inhibitors (PPI), administration of PPI, at least as bolus doses, is a regular practice.

Systemic steroid use with the purpose of preventing strictures is to be avoided as meta-analysis analyzing steroid use in corrosive injury has shown that steroids do not provide this benefit. Also, the risk of infections may be increased with steroid use. There is always the theoretical possibility of steroids masking features of inflammation arising from bowel perforation. Systemic steroids are indicated only in cases with airway edema.

Antibiotics are not routinely indicated. They are used only in cases with perforation. In addition, broad spectrum antibiotics may be relevant in cases receiving steroids for airway edema.

When there is overt clinical or radiological evidence of perforation, emergency laparotomy is required. In case of high index of suspicion of perforation, laparotomy may be indicated even in the absence of radiological evidence. When there is ambiguity regarding perforation in a clinically stable patient, CT may be useful to look for evidence of perforation. If there is no suspicion of perforation on clinical and radiological assessment, the patient is subjected to endoscopic assessment of mucosal injury. The decision for early surgery is not entirely dependent on overt clinical or radiological signs of perforation. In case of acidosis, renal injury or hemodynamic instability, early surgery is essential in view of the high suspicion of perforation. Any clinical suspicion of perforation based on the general condition of the patient and the quantity of corrosive ingested, should lead to an early surgical exploration.

In patients in whom endoscopic assessment of mucosal injury has been done, the grade of injury guides further management. Children with normal mucosa can be discharged immediately. Children with grades 1 and 2A injury can be allowed to take orally and can be discharged after a brief period of observation when oral intake is satisfactory. Children with grades 2B and 3 injuries are restricted from oral intake. In cases of grades 2B and 3A injuries, where oral intake is restricted, the choice of nutrition delivery is between total parenteral nutrition (TPN), jejunostomy feeding and endoscopically placed nasoenteral tube feeding. Most centers, at least in developing countries, avoid TPN due to the high cost and high frequency of infections. Kochhar et al., in a retrospective study comparing nasoenteric feeding and jejunostomy feeding, had shown that nasoenteric feeding maintains a comparable nutrition status without increased stricture rates. The tube also provides a lumen for guidewire passage during future dilatation. This study also included cases of 3B mucosal injury that did not require a laparotomy, who were fed by nasoenteral feeding.

The role of emergency surgical procedure in the presence of evidence of perforation or a massive hemorrhage is quite obvious. These situations are dealt with by esophagectomy and cervical esophagostomy when the esophagus is perforated. The area of the stomach with transmural involvement may need resection. The entire stomach may need resection. A gastrostomy during surgery provides an accurate assessment of the extent of involvement. There is no role for surgical closure of perforations. Distal jejunostomy is required to maintain nutrition. In case of extensive grade 3B injuries, laparotomy may be required to look for transmural extensive necrosis that can be a harbinger of perforation. The surgery may result in variable degree of resection and a jejunostomy for feeding. The role of laparoscopy in such situations is controversial in view of long operating time involved in the procedure and the difficulty in thorough assessment of extent of injury.

Management of Strictures

Stricture frequency increases with increasing grades of mucosal injury. Systemic steroids do not prevent strictures. Strictures in the esophagus present with dysphagia and aspiration pneumonia while strictures in the antral and pyloric area present with features of gastric outlet obstruction. It is always preferable to have a contrast radiograph before an endoscopic evaluation of the stricture as it gives an idea of the position, number and length of strictures and information on the presence of diverticulae. On radiography with oral contrast, stricture is seen as an area of narrowing with hold-up of contrast proximal to the stricture. Depending on the chronicity of the stricture, there can be variable degrees of proximal dilatation. Diverticulae are common in corrosive strictures, especially those presenting late. Barium would be the preferable contrast

except in children with severe dysphagia where there is a possibility of aspiration of the contrast.

Stricture dilatation before 3 weeks after corrosive injury is not advisable due to the high risk of perforation. At the same time, delayed dilatations lead to a nonvisualization of lumen for dilatation, strictures refractory to dilatation and poor nutrition of the child. Long strictures are common after corrosive injury, where Savary-Gillard (bougie) dilator may be preferred to a balloon dilator. Refractory strictures may require local triamcinolone injection or mitomycin application. In cases presenting months after corrosive injury, dilatation may not be possible and surgical correction may be the only option. Detailed discussion of surgical reconstructive procedures to correct the late sequelae of corrosive injury is beyond the scope of this review.

Long-term Complications of Corrosive Injury

The long-term complications include dysmotility and possible risk of dysplasia and malignancy in the affected tissue.

CONCLUSION

In summary, the optimal management of corrosive injury is dependent on adherence to the basic tenets of life support, avoidance of lavage or emesis, early and optimal selection of patients for emergency surgical resection, decision making guided by endoscopic evaluation, close attention to nutrition, and avoiding delay in stricture detection and management.

The free availability of acids in the unregulated market is a problem in many developing countries where acids are used as toilet cleaners, leading to a high frequency of corrosive injury. Rules governing concentration of household caustics and child resistant packaging of toilet cleaners and other corrosives need to be strictly implemented.

Clinical Pearls

- Oral manifestations and symptoms do not predict the degree of esophageal and gastric mucosal injury
- Blind nasogastric tube insertion, lavage, emesis, charcoal and milk are to be avoided after corrosive injury
- Steroids are indicated only in cases of airway edema
- Esophagogastroduodenoscopy is indicated in all children with CI who do not have perforation or severe hypopharyngeal injury.

KEY POINTS

- ☞ Early recognition of airway compromise and perforation is essential to ensure survival
- ☞ Endoscopic assessment of severity of mucosal injury directs early management and prognosticates the likelihood of strictures
- ☞ Existing data is insufficient to support use of systemic corticosteroids for prevention of strictures
- ☞ Routine barium esophagogram at 3 weeks after corrosive ingestion is necessary for early diagnosis and management of strictures.

SUGGESTED READINGS

1. Ananthakrishnan N, Parthasarathy G, Kate V. Acute corrosive injuries of the stomach: a single unit experience of thirty years. ISRN Gastroenterol. 2011;2011:914013.
2. Betalli P, Falchetti D, Giuliani S, Pane A, Dall'Oglio L, de Angelis GL, et al. Caustic ingestion in children: is endoscopy always indicated? The results of an Italian multicenter observational study. Gastrointest Endosc. 2008;68:434-9.
3. Chirica M, Resche-Rigon M, Bongrand NM, Zohar S, Halimi B, Gornet JM, et al. Surgery for caustic injuries of the upper gastrointestinal tract. Ann Surg. 2012;256:994-1001.
4. Do˘gan Y, Erkan T, Coku˘gra¸s, Kutlu T. Caustic gastroesophageal lesions in childhood: an analysis of 473 cases. Clin Pediatr. 2006;45:435-8.
5. Gaudreault P, Parent M, McGuigan MA, Chicoine L, Lovejoy FH Jr. Predictability of esophageal injury from signs and symptoms: a study of caustic ingestion in 378 children. Pediatrics. 1983;71:767-70.
6. Kochhar R, Poornachandra KS, Puri P, Dutta U, Sinha SK, Sethy PK, et al. Comparative evaluation of nasoenteral feeding and jejunostomy feeding in acute corrosive injury: a retrospective analysis. Gastrointest Endosc. 2009;70:874-80.
7. Kochhar R, Ray JD, Sriram PV, Kumar S, Singh K. Intralesional steroids augment the effects of endoscopic dilation in corrosive esophageal strictures. Gastrointest Endosc. 1999;49:509-13.
8. Lakshmi CP, Vijayahari R, Kate V, Ananthakrishnan N. A hospital based epidemiological study of corrosive alimentary injuries with particular reference to the Indian experience. Natl Med J India. 2013;26(1):31-6.
9. Uhlen S, Fayoux P, Vachin F, Guimber D, Gottrand F, Turck D, et al. Mitomycin C: an alternative conservative treatment for refractory esophageal stricture in children? Endoscopy. 2006;38:404-7.
10. Watson WA, Litovitz TL, Rodgers GC Jr, Klein-Schwartz W, Reid N, Youniss J, et al. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med. 2005;23:589-666.
11. Zargar SA, Kochhar R, Mehta S, Mehta SK. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. Gastrointest Endosc. 1991;37:165-9.

CHAPTER 82

Chronic Abdominal Pain

Sarah Paul, John Matthai

INTRODUCTION

Chronic (recurrent) abdominal pain is the commonest abdominal symptom that a pediatrician confronts in his practice. Modifying the conventional definition by Apley, the symptom duration has recently been reduced from 3 to 2 months and the preferred term as chronic abdominal pain (CAP). Advances in investigative facilities over the years have failed to yield a cause in a majority of children. This has led to the concept of functional abdominal pain, wherein the pain is real and not imaginary, and may be related to stress, environmental and familial factors.

CLASSIFICATION

Rome III criteria laid down in 2006 categorized pain related functional gastrointestinal disorders (FGIDs) into five groups (Table 1) and laid down diagnostic criteria for each.

Red Flag Signs

Chronic abdominal pain may not always be functional. The red flag signs that suggest a possible organic basis are given in box 1.

Clinical Pearl

- Do not ignore red flag signs in abdominal pain. Investigate children with any of them.

TABLE 1: Rome III criteria-H2: abdominal pain-related functional gastrointestinal disorder

H2a	Functional dyspepsia
H2b	Irritable bowel syndrome
H2c	Abdominal migraine
H2d	Childhood functional abdominal pain
H2d1	Childhood functional abdominal pain syndrome

Box 1: Red flag signs in chronic abdominal pain

- Clearly localized/radiating pain
- Pain that wakes the child from sleep
- Gastrointestinal blood loss
- Deceleration of linear growth
- Family history of inflammatory bowel disease
- Celiac disease or peptic ulcer
- Perirectal disease
- Dysphagia
- Persistent vomiting
- Nocturnal diarrhea
- Unexplained fever
- Arthralgia, rash
- Delayed puberty
- Weight loss

Functional Dyspepsia

Diagnostic Criteria

Diagnostic criteria must include all of the following (at least once per week for at least 2 months):

- Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
- Not relieved by defecation or associated with the onset of a change in stool frequency or stool form [i.e., not irritable bowel syndrome (IBS)]
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms.

Evaluation

The dyspeptic symptoms may follow a viral infection. Delayed gastric emptying, disordered gastric myoelectrical activity, and altered antroduodenal motility are implicated in pathogenesis. An upper gastrointestinal (GI) endoscopy is not mandatory for making a diagnosis, unless the patient has dysphagia or symptoms improve with antacids and relapse on withdrawal or *Helicobacter pylori* disease is suspected.

Treatment

Avoidance of drugs particularly analgesics, and specific foods that aggravate symptoms should be avoided. Antacids and

prokinetics may offer symptom relief in some patients, but their routine use is not recommended without an upper GI endoscopy. A search for psychological factors may be made in appropriate settings.

Irritable Bowel Syndrome

Diagnostic Criteria

Diagnostic criteria must include all of the following (at least once per week for at least 2 months):

- Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with two or more of the following, at least 25% of the time:
  - Symptoms improved with defecation
  - Onset associated with a change in frequency of stool (4 or more stools per day and 2 or less stools per week)
  - Onset associated with a change in form of stool
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms.

Evaluation

Visceral hypersensitivity related to genetic predisposition and early stressful events is a likely cause. Anxiety, depression, and multiple somatic complaints are often reported not only by the patient, but also by the parents. In the absence of red flag signs, a positive diagnosis of IBS can be made without any investigations.

Treatment

A confident diagnosis, reasonable explanation of pain experience, and reassurance are by themselves therapeutic. While peppermint oil is reported beneficial in children, antidepressants have not been proven useful.

Clinical Pearl

- Abdominal discomfort associated with a change in frequency or form of the stool and improves on defecation suggests irritable bowel syndrome.

Abdominal Migraine

Diagnostic Criteria

Diagnostic criteria must include all of the following (two or more times in the preceding 12 months):

- Paroxysmal episodes of intense acute periumbilical pain that lasts for 1 hour or more
- Intervening periods of usual health lasting weeks to months
- The pain interferes with normal activities
- The pain is associated with two or more of the following: anorexia, nausea, vomiting, headache, photophobia, and pallor
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms.

Evaluation

Cyclic vomiting syndrome, migraine headache, and abdominal migraine are believed to be the spectrum of the same disease with overlap. Family history of migraine and motion sickness, are therefore, often present. In appropriate settings, subacute obstruction of the intestine, urinary and biliary tract, as well as chronic pancreatitis and porphyria should be ruled out. Response to migraine prophylactic drugs is supportive evidence.

Treatment

Avoidance of potential triggers, like caffeine, prolonged fasting, sleep deprivation, and exposure to flickering lights, may be suggested. In those with recurrent episodes, propranolol, cyproheptadine, and sumatriptan can be tried.

Childhood Functional Abdominal Pain

Diagnostic Criteria

Diagnostic criteria must include all of the following (at least once per week for at least 2 months):

- Episodic or continuous abdominal pain
- Insufficient criteria for other FGIDs
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms.

Evaluation

These children are not troubled by their symptoms and parental anxiety is the main compounding factor. No investigations are necessary in the absence of any red flag signs, provided the parents can be convinced of the diagnosis.

Treatment

Parents need to be reassured that there is no organic basis. Placebo drugs should be discouraged. Psychological evaluation is not necessary.

Childhood Functional Abdominal Pain Syndrome

Diagnostic Criteria

Diagnostic criteria must include childhood functional abdominal pain at least 25% of the time, and one or more of the following (at least once per week for at least 2 months):

- Some loss of daily functioning
- Additional somatic symptoms, such as headache, limb pain, or difficulty in sleeping.

Evaluation

A limited screening which includes complete blood count, erythrocyte sedimentation rate or C-reactive protein, urinalysis, and urine culture is indicated. Other investigations may be decided by the clinician depending on the predominant symptom and degree of functional impairment. Anxiety depression and somatization may be seen in the patient and parents.

Treatment

The contribution of psychosocial factors should be evaluated and behavioral therapy can give positive results.

APPROACH TO A CASE OF CHRONIC ABDOMINAL PAIN

Children presenting with CAP can broadly be classified into three groups, based on the pattern of pain (Table 2).

1. Isolated paroxysmal periumbilical CAP
2. Chronic abdominal pain with dyspepsia
3. Chronic abdominal pain with altered bowel habits.

Clinical Pearl

- Isolated paroxysmal periumbilical pain in children is most commonly functional pain.

MANAGEMENT OF FUNCTIONAL PAIN

The first step in management is making a positive diagnosis. Parental counseling should be well planned with an unequivocal reassurance that there is no organic disease and that the prognosis is good. They need to understand that the pain is real and the child is not feigning, but there is no need for medication. Hospitalization is ideally avoided since it is likely to reinforce pain behavior. The treatment aims to normalize lifestyle (school attendance, extracurricular activities, sleep) by benign negligence or distraction techniques. It is also important to identify and reduce stress/triggers at home, neighbourhood or with peers. Any form of secondary gain should be minimized by preventing the child from using the pain to avoid unpleasant but essential responsibilities. Diet changes have little role in reducing pain, but a regular balanced diet with adequate fibers must be insisted on. Though some small studies have reported benefits, most do not show any statistically significant difference between amitriptyline and placebo in functional GI diseases in children. Interaction with the teachers may help identify children with special needs (specific learning disability, attention deficit hyperactivity disorders). They can be informed directly or through the parents that they need to be sympathetic to the child while not creating panic. Consultation with a psychiatrist is not recommended unless there are compelling reasons to do so, since it can affect the morale and outlook of the parents and the child.

TABLE 2: Classification of chronic abdominal pain based on the pattern of pain

Isolated paroxysmal periumbilical abdominal pain	
Functional pain 95%	• Organic abdominal pain <5% • In test: malrotation, Crohn's disease, adhesions • Renal: stone colic, PUJ obstruction • Infection: tuberculosis, *Yersinia* • Others: food allergy, dysmenorrhea
CAP with dyspepsia	
Functional pain 90%	• Organic abdominal pain 10% • GERD, *Helicobacter pylori*, *Giardia* • Pancreatitis, biliary disease • Food intolerance, drugs
CAP with altered bowel habits	
Functional pain 75%	• Organic abdominal pain 25% • Constipation, IBD, TB, parasites • Lactose intolerance, food allergy • Gynecological, drugs

CAP, chronic abdominal pain; PUJ, pelvi-ureteric junction, GERD, gastro-esophageal reflux disease; IBD, inflammatory bowel disease; TB, tuberculosis.

Clinical Pearl

What to tell the parents?

- The pain in functional abdominal pain is real, not imaginary. Do not deny the presence of pain. The reassurance is only that there is no organic basis.

KEY POINTS

- ☞ Functional gastrointestinal (GI) disorders are the most common cause of chronic abdominal pain in children
- ☞ Functional dyspepsia, irritable bowel syndrome, and functional abdominal pain are the most common causes
- ☞ Look for red flag signs before considering functional disorders
- ☞ Isolated paroxysmal periumbilical pain is most likely functional
- ☞ Chronic abdominal pain with dyspepsia or altered bowel habits warrant consideration of upper/lower GI disorders
- ☞ Children with functional pain need reassurance and return to normal lifestyle at the earliest, after an attempt to correct or reduce trigger/stress factors.

SUGGESTED READINGS

1. Bhaskar R, Ghosh M, Pal S, Gupta SD. Recurrent (chronic) abdominal pain in children. In: Bavdekar A, Matthai J, Sathiyasekaran M, Yachha SK (Eds). Pediatric Gastroenterology, 2nd edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2013. pp. 22-36.
2. Caplan A, Walker L, Rasquin A. Validation of the pediatric Rome II criteria for functional gastrointestinal disorders using the questionnaire on pediatric gastrointestinal symptoms. J Pediatr Gastroenterol Nutr. 2005;41(3):305-16.
3. Di Lorenzo C, Colletti RB, Lehman HP, Boyle JT, Gerson WT, Hyams JS, et al. Chronic abdominal pain in children: a clinical report of American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005;40(3):245-8.
4. Milla PJ. Irritable bowel syndrome in childhood. Gastroenterology. 2001; 120(1):287-90.
5. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006;130(5):1527-37.
6. Zeiter DK, Hyams JS. Recurrent abdominal pain in children. Pediatr Clin North Am. 2002;49(1):53-71.

CHAPTER 83

Approach to Global Developmental Delay

Pratibha D Singhi, Naveen Sankhyan

DEFINITION

Global developmental delay (GDD) is an umbrella term used to describe young children with developmental delay. Conventionally, the term developmental delay is reserved for children below 5 years of age. The term mental retardation or more appropriately, "intellectual disability (ID)" is usually applied to older children (>5 years), when intelligent quotient testing is valid and reliable. Global developmental delay implies a significant delay in two or more areas of developmental performance: defined as gross/fine motor, speech/language, cognition, social/personal, and activities of daily living. Significant delay is defined as a developmental level two standard deviations or more below the mean on age-appropriate, standardized, norm-referenced tests. Contrary to popular use, GDD is not a diagnosis by itself and so it should be used only as a basis for reaching a diagnosis. The prevalence of intellectual disability is estimated to be around 1–3% of the population.

APPROACH TO DIAGNOSIS

A systematic approach to a child with GDD will help in the proper and optimum evaluation. The essential components of the diagnostic evaluation of a child with GDD or intellectual disability include the following:

- History: including prenatal and birth history, family history, and construction of a pedigree of three generations
- Physical examination (special emphasis on dysmorphism): neurologic examination, organomegaly
- Psychometric evaluation: to document and objectify the functional level in various domains
- Laboratory tests: radiological evaluation (X-rays and neuroimaging), genetic testing, metabolic tests, etc. as indicated.

CLINICAL ASSESSMENT

History

The clinical assessment of a child with GDD/ID begins with a thorough and directed history (Box 1).

A detailed history is essential to elicit antenatal and perinatal risk factors for GDD/ID. The history should be focused on maternal health during the first trimester of pregnancy including fever, drug intake or toxin exposures, and clues to intrauterine difficulties (oligohydramnios, pre-eclamptic toxemia, poor growth, antenatal bleeding, reduced fetal movements, etc.). The timing and mode of delivery, birth weight, APGAR scores, head circumference at birth, time to independent feeding, and duration of postnatal hospital stay are important objective markers of newborn health status. One needs to remember that a history of delayed cry, although an important clue is insufficient to conclude perinatal insult, unless there is definite suggestion of neonatal encephalopathy (e.g., excessive lethargy, seizures, and feeding difficulties requiring orogastric/nasogastric feeding).

Box 1: Questions to be answered after history in a child with global developmental delay/intellectual disability

- Is it a static or progressive disorder?
- Is there an obvious etiologic cause?
- What is the timing of the possible underlying cause?
- What is the developmental and functional level of the child?
- What are the associated comorbid medical or behavioral conditions (e.g., epilepsy and attention deficit hyperactivity disorder)?
- In what socioeconomic and sociocultural milieu is the child being raised?

Clinical Pearl

- Remember that a history of delayed cry, although an important clue is insufficient to conclude perinatal insult, unless there is definite suggestion of neonatal encephalopathy (e.g., excessive lethargy, seizures, feeding difficulties requiring orogastric/nasogastric feeding).

Postnatal insults such as neuroinfections are common in the resource-poor countries and account for a large number of children with acquired GDD/ID. A detailed developmental history and past history should be elicited for presence of seizures, hospitalizations, and other acute or chronic conditions. A family history of ID can point toward a genetic cause of GDD/ID, for example fragile-X syndrome or other X-linked mental-retardation syndromes. Family history may also point toward an unrecognized metabolic disorder such as phenylketonuria.

Clinical Pearl

- A three-generation family history should be carefully elicited in all children with developmental delay to unearth possible inherited causes.

To recognize patterns of inheritance, it is essential that a carefully elicited history is used to construct a three-generation pedigree and identify consanguinity.

Examination

A child with GDD/ID evaluation with special focus on dysmorphic features. Special attention is to be paid to the size and shape of head, facies, eyes, stature, skin, hearing, hair, and organomegaly. Any abnormalities in the head shape, sutures, and fontanels should be noted. In children with abnormal head size, head circumferences of both parents should be obtained. The head circumference has to be assessed over a period of time to understand the trajectory of head growth. When a child is noted to have an unusual appearance, a diagnosis is significantly more likely. Neurological examination is important to identify cerebral palsy, muscle-tone abnormalities, weakness, paresis, ataxia, and other specific neurological signs. A good physical examination, particularly to look for organomegaly is also essential. Such abnormalities on neurologic examination assist in determining the need for additional investigations such as electroencephalography, neuroimaging or molecular genetic testing, or referral to other specialists such as psychologists, or geneticists for further assessment.

The history and examination provide essential clues to the diagnosis, which can be later confirmed by additional studies, for example, in patients with Pradder-Willi syndrome, the history and examination may be contributory to the diagnosis and the molecular genetic analysis confirms it.

DEVELOPMENTAL ASSESSMENT

The clinical history should be supplemented with standardized testing of developmental level by a clinical psychologist. Standardized tools include screening tests such as the Denver's Development Screening Test, and the Ages and Stages Questionnaire, and more detailed tests such as the Gesell Development Schedules and the Bailey's Developmental Scales. When there is a concern about developmental delay in a child, a developmental quotient should be calculated for each developmental stream. It is a means to simply express a developmental delay in quantifiable terms. The "developmental quotient" is the ratio of the child's developmental age over the chronological age. Typical development is a developmental quotient greater than 70%, and atypical development is a developmental quotient of less than 70%. The term GDD delay is used if a child—younger than 5–6 years of age—has a developmental quotient less than 70% in two or more domains.

INVESTIGATIONS

The choice and the sequence of investigations should be guided by the clinical evaluation, cost of investigations, and availability (Algorithm 1). Some investigations are a part of complete evaluation (e.g., standardized vision, hearing testing, ultrasound, and skeletal X-rays) while others tests offer means to establish the diagnosis (genetic and metabolic testing).

In the absence of a universal thyroid screening in India, thyroid function tests should be done in all children with GDD/ID. Additionally, keeping in mind that large numbers of children in resource-poor countries have acquired causes for GDD/ID, it is prudent to opt for imaging studies as the initial diagnostic testing. Magnetic resonance imaging is the imaging modality of choice, given the higher resolution and better resolution to pick up dysgenesis and white-matter abnormalities.

Genetic Testing

It is preferable to involve experts in clinical genetics whenever possible for the genetic evaluation of GDD/ID.

Cytogenetic Studies

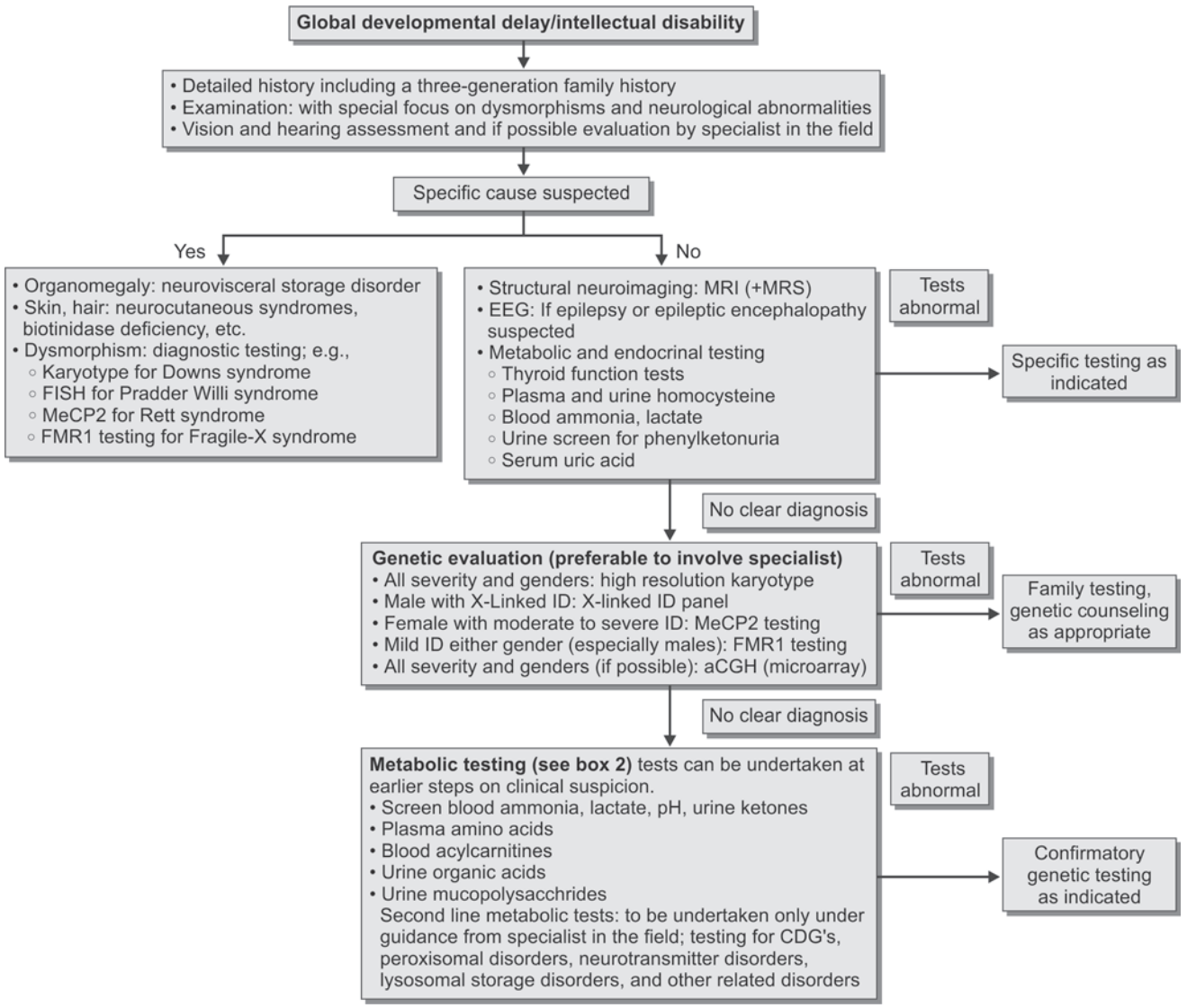
Chromosome abnormalities are found in all categories of intellectual disability, mild to profound and in both sexes. The reported frequency of chromosomal anomalies detected by high-resolution karyotyping (i.e., 550 bands) in patients evaluated for intellectual disability or developmental delays is around 10%. This test is reported to be a valuable initial test for evaluation of GDD.

Fluorescent *in situ* Hybridization Testing (FISH)

About half of all structural chromosome abnormalities include the telomere of the chromosome. Many of these abnormalities may be missed by the standard karyotype. Fluorescent *in situ*

ALGORITHM 1

Approach to diagnosis in a child with global developmental delay/intellectual disability



GDD, global developmental delay; ID, intellectual disability; FISH, fluroscent *in situ* hybridization; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; CDG, congenital disorders of glycosylation; aCGH, array comparative genomic hybridization.

hybridization techniques have been applied to examine the subtelomeric regions of each chromosome for abnormalities that are known to cause intellectual disability. The yield is higher among familial cases as compared with sporadic cases.

Array Comparative Genomic Hybridization Techniques (aCGH)

It is a better technique to evaluate chromosomal abnormalities. It identifies deletions and/or duplications of chromosome material with a high degree of sensitivity in a more efficient manner than FISH techniques. Furthermore, the FISH test is predominantly used to confirm a clinical diagnosis, whereas aCGH does not require an expert clinician to suspect a specific diagnosis. However, it is expensive and not available at most centers in India.

Metabolic Testing (Box 2)

Both genetic testing and metabolic testing is expensive; hence its judicious use is warranted. In such situations, it would be wise to obtain an expert consultation before proceeding with these tests.

Box 2: Indications for screening for inborn errors of metabolism in children with global developmental delay/intellectual disability

- Pregnancy: a history of maternal acute fatty liver of pregnancy or hemolysis, elevated liver enzymes, and low platelets are associated with several fatty acid oxidation disorders
- Family history: parental consanguinity, unexplained neonatal or infant deaths, family history of suspected metabolic disorder
- Others: unexplained hypoglycemia, recurrent encephalopathy, protein aversion, multisystem involvement, possible white matter involvement

KEY POINTS

- ☞ Global developmental delay means a significant delay in two or more areas of developmental performance
- ☞ The term mental retardation or more appropriately, "intellectual disability" is usually applied to older children (>5 years).The essential components of the diagnostic evaluation include: history (including prenatal and birth history), family history, physical and neurologic examinations, laboratory tests, including metabolic, and genetic testing, and imaging.

SUGGESTED READINGS

1. Battaglia A, Carey JC. Diagnostic evaluation of developmental delay/mental retardation: an overview. Am J Med Genet C Semin Med Genet. 2003:117C(1);3-14.
2. Cleary MA, Green A. Developmental delay: when to suspect and how to investigate for an inborn error of metabolism. Arch Dis Child. 2005;90:1128-32.
3. Schroeder S, Gerry M, Gert G, Velazquez F. Final Project Report: Usage of the term "Intellectual disability:" Language, Image and Public Education, in American Association of Intellectual Disability Resource Network International. Center on Developmental Disabilities; Center for the Study of Family, Neighborhood and Community Policy, University of Kansas; 2001. pp. 1-216.
4. Sherr EI, Shevell MI. Global developmental delay and mental retardation/ intellectual disability. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF (Eds). Pediatric Neurology: Principles and Practice, 5th edition. Saunders, Elsevier; 2012. pp. 554-74.
5. Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtiz D, et al: Practice parameter: evaluation of the child with global developmental delay—Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2003;60:367-80.
6. Van Karnebeek CDH, Janswiejer MCE, Leenders AGE, Offringa M. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. Eur J Human Genet. 2005;13:2-65.
7. Williams J. Global developmental delay—globally helpful? Dev Med Child Neurol. 2010;52:227.

CHAPTER 84

Approach to Psychomotor Regression in Children

Anaita Udwadia Hegde, Omkar P Hajirnis

INTRODUCTION

Neurodevelopmental regression is often challenging to clinicians in terms of diagnosis and management. The purpose of this chapter is to outline a systematic approach to a child presenting with suspected neurodevelopmental regression. Reaching a specific diagnosis is of pivotal importance for providing appropriate early therapy, prognosis, and genetic counseling. Although the causes of psychomotor retardation are individually rare, the combined estimate can be as high as about 1 in 2,000 live births.

DEFINITION

Neuroregression is defined as loss of previously achieved milestones in a previously healthy child with progressive loss of speech, hearing, vision, locomotion, bulbar function, and cognitive abilities. They are often associated with seizures. It is also extended to a decrease in the normal rate of acquisition of developmental milestones, followed by a developmental plateau.

CLINICAL APPROACH

A history of loss of skills helps distinguish the neurodegenerative from static, nonprogressive conditions. The onset may be insidious but is sometimes acute and may hence cause diagnostic confusion. The regression may thereafter progress at varying speeds or also have an intermittent plateauing of milestones prior to the next period of deterioration, which may be triggered by factors like viral infections. The presentations can be varied from behavioral changes to recurrent seizures mimicking epileptic encephalopathies. It is a dictum that greater the genetic deficiency, earlier and more aggressive is the presentation. Knowing the age at which signs first appear helps enormously in narrowing the diagnosis. The diagnostic process begins with a detailed family history as inheritance patterns are disease specific and a history of consanguinity is especially important in autosomal recessive disorders.

Clinical Pearl

- It is important to differentiate between developmental delay and developmental regression.

The four-step approach described below provides a useful strategy for initial evaluation of patients with neurodegenerative diseases:

- Identify the form of inheritance: autosomal recessive, autosomal dominant, X-linked, and mitochondrial inheritance
- Age at onset of regression: based on this, the disorders can be divided into neonatal, infantile, late infantile, and childhood or juvenile onset
- Determine from the history the predominant neuroanatomical system involved: gray matter, white matter, basal ganglia, cerebellar, spinal cord, etc.
- Review other system involvements: involvement of skin, liver, spleen, dysmorphic features, ophthalmic changes, presence of seizures, peripheral neuropathy, etc.

Step 1: Inheritance

A detailed family tree or a pedigree chart helps to define different modes of inheritance. The most common modality of inheritance is autosomal recessive, seen commonly in our circumstances due to high degree of consanguineous marriages. It is important to note that mitochondrial disorders can be inherited by maternally-transmitted modalities or an autosomal pattern of inheritance. This is because mitochondria contain two types of genetic material, namely mitochondrial deoxyribonucleic acid (DNA) which can only be passed on from the mother and nuclear DNA which is passed on from both parents. A few examples of neurodegenerative disorders with their modes of inheritance are listed in the table 1.

TABLE: 1 Neurodegenerative disorders and their inheritance patterns

Inheritance	Neurodegenerative disorders
Autosomal recessive	• Disorders involving white matter ○ Canavan's disease ○ Krabbe's disease ○ Metachromatic leukodystrophy • Disorders involving gray matter ○ Progressive myoclonic epilepsies (Lafora body disease, etc.) ○ Progressive infantile poliodystrophy ○ Sialidosis type 1 ○ Neuronal ceroid lipofuscinosis (variable) • Disorders involving predominantly basal ganglia ○ Wilson's disease ○ Pantothenate kinase-associated neurodegeneration • Spinocerebellar degeneration/spinal cord and peripheral nerve conditions ○ Friedreich's ataxia ○ Spinal muscular atrophy ○ Infantile neuroaxonal dystrophy ○ Refsum's disease
Autosomal dominant	• Juvenile Huntington's disease • Dystonia musculorum deformans • Spinocerebellar ataxia • Familial spastic paraplegia • Charcot-marie-tooth disease
X-linked recessive	• Pelizaeus-Merzbacher disease • Adrenoleukodystrophy • Menke's kinky hair syndrome
Mitochondrial	• Alpers-Huttenlocher syndrome • Leigh's syndrome • Kearns Sarne syndrome • Myoclonic epilepsy with ragged red fibers • Leber's hereditary optic neuropathy • Mitochondrial encephalomyopathy with lactic acidosis and stroke like episodes

Step 2: Age of Onset

The age of onset of neuroregression helps us classify the disorders. It goes without saying that the earlier the onset, the more severe and progressive is the disorder. Those who manifest late in childhood or adolescence usually have milder symptoms and the progress is slower as compared to those who manifest early and progress faster. Age of onset is divided into neonatal (0–1 month), infantile (1–12 months), late infantile (1–5 years), childhood (5–10 years), and adolescent or juvenile onset (5–15 years).

Age-related Presentations

Neonatal onset (0–1 month): acute encephalopathy presents early in life with recurrent vomiting, poor feeding, lethargy, and dehydration. This suggests a gray matter involvement initially representing a toxic or intoxication encephalopathy. Liver involvement may be evident in few disorders presenting with jaundice, liver failure, and failure to thrive.

Infancy onset (1–12 months): onset at this age usually presents with loss of interest in surroundings which can be either visual or in nonverbal communication. The inability to roll over, sit, use the hands in play, and vocalize suggests neurologic difficulties at this age.

Late infantile age group onset (1–5 years): the changes noted in this age group are more commonly in the speech and behavior along with motor disabilities. They may exhibit clumsiness, tremors, and gait abnormalities. They can present primarily with seizures.

Juvenile age group onset (5–15 years): in disorders of childhood and adolescence, the onset is more insidious and the progression slower than in disorders appearing earlier. Regression in this age group can present with seizures along with deterioration of school performance, lack of new learning skills, handwriting changes, poor concentration, and memory.

Step 3: Neuroanatomical Localization

The next most important feature to assess from the history and examination is the onset of symptoms and progression to the present state. The first sign or symptom of neuroregression usually but not always gives a clue to the neuroanatomical localization. For example, gait or motor regression at the onset is suggestive of white matter pathologies, whereas seizures, dementia, and cognitive decline is more suggestive of gray-matter pathologies. Those who start with chorea, dystonia, and involuntary movements suggest that the primary area of involvement is the basal ganglia. Over a period of time, symptoms evolve to involve multiple neuroanatomical sites; for example, Krabbe's disease starts with increase in tone or loss of motor milestones suggestive of white matter pathology. There may also have some dystonia, indicative of basal ganglia involvement and over time, the child will become loose with absent reflexes suggestive of additional peripheral neuronal involvement.

Hence by careful history taking and detailed general and nervous system examination, it is easier to determine which pathways are involved and the range of diagnostic possibilities is more easily circumscribed (Algorithm 2).

Clinical Pearl

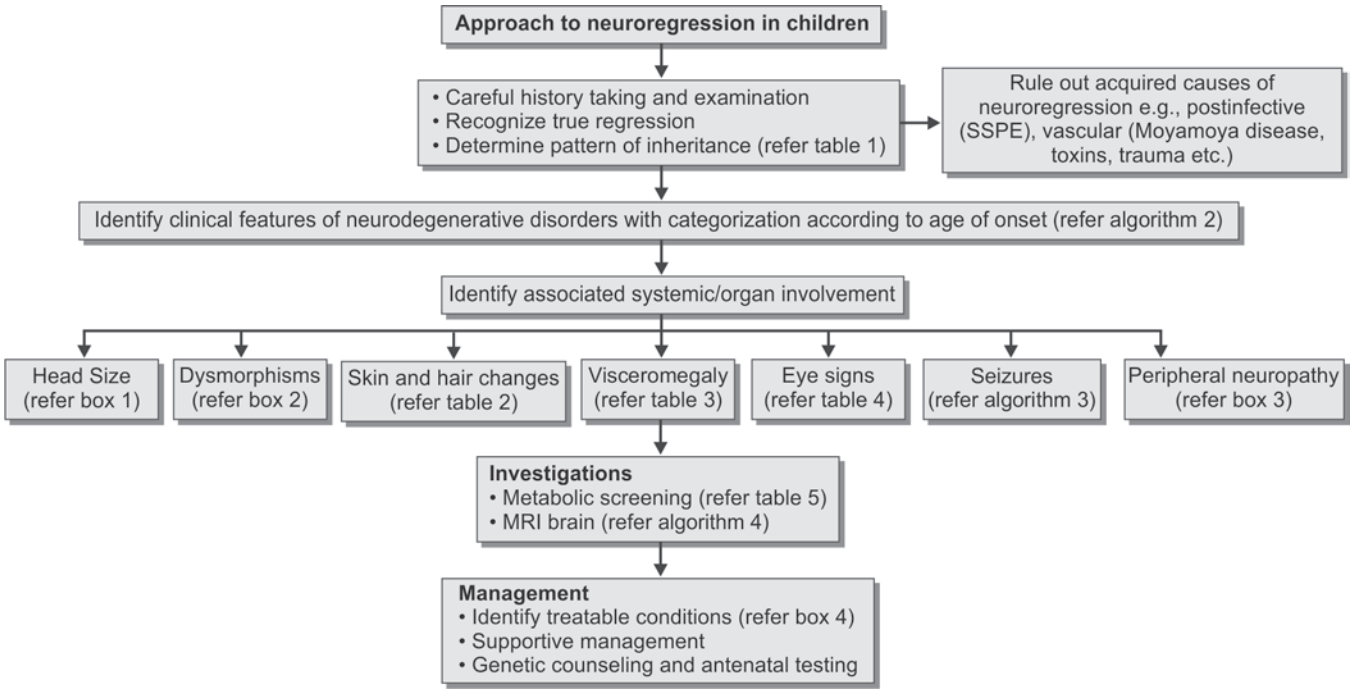
- The first sign of neuroregression usually correlates best with neuroanatomical localization.

Step 4: Identifying Associated System/Organ Involvement

Multiple systems get involved with different degenerative disorders. The physician needs to carefully screen other associated systemic involvements beginning with a detailed head-to-toe general examination. The examination should

ALGORITHM 1

Approach to psychomotor regression in children



SSPE, subacute sclerosing panencephalitis.

begin with height, weight, and head-circumference measurements. Many disorders eventually lead to acquired microcephaly due to brain atrophy; others are noted for megalencephaly. Dysmorphisms may be evident at birth or may be noted later as the disorder manifests (Boxes 1 and 2).

A careful observation of the skin and hair and a full assessment of the chest, abdomen, and extremities are part of the examination (Tables 2 and 3).

A detailed ophthalmologic examination with fundoscopy is pivotal and the various disorders associated with eye abnormalities are listed in table 4.

Seizures may be a presenting complaint or may present as the disease progresses. The age of onset and also the seizure type provides useful information to arrive at the diagnosis (Algorithm 3). The peripheral nervous system may be involved in certain neurodegenerative disorders giving rise to diminution or absence of deep-tendon reflexes and sensation (Box 3).

Thus, all the features and clues mentioned above along with a careful history and examination help to arrive at a diagnosis. Each associated system needs to be examined in detail to be able to put all the pieces of the puzzle together.

Box 1: Neurodegenerative disorders with megalencephaly

- Alexander disease
- Tay-Sachs disease
- Canavan's disease
- Sandhoff's disease
- Glutaric aciduria type I

Box 2: Neurodegenerative disorders with dysmorphic features

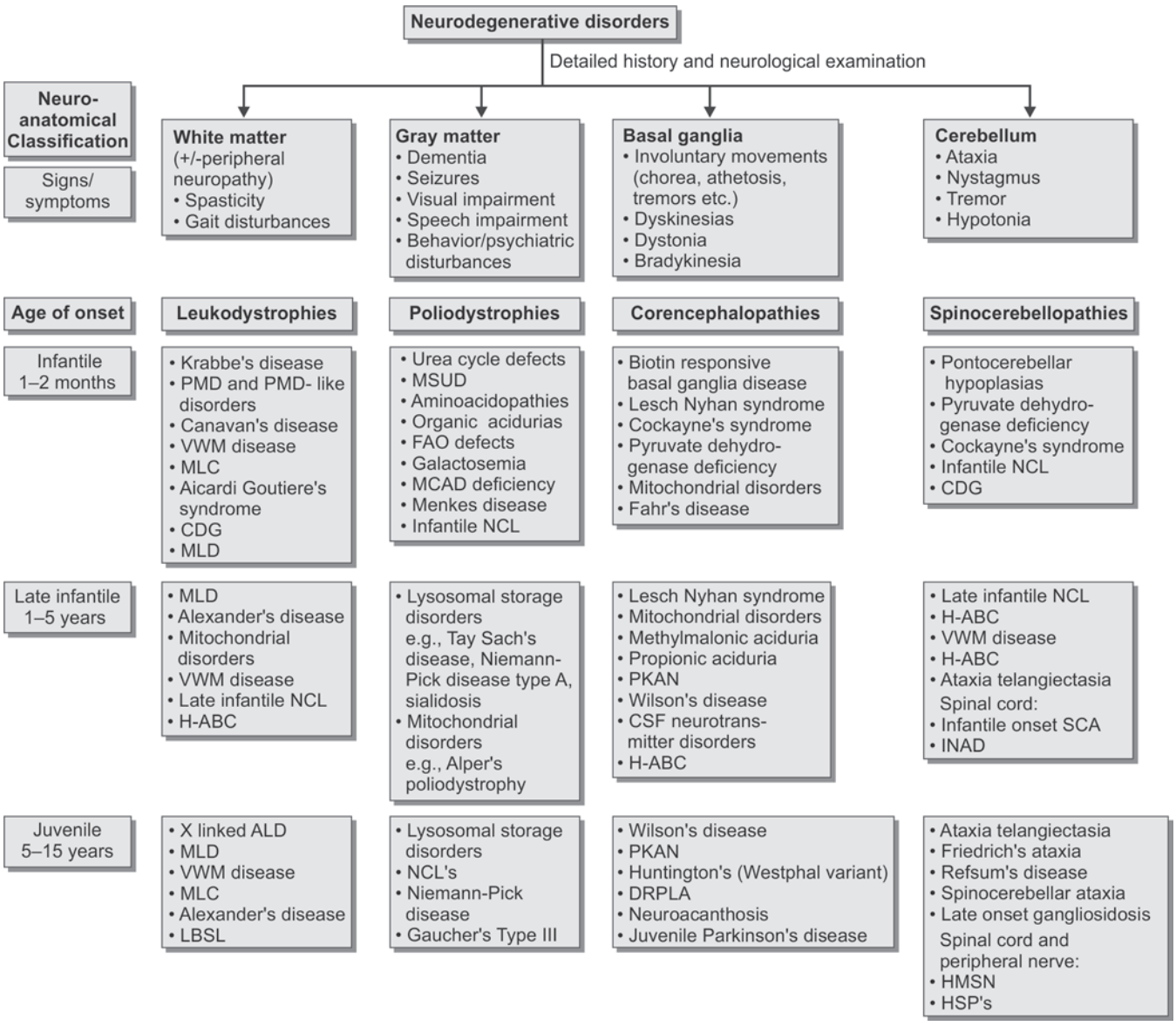
- Zellweger's syndrome
- Inclusion-cell disease
- Smith-Lemli-Opitz syndrome
- 18 q syndrome
- Pyruvate dehydrogenase deficiency
- Mucopolysaccharidoses
- Oligosaccharidoses
- Mucolipidosis
- Prader-Willi syndrome
- Cockayne's syndrome
- GM1 Gangliosidosis

TABLE 2: Hair and skin changes in neurodegenerative disorders

Hair changes	Skin changes
• Menkes syndrome (kinky, colorless or steel-colored and easily broken—Pili torti) • Biotinidase deficiency (alopecia and fine, brittle hair) • Homocystinuria (thin and fair hair) • Cockayne's syndrome (fine, thin, and dry hair) • Mucopolysaccharidosis (alopecia areata and pale-colored hair) • Arginosuucinic acidurias (sparse brittle hair) • Ataxia telangiectasia (progeroid changes like premature graying of hair) • Multiple sulfatase deficiency (hypertrichosis)	• Phakomatosis ○ Neurofibromatosis ○ Tuberous sclerosis ○ Sturge-Weber syndrome • Angelman's syndrome • Hypomelanosis of Ito • Incontinentia pigmenti • Homocystinuria (pale, pink skin, malar rash, livedo reticularis) • Ataxia telangiectasia (vitiligo, warts, granulomas) • Cockayne's syndrome (photosensitivity) • Multiple sulfatase deficiency (ichthyosis)

ALGORITHM 2

Clinical features of neurodegenerative disorders with categorization according to age of onset



PMD, pelizaeus merzbacher disease; VWM, vanishing white matter disease, CDG, congenital defects of glycosylation, MLC, megalencephalic leukoencephalopathy with subcortical cysts; MSUD, maple syrup urine disease; FAO, fatty acid oxidation, MCAD, medium chain acyl-coa dehydrogenase, NCL, neuronal ceroid lipofuscinosis, ALD, adrenoleukodystrophy, PKAN, pantothenate kinase-associated neurodegeneration, H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum, INAD, infantile neuroaxonal dystrophy; DRPLA, dentatorubral-pallidoluysian atrophy; SCA, spinocerebellar ataxia; HMSN, hereditary motor sensory neuropathy; HSP, hereditary spastic paraplegia, LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation, MLD, metachromatic leukodystrophy.

INVESTIGATIONS

The investigations should cater to the common causes seen in each age group and proceed from common to rarer causes. All disorders that are potentially treatable or have genetic implications should be screened in all cases. For example, thyroid function tests should be done as hypothyroidism can present with no obvious signs in infancy. Although below mentioned is an exhaustive list of investigations, the physician should prioritize from specific clues in the history and physical examination. The basic metabolic screen which includes blood, urine, and sometimes the cerebrospinal fluid examination should be done initially along with neuroimaging [magnetic resonance imaging (MRI) brain] for suspected metabolic disorders. More advanced tests should be prioritized according to the condition suspected. Now genetic diagnosis is the gold standard of diagnosis and wherever possible should be attempted as it is useful not only for diagnosis but also for future genetic counseling (Table 5).

TABLE 3: Visceromegaly associated with neurodegenerative disorders

Hepatosplenomegaly
• Lipid storage disorders
  ○ Gangliosidosis
  ○ Mucolipidosis
  ○ Farber disease
• Mucopolysaccharidosis
  ○ Hurler's syndrome
  ○ Hunter's syndrome
• Glycogen storage disorders (GSD)
  ○ GSD Type IV
	Hepatomegaly
	• GSD Type 1
	• GSD Type II, VI, IX
	• Wolman's disease
	• Zellweger's syndrome
	• Hunter's syndrome
	• Glycogenosis Type II

Splenohepatomegaly • Gaucher's disease • Niemann-Pick disease	**Splenomegaly** • Alpha mannosidosis • Hurler's syndrome and other mucopolysaccharidosis • Tangier disease • Sandhoff's disease

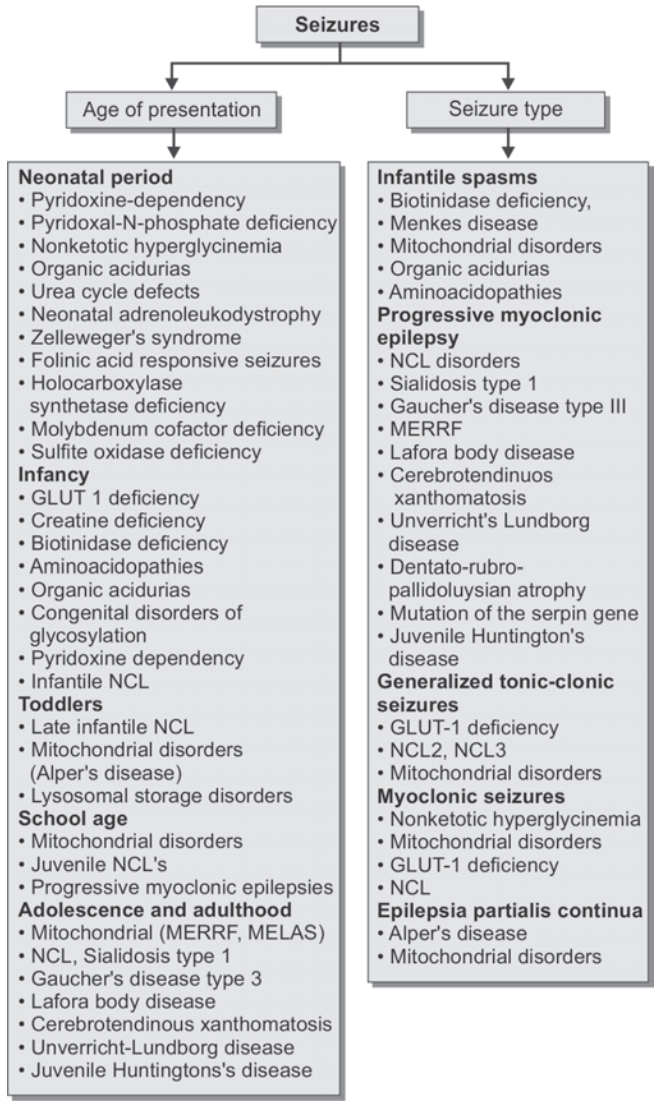
TABLE 4: Eye abnormalities associated with neurodegenerative disorders

Eye abnormalities	
Cornea	**Pigmentary retinopathy**
• Wilson's disease • Hurler's disease • Maroteaux-Lamy syndrome • Morquio's disease • Mucolipidosis type IV • Mannosidosis • Fucosidosis • Aspartylglucosaminuria	• Fetal cytomegalovirus infection • Fetal toxoplasmosis • Hallervorden-Spatz disease • Kearns-Sayre syndrome • Neuronal ceroid lipofuscinosis • Zellweger's syndrome • Cockayne's syndrome • Congenital disorder of glycosylation • Abetalipoproteinemia
Conjunctiva	**Cherry-red macula**
• Ataxia telangiectasia	• GM1 gangliosidosis • Niemann-Pick disease, types A and B • Tay-Sachs disease • Sialidosis type I
Lens	**Optic atrophy**
• Homocystinuria • Myotonic dystrophy • Galactosemia • Lowe syndrome • Fabry's disease • Cerebrotendinous xanthomatosis	• Adrenoleukodystrophy • Metachromatic leukodystrophy • Globoid cell leukodystrophy • Pelizaeus-Merzbacher disease • Mitochondrial–MELAS, LHON • Canavan disease • Sulfite oxidase deficiency • 3-methylglutaconicaciduria III
Cortical blindness	**Abnormal eye movements**
• MELAS syndrome	• Opsoclonus myoclonus syndrome (with progressive ophthalmoplegia) • AD spinocerebellar ataxias • Ataxia telangiectasia • Gaucher's disease, types 2 and 3 • Kearns-Sayre syndrome • Niemann-Pick disease type C • Pelizaeus-Merzbacher disease

AD, autosomal dominant; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; LHON, Leber's hereditary optic neuropathy.

ALGORITHM 3

Epilepsies associated with neurodegenerative disorders



NCL, neuronal ceroid lipofuscinosis; MERRF, myoclonic epilepsy with ragged red fibers, MELAS, mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, GLUT, glucose transporters.

The workup involves neuroimaging in most cases. Magnetic resonance imaging with or without contrast is preferred over computed tomography. It is useful for visualizing cerebral malformations and for documenting the degree of cerebral atrophy or white matter changes, such as those that occur in various leukodystrophies. Magnetic resonance imaging with contrast is ordered in suspected adrenoleukodystrophy, Alexander's disease, etc. Specific spectroscopy is useful in mitochondrial disorders, Canavan's disease, and creatine deficiency. Increased N-acetylaspartate peak is detected in Canavan's disease, and in mitochondrial disorders a high lactate peak may be found. Magnetic resonance imaging with angiography is done in suspected Menke's disease to demonstrate tortuous vessels.

Box 3: Peripheral neuropathies associated with neurodegenerative disorders

Episodic neuropathy
- Acute intermittent porphyrias
- Tyrosinemia type I

Progressive neuropathy
- Metachromatic leukodystrophy
- Refsum's disease
- Mitochondrial neuropathy/myopathy (Leigh's syndrome, neuropathy ataxia and retinitis pigmentosa syndrome, etc.)
- Abetalipoproteinemia
- Pyruvate dehydrogenase deficiency
- Friedreich's ataxia
- Juvenile GM2 gangliosidosis
- Krabbe's disease (late infantile form)
- Adrenomyeloneuropathy
- Cockayne's syndrome
- Methylenetetrahydrofolate reductase deficiency
- Carbohydrate deficient glycoprotein syndrome
- 3-hydroxy dicarboxylic aciduria
- Familial dysautonomia

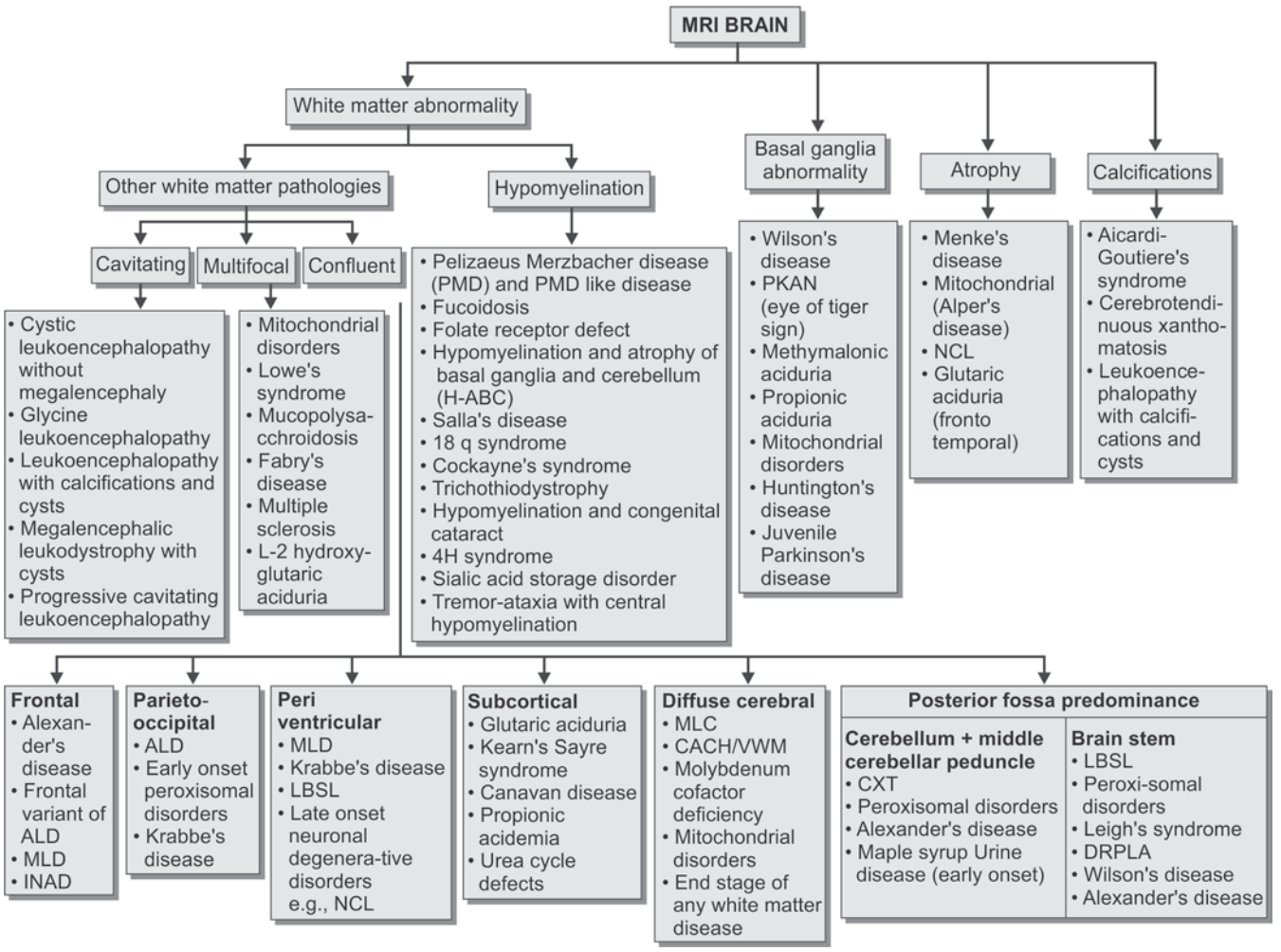
TABLE 5: Investigations for suspected metabolic/neurodegenerative disorders

Test/Study	Abnormalities of Interest
Urine	
• Collect each fresh sample separately in clean container and store at 4°C (short term). • Freeze at –20°C for long-term storage. Compare samples collected before and after treatment.	• Smell (special odor), look (special color) • Acetone • Reducing substances • Ketoacids (DNPH) • pH • Electrolytes • Sulfite oxidase • Uric acid • Aminoacids • Organic acids (quantitative) • 24-h urine copper excretion • MPS screening and electrophoresis
Blood	
• 5 mL plasma (heparinized or plain tube) • 5–10 mL whole blood in EDTA (for molecular DNA studies) • Blood on filter paper (Guthrie's test)	• Complete blood count • Electrolytes (for anion gap, glucose, calcium) • Blood gas (pH, pCO_2, HCO_3^-, pO_2) • Uric acid • Prothrombin time • Liver function tests • Thyroid function tests • Plasma ammonia (on ice) • Lactic acid (on ice; stat processing) • Pyruvic acid (requires specialized deproteinization tube) • Serum ketones • Serum homocysteine • Serum vitamine B12 levels • Serum copper and ceruloplasmin
	• Free fatty acids • Plasma amino acids • Plasma organic acids • Acylcarnitine profile
Advanced workup	• Very long-chain fatty acids • Immunoglobulin levels • Autoantibodies • White cell enzyme studies to look for vacuolation of lymphocytes • Isoelectric focusing of transferrin
Cerebrospinal fluid	
Neurotransmitters are collected in specific tubes and transported in dry ice; collect minimum 2 mL stat (on ice) for chemistries and lactate	• Opening and closing pressures • Cell count, protein, glucose with simultaneous blood glucose (For suspected GLUT1 deficiency—4 h minimum fasting needed) • Lactate • Pyruvate • Neurotransmitters
Genetic analysis	• DNA analysis of specific suspected disorders
Bone marrow examination	• For foam cells, sea blue histocytes, etc.
Skin biopsy	• Enzyme analysis in cultured fibroblasts (lysosomal disorders) • Staining for lipids, glycogen, cholesterol, fatty acids • NP-C (cholesterol esterification, filipin staining) • DNA analysis • Electron microscopy for storage inclusions (lysosomal, mitochondrial NCL)
Muscle biopsy	• Light and electron microscopy, immunohistochemistry, trichrome for ragged red fibers, lipid storage, etc.
Liver biopsy	• Staining for accumulation of lipids, glycogen, cholesterol, fatty acids, immunohistochemistry
EMG/SSEP	• Lower motor neuron disease patterns • Neuropathies • Myopathies
EEG	• Associated seizures (clinical and sub clinical) and their pattern
ERG	• In suspected retinitis pigmentosa
BERA	• In suspected hearing loss
USG abdomen	• Organomegaly, nephrocalcinosis, renal cysts
2D echocardiography	• Cardiomyopathy in storage disorders, rhabdomyosarcomas in tuberous sclerosis
X-ray screening	• For dysostosis multiplex in MPS, assessment of bone age

NCL, neuronal ceroid lipofuscinosis; NP-C, niemann-pick type c disease, NTBC, nitisinone, DNPH, 2 4-dinitrophenylhydrazine, GLUT, glucose transporter; MPS, mucopolysaccharidosis; EMG/SSEP, electromyography/somatosensory evoked potentials; EEG, electroencephalogram; ERG, electroretinography; BERA, brainstem evoked response audiometry.

ALGORITHM 4

Approach to neuroregression according to major neuroimaging pattern



MLD, metachromatic leukodystrophy; ALD, adrenoleukodystrophy; INAD, infantile neuroaxonal dystrophy, LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; NCL, neuronal ceroid lipofuscinosis; MLC, megalencephalic leukoencephalopathy with cysts; CACH/VWM, childhood ataxia with central hypomyelination/vanishing white matter; CXT, cerebrotendinous xanthomatosis; PKAN, pantothenate kinase-associated neurodegeneration.

Thus, the MRI is an important ancillary test in approaching neuroregression and helps the clinician to delineate disorders based on the findings on it (Algorithm 4).

Clinical Pearl

- Carefully planned investigations are needed rather than ordering a battery of tests

MANAGEMENT

The specific cause of regression in childhood can be difficult to elucidate and a large number of children remain undiagnosed. It is essential to maintain the child's quality of life and help in supportive care. Careful attention to nutrition helps in maintaining general well-being. Symptomatic treatment of disturbed sleep, behavior and mood disturbances should be done. A small number of disorders have specific treatment and maximum effort should be made to diagnose these conditions. They can be enumerated as in the box 4.

Bone marrow transplantation has been tried in various disorders and has shown promise when it has been done at a stage where irreparable brain damage has not occurred. This includes lysosomal storage disorders, metachromatic leukodystrophy, Gaucher's disease, mucopolysaccharidosis, and adrenoleukodystrophy.

Every effort should be made to prevent the family from having another affected child with the help of antenatal screening.

Box 4: Treatable neurodegenerative/metabolic conditions

- Wilson's disease—D-Penicillamine and other chelating agents
- Aminoacidopathies—specific diets. Nitisinone in tyrosinemia
- Pyridoxine and pyridoxal phosphate dependent seizures—pyridoxine
- Biotinidase deficiency and biotin responsive basal ganglia disease—biotin
- Glucose transporter-1 deficiency—ketogenic diet
- Folinic acid responsive seizures—folinic acid
- Creatine deficiency syndromes—creatine
- Serine biosynthesis disorders—L-serine and glycine
- Neurotransmitter disorders—dopamine in some cases
- Inborn errors of folic acid and cobalamin synthesis—folic acid and vitamin B12
- Homocysteinemia, methylenetetrahydrofolate reductase—B12, folic acid, pyridoxine
- Gaucher's disease, Fabry's disease, mucopolysaccharidosis, Pompe's disease—enzyme replacement

ANTENATAL TESTING AND COUNSELING

Having an accurate genetic diagnosis helps immensely for genetic counseling and antenatal testing. A clear explanation of the inheritance pattern will clear up misunderstandings in the family about who is "at fault". Once a genetic diagnosis is made, this should be used to screen other family members. This is especially important for younger, as yet asymptomatic, siblings who might benefit greatly from specific therapies if these are instituted prior to the development of symptoms or in the early symptomatic period.

Clinical Pearl

- Every effort should be taken to diagnose treatable causes of psychomotor regression.

The following is an algorithmic flowchart to aid the physician in approaching a child with psychomotor regression. However, significant overlaps exist and also disorders with atypical presentations can confuse the physician. A systematic clinical approach with a sound theoretical knowledge helps in reducing the investigative burden on the patient.

KEY POINTS

- ☞ Never ignore a parent's concerns. A history of loss of milestones helps distinguish neuroregression from developmental delay
- ☞ A detailed pedigree chart helps to identify different modes of inheritance. The most common modality in neurodegenerative conditions is autosomal recessive type
- ☞ The dictum is earlier the onset, more severe and aggressive is the disorder due to greater genetic deficiency. The regression may progress at varying speeds and some may evolve with time
- ☞ The presenting symptom is usually but not always a pivotal clue to the neuroanatomical localization. Magnetic resonance imaging with or without contrast is preferred over computed tomography as the neuroimaging of choice and is an important ancillary test in approaching neuroregression
- ☞ The disorders that have specific treatment should always be looked out and diagnosed promptly
- ☞ Although most disorders do not have specific treatment, maximum effort should be made to reach a genetic diagnosis for genetic counseling and antenatal testing later. Every effort should be made to prevent the family from having another affected child.

SUGGESTED READINGS

1. Barkovich AJ. An approach to MRI of metabolic disorders in children. Journal of Neuroradiology. 2007;34:75-88.
2. Cognitive and motor regression. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF (Eds). Swaiman's Pediatric Neurology: Principles and Practice, 5th ed. Elsevier Saunders; 2012. pp. 575-603.
3. Metabolic and heredodegenerative disorders of central nervous system. In: Aicardi J (Ed). Diseases of the Nervous System in Childhood, 3rd edition. Mac Keith Press; 2009. pp. 243-371.
4. Metabolic disorders and leukodystrophies. In: Sims KB, Peters JM, Musolini PL, Elibol MZ (Eds). Handbook of Pediatric Neurology. Lippincots Williams and Wilkins; 2014. pp. 155-91 and 206-20.
5. Neurology—degenerative brain disorders. In: Forfar & Arneil's Textbook of Pediatrics, 7th ed. Churchill Livingstone; 2008. pp. 898-903.
6. Psychomotor retardation and regression In: Fenichel's Clinical Pediatric Neurology: A Signs and Symptoms Approach, 6th ed. Elsevier Saunders; 2009. pp. 119-52.
7. Schiffmann R, van der Knaap MS. An MRI-based approach to the diagnosis of white matter disorder. Neurology. 2009;72(8):750-9.

CHAPTER 85

Approach to a Child with First Seizure

Anju Aggarwal, Anaita Udwadia Hegde

INTRODUCTION

In 2005, a Task Force of the International League Against Epilepsy (ILAE) formulated conceptual definition of a "seizure" where an epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Epilepsy was defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures more than 24-hours apart. A seizure that is provoked by a transient factor acting on an otherwise normal brain to temporarily lower the seizure threshold, does not count toward a diagnosis of epilepsy. However, conceptually, epilepsy also exists after at least one unprovoked seizure, when there is high risk for another, although the actual required risk is debatable.

The term "provoked seizure" is considered being synonymous with a "reactive seizure" or an "acute symptomatic seizure".

NEWER DEFINITIONS

In the need to address circumstances with high risk for future seizures after a first unprovoked seizure, the ILAE commissioned a Task Force in December 2013 to formulate an operational definition of epilepsy for the purposes of clinical diagnosis (Box 1).

STATISTICS

About 2–5% of children experience a seizure one time or the other in their lifetime. This includes both febrile and afebrile seizures. After a single unprovoked seizure, risk for another is 40–52%. With two unprovoked nonfebrile seizures, the chance by 4 years of having another is 73%, with a 95% confidence interval (CI) of 59–87%, subsequently herein portrayed as approximately 60–90%.

Box 1: Operational (practical) clinical definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions:

- At least two unprovoked (or reflex) seizures occurring >24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome
- Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years

Risk of Recurrence after First Status Epilepticus

- The recurrence risk after a prolonged event or status epilepticus is the same as that of a brief seizure.
- However, if they do recur they have a higher chance of getting a repeat status epilepticus.

Clinical Pearls

- If an event is ambiguous, it is better to wait for a recurrence for clarification
- Misdiagnosis of an "epileptic" seizure may be more stigmatizing than a delayed diagnosis of epilepsy.

High Risk Factors Associated with Recurrence after First Unprovoked Seizure

- Pre-existing static brain abnormalities
- Focal neurological deficits
- Focal seizure semiology (including Todd's paresis)
- Focal/generalized epileptiform activity on electro-encephalogram (EEG)

- Tumors or other progressive lesions
- Status epilepticus
- Family history of epilepsy
- Previous febrile seizures.

Fctors Known to Provocate Seizures and Epilepsy

Fctors known to provocate seizures and epilepsy are given in table 1.

TABLE 1: Factors provoking seizures and epilepsy

Acute symptomatic seizures	Susceptible to epilepsy
• Fever • Head injury • Hypoglycemia • Electrolyte disturbance • Brain infections • Stroke • Hemorrhage • Drugs • Minor risk of epilepsy (3–10%)	• Sleep deprived • Severe psychological stress • Extremes of emotion • Fatigue • Infections • Family history • Higher risk of epilepsy (50–70%)

Clinical Evaluation after a First Seizure in a Child

Whenever a child comes with first episode of seizure, what we need to know is:

- Is it a seizure or other events which mimic seizures?
- What is the type of seizure?
- What is the possible etiology?
- What investigations are required?
- Does he or she require therapy?
- Prognosis in terms of recurrence of seizure or remission of epilepsy?

HISTORY

A good clinical history is what is going to help us decide the type of seizure and distinguish it from nonepileptic events. Best is to elicit history from the care taker or parent who has witnessed the seizure. If not possible, history should be elicited again after the initial control of seizure activity.

Questions that need to be addressed are:

- What was the child doing when he had a seizure?
- What happened in intricate detail?
- Did the eyes turn to one side?
- Did the child become stiff?
- Did the child have clonic movements or jerks or just brief flickering of eyes?
- How long the seizure did last?
- Was the child unconscious after that and for how long?
- Did the child experience any weakness of any limb after the seizure?
- Did the child pass urine and stool during the episode?
- Did the child suffer any injury during the seizure?

History should include a detailed antenatal history of mother, birth history, and developmental history to find out any associated risk factors or etiology of seizures.

EXAMINATION

In addition to the vitals including a blood pressure reading and general physical examination, one should look for neurocutaneous markers, microcephaly, dysmorphic features, and signs of raised intracranial pressure. Detailed neurological examination is required to detect neurological deficit, altered sensorium and meningeal signs should be looked for.

Clinical Pearl

- Determination of type of seizure and distinction from nonepileptic events is best done by clinical history (preferably from the person who has witnessed the seizure).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of seizures can range from a variety of clinical presentations. Understanding the occurrence and nature of minor events is crucial to make an accurate diagnosis. These are principally:

- Loss of awareness
- Generalized convulsive movements
- Drop attacks
- Transient focal motor attacks
- Transient focal sensory attacks
- Facial muscle and eye movements
- Psychic experiences
- Aggressive or vocal outbursts
- Episodic phenomena in sleep
- Prolonged confusional or fugue states.

Some of the common differential diagnoses are described below:

Syncope with Secondary Jerking Movements

People who faint often have small, brief myoclonic twitches of the extremities which can be prominent with prolonged cerebral hypoperfusion.

Nonepileptic Attack Disorder

Nonepileptic attack disorder (NEAD), previously known as pseudoseizures typically gives rise to episodes of two broad types:

1. Attacks involving motor phenomena
2. Attacks of lying motionless.

A child with NEAD will have a seizure-like-episode only during the awake state, may remember the sequence of events well, will not have any injury during seizure, may have family history of seizure and may not have seizure-like-movements of any particular seizure type. They may talk during the seizure like activity, usually will not have cyanosis or incontinence. They usually do not have any postictal changes. Seizure can be precipitated or mimicked on suggestion.

Breath Holding Spells

Children of breath-holding-spells will have seizure like activity only during awake period when the child is not attended , usually not followed by neurological deficit; may be associated with anemia, usually seem to occur in children less than 2 years.

Sleep Disorders

At times sleep disorders as night terrors mimic seizures usually seen in children 4–8 years of age. Child wakes up with sweating, tachycardia, tachypnea, fear, and anxiety. They do not remember the event. These are usually self-limiting. Nightmares occur in children 5–12 years, who suddenly get up during rapid eye movement sleep with an unpleasant dream; they have autonomic activity and are able to describe the event.

Primary Cardiac or Respiratory Abnormalities Presenting with Secondary Anoxic Seizures

Episodes of complete heart block may have syncopal features followed by collapse and secondary anoxic seizures. Usually the attacks last for less than 1 minute.

Involuntary Movement Disorders and Other Neurological Conditions

There is no alteration in consciousness. Some of the common examples include paroxysmal kinesigenic choreoathetosis, idiopathic torsion dystonia, etc.

Hyperekplexia

Attacks are characterized by excessive startle, may cause stiffening, and collapse with a sudden jerk of all four limbs. Attacks are provoked by sudden unexpected stimuli, usually auditory. Hyperekplexia needs to be distinguished from seizures induced by startle.

ROLE OF INVESTIGATIONS

Investigations after first unprovoked seizure:

- Routine labs: complete blood counts, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, calcium, and magnesium based on individual clinical circumstances—based on suggestive history, clinical findings or failure to return to baseline alertness
- Lumbar puncture: nonfebrile seizure does not warrant a lumbar puncture
  - In less than 6-months-old or with persistent alteration of alertness and meningeal signs, lumbar puncture should be performed
- Electroencephalogram is recommended as part of the diagnostic evaluation of a child with a first unprovoked seizure, preferably 5–7 days after the seizure
- Neuroimaging
  - Emergency imaging:
    - Computed tomography (CT) Scan is equally effective as magnetic resonance imaging
    - Child of any age who experiences postictal focal deficit not resolving/not returned to baseline after many hours
    - Suspicion of structural lesion
  - Nonemergency imaging:
    - Magnetic resonance imaging is routinely much better for all epilepsies
    - Some indications for CT scan especially in our country where cost is a major issue.

Clinical Pearl

- A normal electroencephalogram does not rule out and an abnormal electroencephalogram does not prove epilepsy; it is only a supportive investigation.

TREATMENT RECOMMENDATIONS

- Treatment with antiepileptic drugs is not indicated for the prevention of epilepsy after the first unprovoked seizure
- Treatment is considered in circumstances where the benefit of reducing risk of second seizure outweighs the risk of pharmacologic and psychosocial side effects.

Clinical Pearl

- Treatment decision is made depending on the risk of recurrence of seizure in a particular situatio.

COUNSELING AND EMERGENCY HOME MANAGEMENT

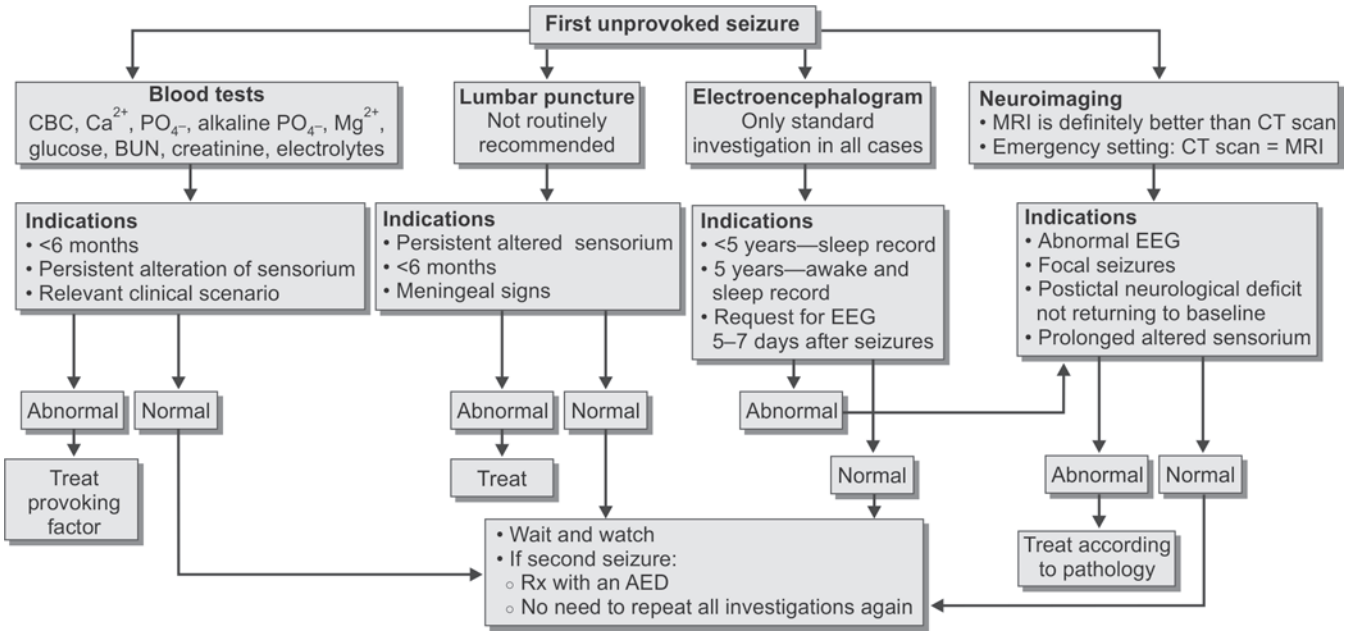
Education of the child and parents about seizures, epilepsy and, medication plays an important part in reducing the emotional stress on the family. Providing the child and family with written material on epilepsy and antiepileptic medications can be very helpful.

It is important to review appropriate seizure precautions with the family, including proper positioning of a child during a seizure and issues regarding water safety and driving. The parents and other care givers can be taught the emergency management of a seizure when prolonged beyond 3–4 minutes with usage of intranasal or buccal midazolam or rectal diazepam as per the age and weight of the child.

The following is an algorithmic approach (Algorithm 1) to management of a first unprovoked seizure in a child.

ALGORITHM 1

Management of first unprovoked seizure



CBC, complete blood count; Alk PO_4, alkaline phosphatase; BUN, blood urea nitrogen; EEG, electroencephalogram; N, normal; Abn, abnormal; AED, antiepileptic drugs; MRI, magnetic resonance imaging; CT, computed tomography.

KEY POINTS

- ☞ Simple febrile seizures do not require any investigates as magnetic resonance imaging or electroencephalogram (EEG). Investigations as to the cause of fever should be carried out
- ☞ First nonfebrile seizure requires a detailed clinical evaluation, electroencephalogram, and neuroimaging whenever possible
- ☞ There is no long-term difference if treated after the first or second seizure
- ☞ Antiepileptic drug treatment is not usually started after a first unprovoked seizure, unless the clinical or EEG features suggest a high risk of recurrence
- ☞ Patient education is perhaps the most important and often neglected aspect of management of seizures and hence needs to be stressed on when explaining to the care givers.

SUGGESTED READINGS

1. Arzimanoglou A, Guerrini R, Aicardi J. In: Arzimanoglou A, Guerrini R, Aicardi J (Eds). Aicardi's Epilepsy in Children, 3rd ed. Lippincott Williams & Wilkins; 2004, pp. 11-114.
2. Freeman JH. Practice parameter: evaluating a first nonfebrile seizure in children: Report of the Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. Neurology. 2001;27:56:574.
3. Michoulas A, Farrell K, Connolly M. Approach to a child with a first afebrile seizure. BCMJ. 2011:53:274-7.
4. Waite Sehelly R, Chu-shore CJ, Neumeyer AM. Pediatric First Seizure. [online]. Available from: emedicine.medscape.com/article/1179097 [Accessed December, 2015].

CHAPTER 86

Medical Management of Epilepsy

Veena Kalra, Omkar P Hajirnis

INTRODUCTION

The aim is restoration of normal life through complete seizure control with minimal or no drug side effects. It is imperative to develop a management algorithm based on knowledge of the epilepsy disease, likely outcome, and rational use of antiepileptic drugs.

The basic steps in management of epilepsy are as follows:

- Differentiate a seizure from nonseizure event
- Identify cause of seizures and distinguish provoked seizure
- Diagnose epilepsy and epilepsy syndrome
- Distinguish benign and severe epilepsy syndromes.

Clinical Pearls

- The first step in approaching a child with seizure disorder is to determine whether the event in the patient is truly a seizure or not
- It is surprising to note that many other paroxysmal events are misdiagnosed as seizures and the consequences of this can be disastrous.

DEFINITIONS

First-line-antiepileptic drug: it is a drug internationally recognized as appropriate treatment for pediatric epilepsy as monotherapy.

Add-on-antiepileptic drug: it is a drug recognized internationally as appropriate for treatment of pediatric epilepsy not as monotherapy but in addition to another already existing antiepileptic drug.

STATISTICS

- First antiepileptic drug: will make 50% of children seizure free
- Second antiepileptic drug: an additional 15% will become seizure free
- Third antiepileptic drug: an additional 1–3% will become seizure free.

Thus, after three first-line-antiepileptic drugs, a maximum of 66% will be seizure free.

- With two antiepileptic drugs together: 3% more will be seizure free
- With three antiepileptic drugs together: no additional benefit seen.

Thus, about 30% of patients by definition will fall under "intractable epilepsy".

Clinical Pearl

- Children with treatment-resistant epilepsy are defined as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic-drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".

MANAGEMENT OF THE FIRST SEIZURE

- The first seizure is not designated epilepsy and management approach is to treat the seizure and identify its cause
- The first generalized seizure may not recur in 50–60% cases. Anticonvulsant therapy, is therefore, not indicated for the first generalized seizure
- Predicts high recurrence risk (80%) in symptomatic seizures and in patients with abnormal electroencephalogram (EEG) versus a 40% risk with a normal EEG.

Anticonvulsant therapy is started after the first episode in the following situations:

- If first seizure is a partial seizure—it merits anticonvulsant therapy as the recurrence risk is high (60–80%) and it may be symptomatic
- Examples of first seizures which merit treatment are myoclonic seizures and absence attacks
- Acute symptomatic seizures, e.g., ring-enhancing lesions, etc.

Indications of Electroencephalogram

Electroencephalogram is recommended as part of the diagnostic evaluation of a child with a first unprovoked seizure, preferably 5–7 days after the seizure.

Table 1 highlights the clinical usefulness of an EEG in epilepsy management.

Neuroimaging

Conventional radiography has no place in epilepsy management. Magnetic resonance imaging scan with epilepsy protocol is the preferred modality. It is far superior to computed tomography scan for epileptogenic lesion identification, focal cortical dysplasias, etc. and thus helps to distinguish symptomatic epilepsies of partial/generalized nature from idiopathic epilepsy. In intractable epilepsy, advanced MRI techniques, volumetric evaluation of hippocampi, etc. are useful. However, a large number of epilepsies do not require neuroimaging, e.g., absence attacks.

Functional scans like positron emission tomography/single-photon emission computed tomography scans are useful in presurgical evaluation of patients in addition to MRI scans.

WHEN TO LOOK BEYOND ANTIEPILEPTICS

- If patient has a clear-cut, well-defined focal cortical dysplasia—surgery is best option

TABLE 1: Indications of electroencephalogram

Usefulness	Remarks
• Differentiate seizures from nonseizures	• Interictal electro-encephalogram (EEG) may be normal in epilepsy (30%) and abnormal in normal children (7–10%). Ictal record must show epileptiform activity
• Classify seizures and epilepsy type	• Interpreter fallacies are common
• To identity background rhythm and origin of epileptic focus	• Background rhythm data important: ○ Hyperventilation, photic stimulation, and sleep/sleep deprived record essential ○ Helps to locate epilepsy-related-lesion
• Classify epileptic syndromes and to distinguish: ○ Complex-partial-seizures ○ Absence seizures ○ Epileptic syndromes	• Ictal recording is necessary
• In intractable epilepsy, to localize epileptogenic focus	• Helps to take therapy decision, identify nonconvulsive status
• Monitoring of status epilepticus and nonconvulsive status	• EEGs essential for diagnosis of epilepsy syndromes
• Underlying disease state identification	• May point to metabolic/genetic basis of epilepsy

- Identifiable unilateral structural lesions on MRI
- Hemiatrophy due to congenital, perinatal, or acquired causes
- Tumors
- Suspected Rasmussen's encephalitis
- Conditions listed for ketogenic diet.

The above conditions require early referral to specialized centers.

DRUG TREATMENT OF EPILEPSY

How to Start Treatment

- Start low, go slow
- Reach maximum dose/side effects before you discard the drug
- Dosage to ideally once-a-day or twice-a-day
- Adjust to the child's daily activity
- Add a second (first-line-drug); achieve control; then try and taper off the first antiepileptic drug
- If seizure frequency is decreased but not stopped after the first antiepileptic drug, add a second drug; use rational polytherapy.

The following logistic approach provides a simple clinical approach to drug for the treatment of epilepsy:

How to Choose the First Drug?

Start with the correct "first line" antiepileptic drug. "Correct"—good efficacy (effectiveness) and low on side-effects (tolerability).

Efficacy is the time to "repeat seizure" after starting the drug while tolerability is the time to "withdrawal" due to ineffectiveness or side-effects.

Clinical Pearls

- Effectiveness = Efficacy + Tolerability
- When two drugs are equally effective, tolerability is the deciding factor.

Table 2 provides a useful guide to choose and start the appropriate first-line antiepileptic drug. However, the decision regarding specific drug depends upon the age, seizure type, side effects, cost, and life style of the patient.

Clinical Pearl

- Whenever in doubt as to seizure type or syndrome, sodium Valproate is the best first choice for first-line therapy

Table 3 enumerates the dosing guidelines for the various commonly used antiepileptic drugs.

Do I Use an Established Antiepileptic Drug or Try a Newer Antiepileptic Drug?

Evidence-based medicine proves that the efficacy is similar in most first-line antiepileptic drugs, new or old. Thus, it is important to choose your drug by identifying the seizure type and knowing the common side effects of the drug in relation to your patient.

TABLE 2: Choosing the appropriate antiepileptic drug

Partial seizures		Generalized seizures		Absence	Myoclonics
First line	**Add on**	**First line**	**Add on**		
• Carbamazepine • Oxcarbazepine • Sodium valproate • Topiramate • Lamotrigine • Levetiracetam • Phenytoin • Gabapentin	• Clobazam • Clonazepam • Levetiracetam • Zonisamide • Tiagabine* • Pyridoxine	• Valproate • Topiramate • Levetiracetam • Lamotrigine • Phenobarbitone • Vigabatrin (IS) • Gabapentin	• Clobazam • Clonazepam • Levetiracetam • Pyridoxine	• Valproate • Ethosuximide* • Lamotrigine	• Valproate • Lamotrigine • Topiramate • Zonisamide • Levetiracetam

*Not available in India

TABLE 3: Dosing guidelines for established and new antiepileptic drugs in children

Established AED	Starting dose (mg/kg/day)	Maintenance dose (mg/kg/day)	Dosing interval
Phenobarbital	3–5	3–5	OD or BD
Phenytoin	5–8	5–8	OD or BD
Carbamazepine	5–10	20–30	BD or TDS
Valproate	10–15	20–60	OD or BD
Clonazepam	0.025	0.025–0.1	BD or TDS
Clobazam	0.25	0.5–1	OD or BD
Ethosuximide	10	15–30	OD or BD
New antiepileptic drugs			
Oxcarbazepine	5–10	10–50	BD or TDS
Lamotrigine • Monotherapy • With valproate	 0.4 0.15	 2–8 1–5	 BD BD
Topiramate	1–3	3–8	BD
Levetiracetam	10	20–60	BD or TDS
Vigabatrin	40	50–150	OD or BD
Zonisamide	2–4	5–6	BD
Gabapentin	10	20–50	TDS

OD, once-a-day; BD, twice-a-day; TDS, thrice-a-day.

What are the Common Side Effects of Each Drug I Should Know?

The usual dose-related side-effects of most antiepileptic drugs include drowsiness, dizziness, nystagmus, cognitive decline, gastrointestinal dysfunction, etc.

Specific side effects

- Carbamazepine: diplopia, dizziness, cognition, or counts
- Sodium valproate: weight gain, hair loss, or liver dysfunction
- Phenytoin: hirsutism, coarse facies, gingival hyperplasia, drowsy, ataxia, cognition, or nausea—toxic range
- Phenobarbitone: drowsiness, cognitive decline, ataxia, withdrawal seizures
- Lamotrigine: rash with danger of Stevens-Johnsons syndrome, or hair loss
- Topiramate: weight loss, cognition issues, or incontinence, hypohidrosis leading to pyrexia
- Vigabatrin: visual field cuts
- Levetiracetam: mood swings, or drowsiness
- Benzodiazepine: drowsiness, low tone, or tolerance.

What do I do if there is no Response to First-line Antiepileptic Drug?

- Firstly use all tests available to confirm the seizure type
- Choose a drug with a different mechanism of action to your first-line antiepileptic drug.

The following drug combinations are effective and recommended:

- Valproate + Lamotrigine
- Topiramate + Carbamazepine
- Topiramate + Valproate
- Valproate + Carbamazepine
- Carbamazepine + Phenytoin

Identify an epileptic syndrome and choose a drug known to work on the identified syndrome.

Table 4 and 5 lists the various epileptic syndromes and the preferred drugs for the same.

It is prudent to remember some antiepileptic drugs are known to worsen certain epilepsies. Table 6 depicts the drugs to avoid in certain epilepsies.

DISCONTINUATION OF ANTIEPILEPTIC THERAPY

Epilepsy therapy need not be life-long in most subjects. In most epilepsies, the antiepileptic drug is withdrawn after 2 years of seizure-free period. However, about 20–29% subjects relapse after antiepileptic drugs withdrawal. Drug withdrawal is over 3–6 months and is one drug at a time in cases of polytherapy. When withdrawing on abnormal EEGs, adolescent epilepsies or remote symptomatic epilepsies adequate counseling is required to parents and patient with regards to chances of relapse.

Algorithm 1 depicts the approach to withdrawing antiepileptic drugs.

TABLE 4: Preferred drugs for different epileptic syndromes

Severe myoclonic epilepsy of infancy (Dravet syndrome)	Benign rolandic epilepsy with centrotemporal spikes	Juvenile myoclonic epilepsy	Myoclonic astatic epilepsy	Childhood absence epilepsy
• Clobazam • Valproate • Topiramate • Stiripentol • Levetiracetam • Lamotrigine	• Carbamazepine • Oxcarbazepine • Valproate • Topiramate • Levetiracetam	• Valproate • Lamotrigine • Levetiracetam • Clonazepam	• Clonazepam • Clobazam • Valproate • Lamotrigine • Topiramate • Levetiracetam	• Valproate • Clobazam

TABLE 5: Preferred drugs for different malignant epileptic syndromes

Lennox-Gastaut syndrome	Infantile spasms	Landau-Kleffner syndrome	Rasmussen's syndrome	Progressive myoclonic epilepsies (metabolic epilepsies)
Combination of: • Valproate (VPA) + • Lamotrigine (LMT) + • Topiramate (TPM)) • Zonisamide (ZNS) • Levetiracetam (LVT) • Clobazam (CLBZ) • Clonazepam (CLNZ)	• ACTH • Oral steroids • Vigabatrin • Nitrazepam • Valproate • Topiramate • Clonazepam	• Intravenous immunoglobulin • Steroids • Antiepileptic drugs	• Steroids • Antiepileptic drugs • Surgery	• Zonisamide • Levetiracetam • Valproate

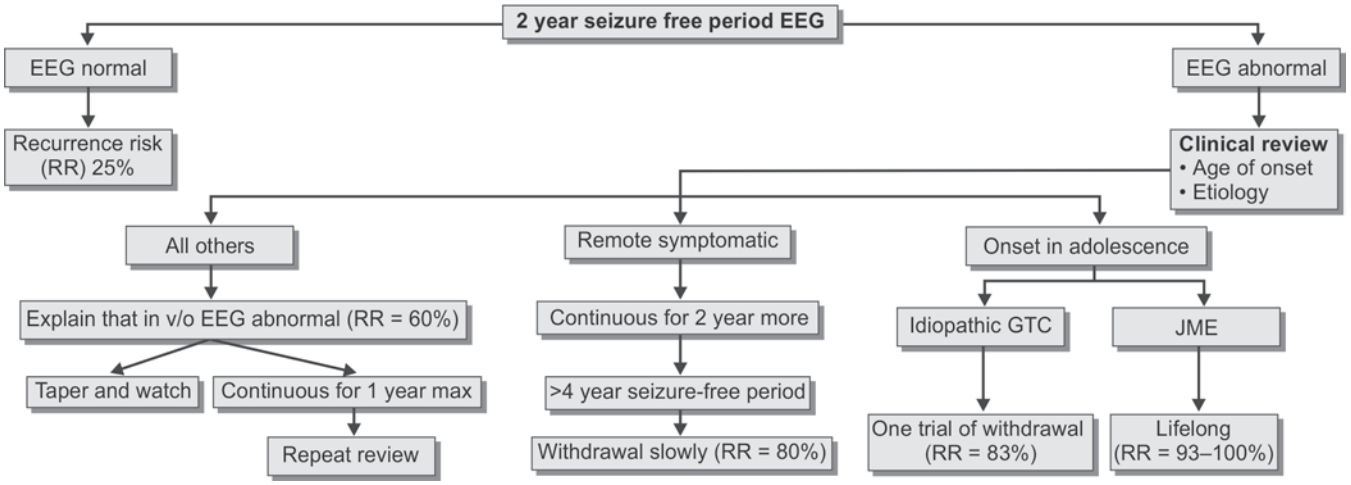
ACTH, adrenocorticotropic hormone.

TABLE 6: Drugs worsening certain epilepsies

Drug	Syndrome	Worsening
Carbamazepine	Absence seizures, juvenile myoclonic epilepsy, progressive myoclonic epilepsies, benign rolandic epilepsy	Absence seizures, myoclonic seizures, or continuous slow wave in sleep
Phenytoin	Absence, progressive myoclonic epilepsies	Absences, cerebellar syndrome
Phenobarbitone	Absence seizures	At high doses, absences
Benzodiazepines	Lennox-Gastaut syndrome	Tonic seizures
Vigabatrin	Absence, myoclonic seizures	Absences, myoclonic seizures
Lamotrigine	Severe myoclonic epilepsy of infancy, juvenile myoclonic epilepsy	At high doses, myoclonic seizures

ALGORITHM 1

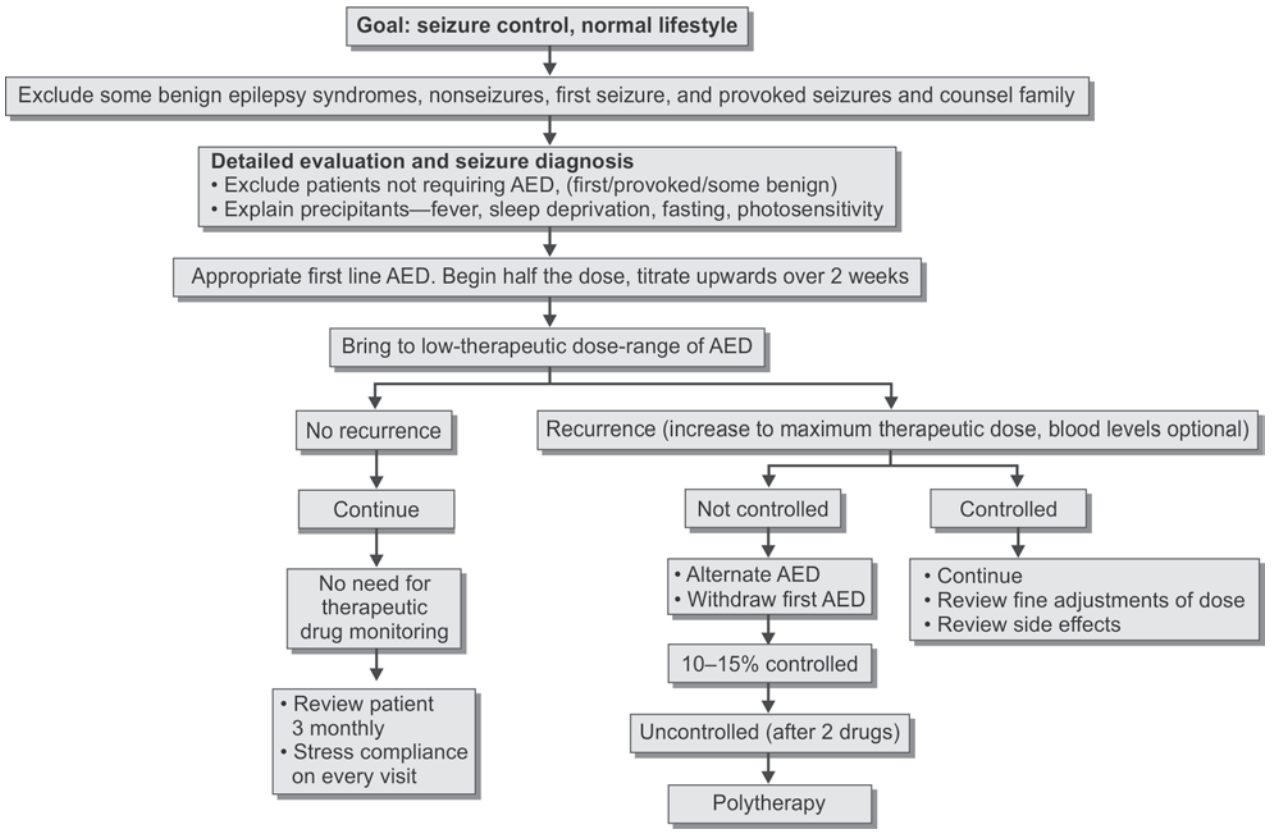
Algorithmic approach to antiepileptic drug withdrawal



EEG, electroencephalogram; GTC, generalized tonic clonic seizure; JME, juvenile myoclonic epilepsy; RR, relative risk; v/o, view of.

ALGORITHM 2

Algorithm for a Newly Diagnosed Epilepsy



AED, antiepileptic drug.

DRUG MONITORING

Therapeutic range is the optimum level of a drug in the body which is effective, but not toxic. However, there are wide variations in blood levels are observed at the same dosage in different patients. Also, there is no correlation between efficacy and toxicity of the antiepileptic drug in the blood for a given patient. There is also a difference between total drug and free drug in the system—total is what is being tested, free is what is effective.

Timing of collection is most important as the trough levels are determined for efficacy and peak levels for toxicity (Table 7).

TABLE 7: Drugs for which therapeutic drug monitoring is available

Drug	Effective plasma concentration (μg/mL)
Carbamazepine	6–12
Lamotrigine	2–16
Phenobarbital	15–40
Phenytoin	10–20
Valproate	50–120

Clinical Pearls

- Treat the patient, not the drug level
- If a value does not make sense—ignore it or repeat it.

PARENTAL COUNSELLING

Explain the Disease

- Explain the nature of the disease and alleviate fears of supernatural involvement
- In vast majority of cases (80%), epilepsy would improve with first-line drug therapy
- Most children are normal and their mental development would not be affected by drugs or disease
- Remind about seizure precipitants:
  - Sleep deprivation
  - Exhaustion
  - Excessive emotion: stress/anxiety/anger/tear/excitement
  - Illness/infection
  - Usually a combination of two or more factors
  - Days to be careful: birthday, exam, festivals, holiday, travelling, or illness

- Must explain how to abort an event at home. Draw, write, whatever is easier for the parent to understand
- The use of intranasal midazolam spray or buccal midazolam or rectal diazepam should be explained to the parents and caretakers in detail
- Explain the need to keep medication near the patient and not at a different venue so that when he/she seizures, the drug is readily available
- Answer all their queries and alley their anxiety regards academics, medicines, social stigmas, marriage, and children.

Drug Therapy

- Compliance: regular drug treatment is the corner stone of therapy
- Safety: the drugs should be kept out-of-reach of children to avoid inadvertent ingestion
- Empowerment: parents should be explained the domiciliary management of acute breakthrough seizures
- Follow-up: appropriate timely drug withdrawal.

Lifestyle

- Maintain a normal healthy lifestyle
- No food restrictions needed
- School teachers should be informed
- Children should carry a card displaying their diagnosis
- Caution is advocated in dangerous activities such as cycling, swimming. and fire particularly during early therapy.

Clinical Pearl

- Domiciliary management of seizures is extremely important and should be taught to every family
- Facility of intranasal midazolam should be available in all schools

FOLLOW-UP

Initially after 6 weeks and then 3 monthly if seizures are controlled. Refer to a higher center if:

- Uncontrolled seizures/side effects
- Suspected syndromes
- Suspected inborn errors of metabolism
- Deteriorating cognition
- Fresh neurological deficits.

KEY POINTS

- ☞ The first step in approaching a child with suspected epilepsy is to confirm that the reported spells are actually seizures rather than another condition such as syncope, migraines, tics, or behavioral events
- ☞ After a second unprovoked seizure, the chances of a third unprovoked seizure are 80–90% within 2 years if treatment is not initiated. Therefore, treatment after the second (rather than the first) unprovoked seizure is recommended
- ☞ The choice of antiepileptic drug in treating the childhood epilepsies will be determined by the epilepsy syndrome (and hence the specific seizures help to define the syndrome), side effects profile and, to an extent, its ease of use (formulation and dosing regimen)
- ☞ Sodium valproate appears to remain the most effective antiepileptic drug in treating most seizure types
- ☞ It is important to be aware of drugs that may exacerbate some seizure types
- ☞ The temptation should be strongly resisted to indulge in polytherapy, as it is always easier to add another drug than to withdraw one
- ☞ There are no convincing data that the simultaneous use of three antiepileptic drugs results in better seizure control than two drugs
- ☞ In order to assess response to treatment, information on baseline seizure frequency and intervals between initial seizures is crucial. Tracking response to seizures is important, either with paper diaries or with online seizure-tracking tools
- ☞ A trial of epilepsy medication discontinuation is usually recommended after 2 seizure-free years. Medications should be discontinued over at least a 6-week period, and if the patient is on polytherapy, only one medication should be weaned at a given time
- ☞ Children with pharmacologically-resistant epilepsy and seizures due to focal abnormalities are potential candidates for epilepsy surgery.

SUGGESTED READINGS

1. Arhan E, Serdaroglu A, Kurt AN, Aslanyavrusu M. Drug treatment failures and effectivity in children with newly diagnosed epilepsy. Seizure. 2010;19(9): 553Y557.
2. Commission on Classification and Terminology of the International League against Epilepsy. [online] Available from: http://www.ilae.org/
3. Epilepsy. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF. Swaiman's Pediatric Neurology: Principles and Practice, 5th ed. Elsevier Saunders; 2012. pp. 811-35.
4. Jerome Engel Jr. Seizures and Epilepsy, 2nd ed. Oxford; 2012.
5. Kossoff EH. Intractable childhood epilepsy: choosing between the treatments. Semin Pediatr Neurol. 2011;18(3):145Y149.
6. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000; 342(5):314Y319.
7. Pestian J, Matykiewicz P, Holland-Bouley K, Standridge S, Spencer M, Glauser T. Selecting anti-epileptic drugs: a pediatric epileptologist's view. Acta Neurol Scand. 2013;127(3):208-15.
8. Vendrame M, Loddenkemper T. Approach to seizures, epilepsies, and epilepsy syndromes. Sleep Med Clin. 2012:7(1):59Y73.
9. Wallace S, Farrell K. Epilepsy in Children, 2nd ed. London: Arnold; 2004.

CHAPTER 87

Approach to Refractory Epilepsies

Neelu A Desai, Vrajesh Udani

INTRODUCTION

Drug refractory epilepsy (DRE) or intractable or pharmaco-resistant epilepsy is epilepsy which does not successfully respond to antiepileptic drug (AED) therapy. About one-third of children with newly diagnosed epilepsy are likely to subsequently develop drug resistant epilepsy which has tremendous implications not only on the child but also on the patient's family members and care givers. Aggressiveness in the diagnosis and treatment of medically refractory epilepsy in children is imperative given the adverse effect of recurrent seizures on early brain development, learning, and memory.

DEFINITION

Conventionally, therapeutic failure of three AEDs defined intractability. Frequency, duration, and severity of seizures are less commonly included in definition of DRE. The International League against Epilepsy defines DRE as failure of adequate trials of two well-tolerated and appropriately chosen and used AED schedules (monotherapies or in combination) to achieve sustained seizure freedom.

International League against Epilepsy Definition of Drug Refractory Epilepsy

Failure of adequate trials of two well-tolerated and appropriately chosen and used AED schedules (monotherapies or in combination), to achieve sustained seizure freedom.

EPIDEMIOLOGY

Incidence and prevalence of DRE is uncertain due to unstandardized definitions as well as misdiagnoses. Almost 20–40% of epilepsy cases become medically resistant. Data from various studies on DRE reveal that with the first drug-trial, 50% patients would become seizure-free. A second medication-trial produced remission in an additional 13%, while with the third drug, only a further 4% would become seizure-free.

Clinical Pearl

- Appropriately chosen first antiepileptic drug will control half the cases of new-onset epilepsy while only one-third of these will be drug resistant.

WHAT ARE THE CONSEQUENCES OF DRUG-REFRACTORY EPILEPSY?

Recurrent seizures are associated with a range of deleterious consequences including death. Uncontrolled epilepsy in infants and children has deleterious effect on early brain development, learning, and memory. Refractory seizures restrict patients' social activities, academic achievements and in adults reduce the ability to hold a driving license or keep a job. It is a great economic burden for society through expenditures in health-care and unemployment. Patients with epilepsy have a mortality rate significantly higher than that of the general population. Sudden unexpected death in epilepsy (SUDEP) accounts for 8–17% of deaths in people with epilepsy.

COMPLICATIONS OF DRUG-REFRACTORY EPILEPSY

- Mortality: underlying neurological disorder, status epilepticus, seizure-related accidents; treatment-related deaths, SUDEP
- Morbidity: increased cognitive, behavioral, and psychiatric problems
- Nonfatal injuries: head injury, burns, drowning, and fractures
- Diminished quality of life: developmental delay, poor-academic performance, unemployment, and other lifestyle restrictions
- Social stigma.

RISK FACTORS OF DRUG-REFRACTORY EPILEPSY

A number of prospective studies have attempted to identify factors that predict the risk of true DRE. Some of these factors are as follows:

- The response to the first AED trial has been found as the most consistent and vital predictive factor for DRE. As mentioned before, half of patients with new-onset epilepsy respond to the first appropriate AED prescribed. With subsequent AED trial, less than 20% are likely to respond. High seizure frequency prior to treatment is consistently identified risk factor for DRE
- Etiology of epilepsy and syndrome classification is also a relevant factor deciding prognosis. Idiopathic syndromes have a better prognosis than symptomatic/cryptogenic epilepsy syndromes. Certain pediatric epilepsy syndromes that are usually medically intractable include early (neonatal) myoclonic encephalopathy, early infantile epileptic encephalopathy, Lennox-Gastaut syndrome, etc.
- Other variables such as electroencephalographic (EEG) findings and the presence or absence of psychiatric comorbidities have been correlated with outcomes in some analyses
- Some findings such as status epilepticus, a long duration of epilepsy, a family history of epilepsy, and febrile convulsions are variable determinants of prognosis. Some studies have also identified an abnormal neurologic examination and/or developmental delay/intellectual disability as risk factors for DRE
- Some studies, but not all, suggest that age at presentation may be a factor in the development of DRE. Some pediatric studies have found that seizure onset in later childhood or adolescence appears more likely to be associated with DRE than seizures with onset between the ages of 5 and 10 years. One series found onset in the neonatal time-period associated with DRE.

PREDICTORS OF TRUE DRUG-REFRACTORY EPILEPSY

- Lack of efficacy with first appropriate AED
- High number of seizures prior to treatment
- Underlying etiology: symptomatic/cryptogenic rather than idiopathic epilepsy syndrome
- Others: early age of onset, abnormal development/neurological examination, EEG abnormality, presence of status epilepticus, and comorbidities.

DIFFERENTIAL DIAGNOSIS

Pseudorefractory Epilepsy

Very often in practice, medical intractability is not true. This apparent treatment failure which is not true intractability could be due to:

- Wrong diagnosis: some paroxysmal events appear like seizures but are not due to abnormal electrical discharges. They could be physiological or psychogenic in nature and do not respond to AEDs. Video EEG is a golden tool to prove or disprove them. In one study almost 20% of patients seen at epilepsy referral centers were nonepileptic attack disorder (NEAD). Some common seizure mimics are mentioned in the table 1.
- Wrong choice of drug: inappropriate drug selection is often responsible for intractability. For example, a narrow-spectrum AED like carbamazepine can worsen seizure frequency in generalized epilepsy, e.g., absence or myoclonic jerks
- Wrong dosage: inappropriate dosages and frequency can also lead to pseudo refractoriness. For example, giving short half-life AEDs, e.g., syrup carbamazepine in once or twice daily-doses.
- Wrong lifestyle: recreational drug or alcohol abuse, sleep deprivation or noncompliance and self-adjustment of drug doses can also lead to improper seizure control.

MANAGEMENT OF DRUG-REFRACTORY EPILEPSY

The treatment of children with medically intractable epilepsy is both challenging and rewarding. True refractory epilepsy needs referral to a Comprehensive Epilepsy Care Center for optimal evaluation and management. This comprises of a pediatric neurologist/epileptologist, electrophysiologist, epilepsy surgeon, neuropsychologist, and counselor.

If initial history, examination, and videos suggest pseudo-refractoriness, appropriate steps should be taken to resolve them. This would include discontinuing AEDs in NEAD and counseling.

TABLE 1: Common seizure mimics in childhood

Neonates	Infants	Children	Adolescents
• Jitteriness • Benign sleep myoclonus • Hyperekplexia	• Breath-holding spells • Colic • Self-gratification • Benign paroxysmal vertigo • Benign paroxysmal torticollis • Sandifer syndrome (gastroesophageal reflux disease) • Shuddering attacks	• Stereotypies • Self-gratification • Sleep disorders • Tics	• Pseudoseizures • Syncope • Migraine • Tics

Antiepileptic Drugs

Medical management with AEDs remains the first-line treatment in patients with epilepsy. A good number of patients respond to small changes in treatment like switching to appropriate monotherapy according to seizure/syndrome, increasing dose, frequency, and assuring strict compliance. Rational polytherapy is recommended in nonresponders to monotherapy, e.g., synergistic combinations like valproate and lamotrigine; AEDs with different mechanisms of action like a sodium channel blocker carbamazepine with a gamma-aminobutyric acid ergic drug like clobazam. Tapering drugs like carbamazepine in generalized epilepsies is rewarding. Drug levels may sometimes help in adjustment of drug dosages.

Seizure Diary

A seizure diary is a very helpful tool in all patients with DRE to document seizure frequency and intensity with specific interventions, e.g., a new AED. This improves drug compliance and helps to identify triggers like menstrual cycle, etc. It often would help to avoid unnecessary polytherapy with ineffective AEDs and identify scenarios where the AED itself leads to paradoxical increase in seizures.

Clinical Pearl

- Seizure diary is an essential tool kept by patient or caregivers of drug-refractory epilepsy, recording frequency and intensity of seizures along with antiepileptic drugs and precipitants.

As mentioned before, of the 30–40% of individuals with DRE about half will continue their seizures despite three appropriate drugs being tried to their full therapeutic potential. Though new AEDs have undoubtedly reduced drug interactions and adverse effects the number of DRE patients who become seizure free after the first 2–3 drugs is not more than 5%. These patients should be evaluated for possibility of epilepsy surgery, ketogenic diet, or vagal nerve stimulation.

Clinical Pearl

- Drug-refractory epilepsy represents a significant portion of all pediatric epilepsies and should be referred early to a Comprehensive Epilepsy Center where all treatment options including epilepsy surgery and the ketogenic diet are available for optimal management.

Epilepsy Surgery

Surgery has the potential of altering the natural history of epilepsy by improving or eliminating seizures in carefully selected patients. Epilepsy surgery should be considered early in appropriate patients with DRE when seizures are sufficiently frequent or severe as to significantly disrupt the patient's quality of life.

Presurgical evaluation would need video-EEG monitoring and high-resolution magnetic resonance imaging (MRI) of brain in all cases. The sensitivity of MRI can be substantially improved by an epilepsy protocol with spoiled gradient sequences to delineate subtle malformations of cortical development like focal cortical dysplasias which often underlie refractory epilepsy. Functional neuroimaging like ictal single photon emission computed tomography (SPECT) can help delineate the ictal onset zone and often complements MRI in the search of the epileptogenic zone (EZ), critical for planning any surgical intervention. Similarly, positron emission tomography (PET) is very useful as a tool to map out glucose metabolism in the interictal state as many EZs are hypometabolic. Post-processing techniques coregistering MRI and functional images enhance the information. Another very important consideration in presurgical evaluation is defining the eloquent cortex for sensorimotor, language, and visual functions. If this overlaps with the EZ, postoperative deficits may be unacceptable (Algorithm 1).

Neuropsychological evaluations help understand the specific cognitive defects a patient has, e.g., verbal or visual memory deficits in hippocampal sclerosis when planning surgery in older children and teenagers.

Surgical options in DRE are either resective or palliative epilepsy surgery.

Resective epilepsy surgery has the best-established efficacy for individuals with lesional epilepsy. Patients with concordant abnormalities on MRI, EEG, SPECT, and PET have a rate of seizure remission as high as 90%.

Disconnective surgery is sometimes employed for palliative treatment in children with catastrophic epilepsy syndromes with no resectable lesion (Table 2).

Ketogenic Diet

Ketogenic diet (high-fat, low protein) in children with DRE is an effective therapy with more than one-third experiencing a 50% or greater reduction in seizures. Behavioral improvement is often an additional bonus. It is tried for about 3 months and if effective, is continued for 2–3 years. Less restrictive modifications like the modified Atkins diet can be used in older children, though with less success (Table 3).

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) has been approved for adjunctive treatment of DRE in adults and children over

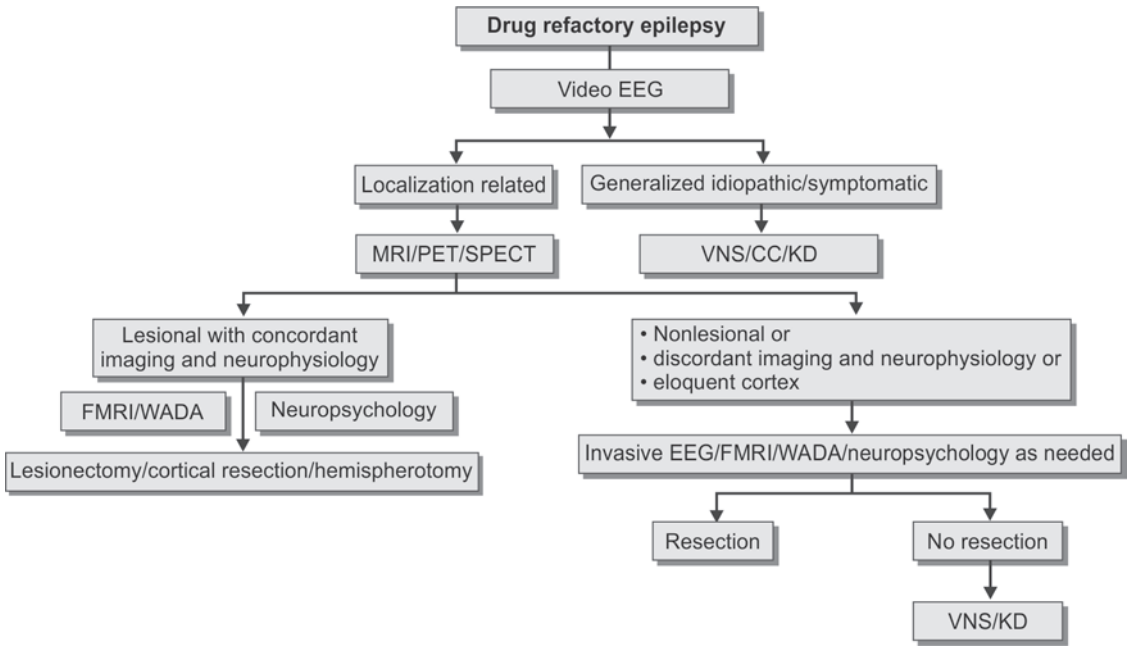
TABLE 2: Resective surgery (curative) and disconnective surgery (palliative)

Resective surgery (curative)	Disconnective surgery (palliative)
• Children with recognized resectable lesions (FCD, MTS) and failed appropriate AED trial • Improvement of seizure control with developmental, cognitive and, behavioral improvement, e.g., lesionectomy or hemispherotomy for hemispheric epilepsies	• Severe uncontrolled epilepsy with no resectable lesion • Prevents falls/injuries, e.g., corpus callosotomy in Lennox-Gastaut syndrome

FCD, focal cortical gradient; MTS, mesial temporal sclerosis; AED, antiepileptic drug.

ALGORITHM 1

Surgical approach in drug refractory epilpsy



CC, corpus callsostomy; VNS, vagus nerve stimulation; KD, ketogenic diet; FMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography; EEG, electroencephalogram.

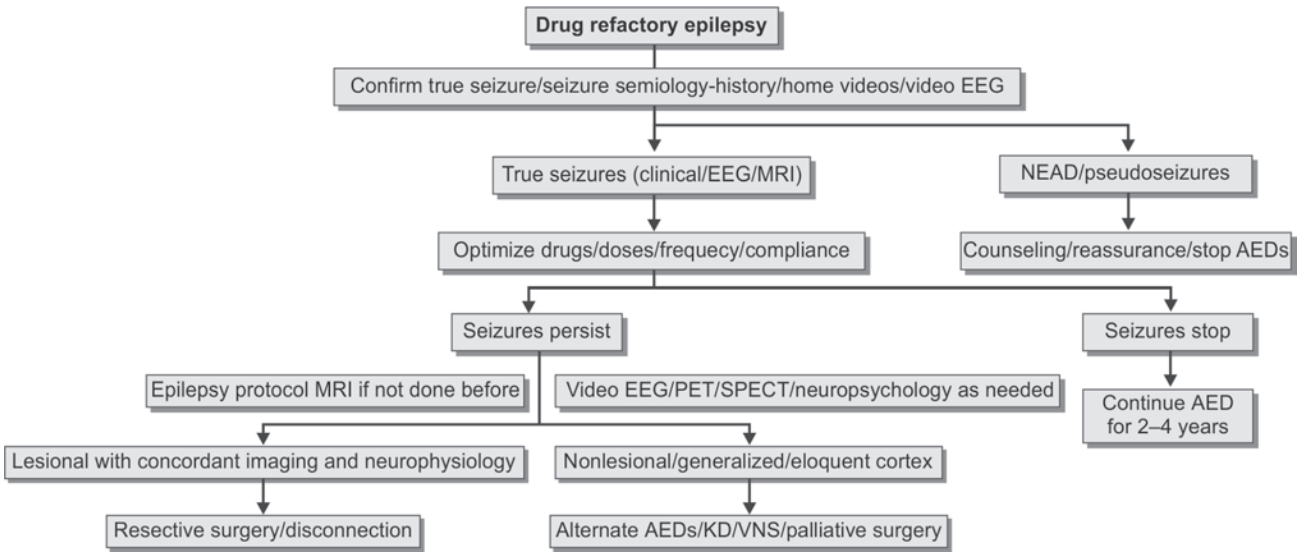
TABLE 3: Ketogenic diet

Indication	Any DRE, West syndrome, epilepsy associated with tuberous sclerosis complex, Dravet syndrome, Doose syndrome, Lennox-Gastaut syndrome, and glucose transporter 1 deficiency
Response	One-third experiencing 50% or greater reduction in seizures, one-sixth achieve seizure freedom; behavioral improvements
Side effects	Gastrointestinal or metabolic side effects, drowsiness, and increased susceptibility to infections
Duration	3-months trial; if effective continued for 2–3 years

DRF, drug-refractory epilepsy.

ALGORITHM 2

Approach to drug refractory epilepsy



CC, corpus callsostomy; VNS, vagus nerve stimulation; KD, ketogenic diet; EEG, electroencephalogram; MRI, magnetic resonance imaging; AEDs, antiepileptic drugs; NEAD, non epileptic attack disorder; PET, positron emission tomography; SPECT, single photon emission computed tomography.

12 years of age. Approximately 30–40% of patients achieve a greater than 50% reduction in seizure frequency. Serious adverse events are rare.

Vagus nerve stimulation is efficacious in patients with well-documented DRE, who are not candidates for intracranial surgery, or whose seizures were not benefitted by prior epilepsy surgery. In resectable lesions, resective surgery is preferred over VNS because of the greater potential for complete seizure remission (Algorithm 2).

KEY POINTS

- ☞ Around 20–40% of patients with epilepsy have incomplete seizure control with antiepileptic drug (AED) therapy alone
- ☞ Most patients with drug resistant epilepsy (DRE) can be identified early in their presentation, after a failure of two appropriate AED trials
- ☞ As many as 20% of patients with apparent DRE will have a nonepileptic paroxysmal disorder. Video EEG monitoring is the gold standard to confirm
- ☞ Predictors of true DRE—lack of efficacy of a first appropriate AED trial, a high number of seizures prior to treatment, and a symptomatic/cryptogenic epilepsy syndrome
- ☞ Individuals with DRE have an increased risk of mortality as well as morbidity. Hence, aggressive treatment is imperative
- ☞ Patients with true DRE should have a high resolution magnetic resonance imaging study to identify a potential surgical lesion. Other neuroimaging studies (e.g., single photon emission computed tomography, positron emission tomography) can be helpful for maximum localization
- ☞ For patients in whom epilepsy surgery is not an option or whose seizures persist after surgery, treatment trials with other AEDs appropriate for their epilepsy syndrome, ketogenic diet or vagus nerve stimulation is suggested.

SUGGESTED READINGS

1. Berg AT, Kelly MM. Defining intractability: comparisons among published definitions. Epilepsia. 2006;47:431-6.
2. Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, et al. How long does it take for partial epilepsy to become intractable? Neurology. 2003;60:186-90.
3. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. Neurology. 2001;56:1445-52.
4. Devinsky O. Patients with refractory seizures. N Engl J Med. 1999;340: 1565-70.
5. Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. Neurology. 2001;57:2259-64.
6. Dlugos DJ. The early identification of candidates for epilepsy surgery. Arch Neurol. 2001;58:1543-6.
7. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy. Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6): 1069-77.
8. Kwan P, Brodie M. Issues of medical intractability for surgical candidacy. In: Wyllie E, Gupta A, Lachhwani D (Eds). The Treatment of Epilepsy and Practice, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2006. p. 983.
9. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314-9.
10. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365:919-26.

CHAPTER 88

Acute Flaccid Paralysis

V Viswanathan, Padma Balaji

INTRODUCTION

Acute flaccid paralysis (AFP) is something that most pediatric neurologists see on a regular basis particularly during certain seasons (mostly during the winter seasons) although they seem to occur most of the year round. These children, who are previously healthy, develop weakness in both legs to start with and then progressing to involve the breathing muscles quickly over a few hours to days. They then develop difficulties in swallowing and invariably end up getting admitted to hospital. In some cases, they may follow mild upper respiratory illnesses or fever.

World health organization defines AFP syndrome as "characterized by rapid onset of weakness of an individual's extremities, often including weakness of the muscles of respiration and swallowing, progressing to maximum severity within 1–10 days. The term 'flaccid' indicates the absence of spasticity or other signs of disordered central nervous system (CNS) motor tracts such as hyper-reflexia, clonus, or extensor plantar responses".

CAUSES OF ACUTE FLACCID PARALYSIS

When one looks at various causes of such paralysis in children, they are many and sometimes very difficult for one to identify the clear cause. Some of these are listed below.

Peripheral Neuropathy

Guillain-Barre syndrome (GBS) and other variants

Anterior Horn Cell Disease

- Acute poliomyelitis presently eradicated in India
- Vaccine-associated poliomyelitis
- Other neurotropic viruses like Japanese B, rabies, non polio enteroviruses
- Acute myelopathy.

Acute Myelopathies

- Transverse myelitis
- Acute disseminated encephalomyelitis
- Spinal cord ischemia
- Spinal cord injury
- Perioperative complication.

Systemic Disease

- Critical illness neuropathy/myopathy
- Conversion disorder.

Metabolic Neuropathy

- Acute porphyria
- Hypokalemia, hypokalemic periodic paralysis, hypophosphatemia.

Muscle Disorders

- Polymyositis, dermatomyositis
- Trichinosis
- Periodic paralysis
- Corticosteroids and blocking agents
- Mitochondrial diseases (infantile type)
- Benign acute childhood myositis and others.

Disorders of Neuromuscular Transmission

- Immune myasthenia gravis presenting in crisis
- Botulism
- Insecticide (organophosphate poisoning
- Tick-bite paralysis
- Snake bite.

Others

- Traumatic neuritis
- Japanese B encephalitis
- Conversion reaction.

CLUES IN HISTORY AND EXAMINATION

- Fever at onset: polio or enteroviral myelitis, transverse myelitis, myositis, epidural abscess, and Koch spine (prolonged history)
- Trauma: head/neck trivial trauma may lead to spinal compression in patients with cervical vertebral instability (patients with Down's syndrome, congenital cervico-vertebral anomalies or juvenile idiopathic arthritis)
- Exposure toxins: lead, Arsenic, or snake envenomation
- Dog bite: rabies and postrabies-vaccine encephalomyelitis.

Preceding Infectious Prodrome/Vaccination

- Guillain-Barre syndrome or transverse myelitis
- Sore throat, neck swelling: diphtheritic polyneuropathy (non/partly immunized).

Precipitating Factors

- Diarrhea: hypokalemia, enteroviral myelitis
- Exertion or postprandial: hypokalemic periodic paralysis
- Intramuscular injection: polio, traumatic sciatic neuritis
- Sensory loss: compressive myelopathy, transverse myelitis
- Early bowel/bladder involvement: compressive myelopathy, transverse myelitis
- Constipation in less than 1 year: botulism (history of honey exposure).

Prominent Autonomic Signs/Symptom

- Guillain-Barre syndrome, rabies, acute myelopathy
- Ascending weakness: Guillain-Barre syndrome, rabies, Varicella zoster virus, ascending myelitis
- Descending weakness: diphtheria, botulism.

Prominent and Early Ptosis

- Myasthenia Gravis, botulism
- Facial weakness: Guillain-Barre syndrome, myasthenia gravis, botulism
- Fluctuating symptoms, fatigability: myasthenia gravis
- Muscle tenderness: myositis, inflammatory myopathy (myalgias may be severe in GBS).

Muscle Stretch Reflexes

- Absent: Guillain-Barre syndrome, poliomyelitis, diphtheria, spinal shock, at level of spinal-cord damage
- Preserved: myasthenia Gravis, periodic paralysis, botulism
- Exaggerated: below level of spinal lesion/upper motor neuron lesion.

Spinal Tenderness, Painful Spine Movement

- Spinal trauma, epidural abscess, or other extra-dural compression
- Neck stiffness: poliomyelitis, enteroviral myelitis, GBS, transverse myelitis.

Clinical Approach

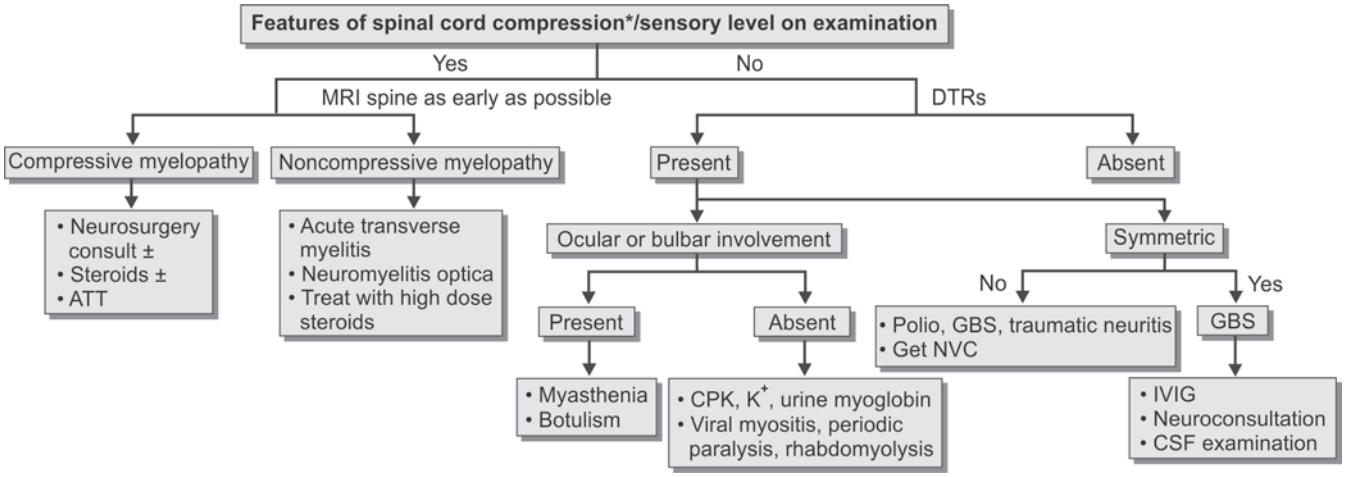
Clinical approach to a child with acute paraplegia or paraparesis is given algorithm 1.

Clinical Pearl

- Investigations only help to reconfirm our clinical findings.

ALGORITHM 1

Approach to child with acute paraplegia or paraparesis



DTR, deep tendon reflexes; CPK, creatine phosphokinase; GBS, Gullain-Barre syndrome; NCV, nerve conduction velocity; CSF, cerebrospinal fluid; ATT, anti-TB treatment; IVIG, intravenous immunoglobins.

*Bony tenderness/deformity, root pains, girdle sensation/early bladder or bowel involvement.

ACUTE INFLAMMATORY POLYRADICULONEUROPATHY (GUILLAIN-BARRE SYNDROME)

This is one of the most common causes of AFP in children. Peripheral nerves are the target of an abnormal immune response. In most cases, there is a history of an antecedent viral infection. Commonest viral infection that precipitates this is usually respiratory infection, although in some gastrointestinal infections may be the cause. Enteritis caused by specific strains of *Campylobacter jejuni* is more often the cause of the acute axonal form of GBS, rather than the demyelinating variety.

The clinical presentation is usually with progressive motor weakness involving more than one limb—usually the legs. Mild sensory symptoms are usually present characterized by dysesthesia and muscle tenderness in the limbs. The weakness progresses to reach a nadir by about 2–3 weeks. Deep tendon reflexes are absent in all the weak muscles. Bilateral facial weakness occurs in about half of the children. Autonomic dysfunction like arrhythmia, labile blood pressure and gastrointestinal dysfunction may be seen. Respiratory involvement is not uncommon in this condition during the initial progressive phase of the illness and so needs close monitoring and appropriate intervention.

Recovery usually begins about 2–3 weeks after the progression stops and is usually complete in most children but takes even as much as 2–3 months in some cases. The prognosis is best when recovery begins early and also in children with the demyelinating variety rather than the axonal type.

Diagnosis is best with the help of nerve-conduction studies which will help to distinguish the axonal variety from the demyelinating type. Cerebrospinal fluid (CSF) examination during the second week may show mild elevation in CSF protein and a few mononuclear leukocytes (usually <10).

Management is primarily supportive with careful monitoring for respiratory function and adequate support including ventilation in some during the initial phase. Plasma exchange and intravenous immunoglobulin hastens the recovery of GBS. Although, we have discussed so much about differential diagnosis in most cases once we have a good reliable history and clinical examination findings, diagnosis is clear, cut and management is straight forward.

All cases of AFP should be notified in the appropriate form to the corporation health officials as it is mandatory that we

TABLE 1: Features to differentiate poliomyelitis, transverse myelitis, Guillain-Barre syndrome, and traumatic neuritis

Signs and symptoms	Poliomyelitis/polio-like enteroviral myelitis	Guillain-Barre syndrome	Transverse myelitis	Traumatic neuritis
Development of paralysis	24–48 h from onset to full paralysis	From hours to 10 days	From hours to 4 days	From hours to 4 days
Fever onset	High, always present at onset of flaccid paralysis, gone the following day	Not common	rarely present	Commonly present before, during and after flaccid paralysis
Flaccidity	Acute, asymmetrical, proximal	Acute, symmetrical, distal	Acute, lower limbs, symmetrical	Acute, asymmetric limb
Deep-tendon reflexes	Decreased or absent	absent	Absent early, hyperreflexia late	Decreased or absent
Sensation	Severe myalgia and backache, no sensory changes	Cramps, tingling, hypoesthesia of palms and soles	Anesthesia of lower limbs with sensory level	Pain in gluteal region
Cranial nerve	Only when bulbar and bulbospinal	Often present, affecting nerves VII, IX, X, XI, XII	Absent	Absent
Respiratory insufficiency	Only when bulbar and bulbospinal	In severe cases	sometimes	Absent
WBC in CSF	High WBCs	<10 WBCs	Normal/mild pleocytosis	Normal
CSF protein	Normal or slightly increased	High	Normal or slightly elevated	Normal
Bladder dysfunction	Absent	Transient	Present	Never
Nerve conduction velocity: third week	Abnormal, anterior horn cell disease (normal during the first 2 weeks)	Abnormal demyelination/ axonal	Normal or abnormal, no diagnostic value	Abnormal in sciatic nerve
EMG 3 weeks	Abnormal	Normal	Normal	Normal/may be abnormal in that muscle subserved by that nerve
Sequelae at 3 months and up to a year	Severe, asymmetrical atrophy, skeletal deformities developing later	Normal/symmetrical atrophy of distal muscles in some	Flaccid/spastic paraplegia in some	Moderate atrophy only in affected lower limb

EMG, electromyography; CSF, cerebrospinal fluid; WBC, white blood cells.

Source: Modified from Global Program for Vaccines and Immunization: Field Guide for Supplementary Activities Aimed at Achieving Polio Eradication. Geneva, World Health Organization, 1996

take samples for polioviruses from the stool specimen, soon after the diagnosis and then they will follow-up the cases and do the needful.

ACKNOWLEDGMENTS

We thank with gratitude to Dr Pratibha Singhi and her team to have permitted me to reproduce her work in this section. We thank Indian Journal of Paediatrics for allowing us to reproduce charts from their publication.

KEY POINTS

- ☞ A good clear history is important
- ☞ Good clinical examination with the history will give us the diagnosis.

SUGGESTED READINGS

1. Fenichel GM. Clinical Paediatric Neurology, 5th ed. Saunders, 2005.
2. Field Guide Surveillance Of Acute Flaccid Paralysis, 3rd ed. 2005
3. Hughes RAC, Wijdicks EFM, Barohn R, Benson E, Cornblath DR, Hahn AF, et al. Practice parameter. Immunotherapy for Guillain-Barre syndrome. Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2003;61:736-40.
4. Paediatric active enhanced disease surveillance (Paeds) study protocol—acute flaccid paralysis (AFP) Australia.
5. Paradiso G, Tripoli J, Galicchio S, Fejerman N. Epidemiological, clinical and electrodiganostic findings in childhood Guillain-Barre syndrome. A reappraisal. Ann Neurol. 1999;46:701-7.
6. Singhi SC, Sankhyan N, Shah R, Singhi P. Approach to a child with acute flaccid paralysis. Indian J Pediatr. 2012;79(10):1351-7.
7. World Health Organization 1993 WHO/MNH/EPI/93.3. Geneva.

CHAPTER 89

Approach to Floppy Infant

Vrajesh Udani, Sarbani S Raha

INTRODUCTION

Floppiness or hypotonia is a common neurologic symptom in infancy. Hypotonia may be secondary to diseases involving brain, spinal cord, nerve, or muscle. Hence, a systematic approach is must while evaluating a floppy infant to avoid ordering many investigations and to reach a proper diagnosis.

Weak infants always have hypotonia but it may exist without weakness.

DEFINITION

Hypotonia is an impairment of the ability to sustain postural control and movement against gravity. Floppy infants exhibit poor control of movements, delayed motor skills, and hypotonic motor movement patterns.

Phasic tone is a rapid contraction in response to a high-intensity stretch. Postural tone is the prolonged contraction of antigravity muscles in response to the low-intensity stretch of gravity. The maintenance of normal tone requires intact central and peripheral nervous system.

A hypotonic infant needs to be evaluated adequately. A detailed history and neurological examination would help us to differentiate between central hypotonia of upper motor neuron origin and motor unit disorders.

Infants who show delay in all aspects of development and have other evidence of brain dysfunction like abnormal eye movements or seizures, dysmorphic features or exaggerated deep-tendon reflexes probably have a central cause of hypotonia. On the other hand, an alert and active infant who has significant motor weakness and absent deep-tendon reflexes is most likely to have a peripheral cause of hypotonia involving anterior horn cells, nerve, neuromuscular junction, or muscle (Box 1).

Box 1: Salient points in history-taking

- Consanguineous marriage
- Reduced fetal movements
- Feeding difficulty in neonatal period
- Family history of sibling death/similar illness
- Static versus progressive
- Choking episodes
- Increased respiratory efforts

EXAMINATION OF A HYPOTONIC INFANT

- Posture: lack of/reduced spontaneous movements; full abduction of legs; arms either extended at the sides of the body or flexed at elbow with hands beside the head (Fig 1A)
- Skeletal: fixed deformities like clubfoot, arthrogryposis, pectus excavatum, hyperlaxity of skin and joints
- Dysmorphic features
- Evidence of hypotonia:
  - Horizontal suspension: the infant is suspended in prone position with the examiner's palm underneath the chest. The hands and legs of a hypotonic infant lies limply forming an inverted "U" posture
  - Vertical suspension: an infant who has hypotonia "slips through" at the shoulders when the examiner grasps him/her under the arms in an upright position
  - Traction response: head lag or hyperextension is evident when the infant is pulled by the arms from a supine to sitting position (Fig 1B)
  - Scarf sign: in a hypotonic infant, on grasping the infant's hand and pulling it across the chest, the elbow can easily be brought well beyond the midline
  - Wheel barrow: in prone position when the child is raised holding his legs in the air, whether he/she can support his weight on hands is tested
- A complete neurological examination should be performed. Of particular importance are the following:
  - Measurement of head circumference

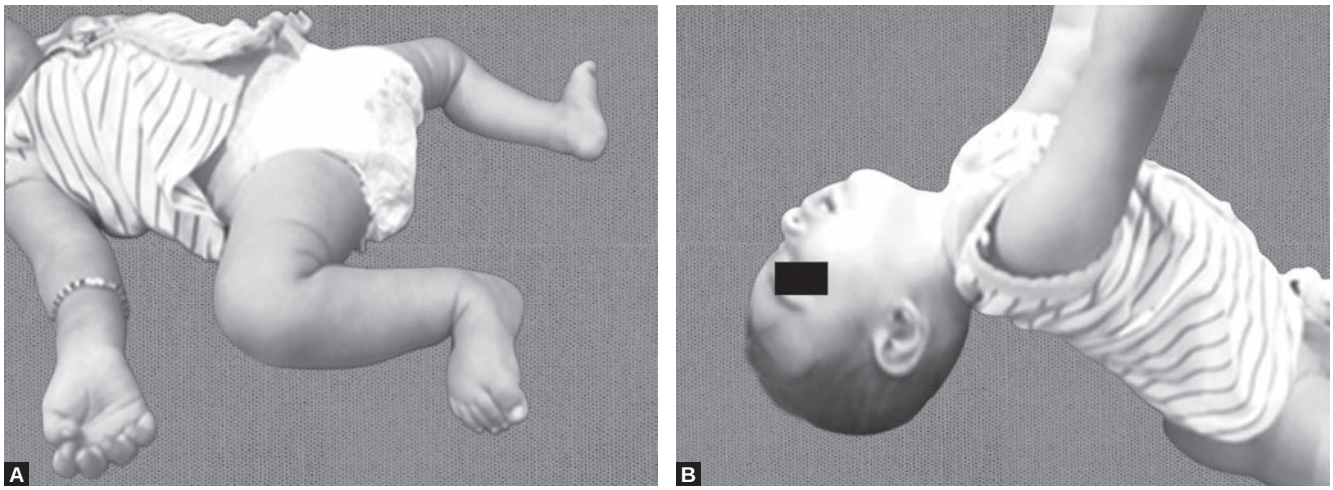
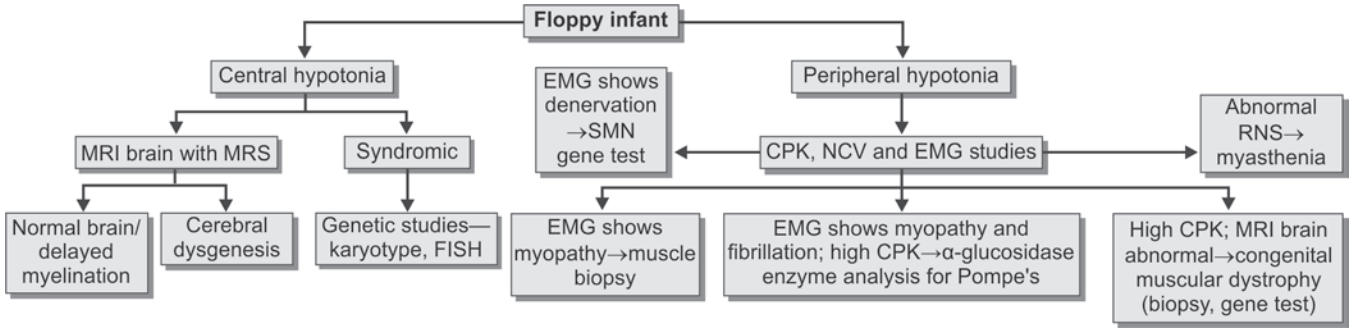


Fig 1: A, Posture of a hypotonic infant; **B,** Traction response

ALGORITHM 1

Suggested approach to a floppy infant and stepwise investigations that would help reach a diagnosis



MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; CPK, creatine phosphokinase; NCV, nerve conduction velocity; EMG, electromyography; RNS, repetitive nerve stimulation; SMN, survival motor neuron; FISH, fluorescence *in situ* hybridization.

- Facies: myopathic/hypotonic
- Hypophonia
- Power: presence of antigravity movements
- Tongue fasciculations, polyminimyoclonus
- Paradoxical respiration
- Examination of mother for myotonia.

A systemic approach and stepwise investigations will go a long way in diagnosing the underlying disorder in a floppy infant (Algorithm 1).

CEREBRAL HYPOTONIA

Neonatal and infantile hypotonia is common in most cerebral disorders. But in some of them, hypotonia is one of the most prominent features, making it difficult to differentiate between a central versus peripheral cause (Box 2).

Box 2: Points favoring central hypotonia

- Global developmental delay
- Dysmorphic features
- Increased tone of neck extensor
- Normal or brisk tendon reflexes
- Other organ involvement

SYNDROMIC HYPOTONIA

An infant with dysmorphism and hypotonia may require chromosomal analysis and fluorescence *in situ* hybridization (FISH) studies to diagnose the appropriate syndrome.

Prader-Willi Syndrome (PWS)

This is caused by deletion of paternally-contributed proximal long arm of chromosome 15 or maternal disomy (both chromosomes 15 received from mother). Hypotonia at birth along with severe feeding problems requiring nasogastric tube feeding is a significant neonatal history in patients of PWS. Delayed milestone is the usual presenting feature. Hyperphagia and obesity develops later in childhood.

Joubert Syndrome

Classic Joubert syndrome is characterized by distinct cerebellar and brainstem malformations, hypotonia, and developmental delays. Often there is presence of oculomotor apraxia and episodic tachypnea. Cognitive disabilities are variable.

Many other syndromes have central hypotonia. Among them, Down syndrome is usually diagnosed early due to presence of typical facies.

NONSYNDROMIC CENTRAL HYPOTONIA

There are patients who have anomalies or abnormalities of central nervous system in absence of any particular syndrome. The neurological examination may reveal global or motor delay in presence of signs suggestive of central hypotonia. These patients may have presence of minor anomalies of the brain broadly classified as cerebral dysgenesis, some of them may have delayed myelination or even normal neuroimaging findings.

Systemic Disease

In a newborn and sometimes in infants, systemic disease can cause hypotonia. Presence of congenital heart disease and in an acute setting, sepsis may be responsible for hypotonia.

Craniocervical Junction Lesions

Obstetric injuries to the cord result in neonatal hypotonia. Later patients may have flexion of arms with flaccid paraplegia. A distended bladder with overflow incontinence is highly suggestive of cord injury in such cases.

BENIGN CONGENITAL HYPOTONIA

This is a nonprogressive neurological disorder characterized by generalized flaccidity of muscles and hypermobile joints. Deep-tendon reflexes are normal or mildly exaggerated. An increased incidence of intellectual disability, learning disability and likewise is evident later in life. A high family incidence is reported. This is a diagnosis of exclusion, and all routine investigations are normal.

Clinical Pearl

- Hypotonia without weakness may suggest a syndromic diagnosis (Down's, Prader-Willi).

MOTOR UNIT DISORDERS

There may be many clues in history and neurological examination that suggest a peripheral cause of hypotonia. A maternal account of reduced fetal movements and polyhydroamnios; "myopathic" facies; tongue fasciculations or polyminimyoclonus; low-pitched cry; and lack of antigravity movements are all markers of a lower motor neuron cause of a floppy infant (Box 3).

Box 3: Evaluation of motor unit disorders

- Creatine phosphokinase, aldolase
- Neostigmine test
- Electrodiagnosis: nerve conduction study, electromyography, repetitive nerve stimulation
- Genetic test: survival motor neuron and congenital muscular dystrophy screening
- Enzyme analysis—alpha glucosidase (acid maltase)
- Muscle biopsy
- Nerve biopsy

Differential Diagnosis (Table 1)

Spinal Muscular Atrophy

These are progressive group of disorders associated with deletions or mutations in exons 7 and 8 of the telomeric copy of the survival motor neuron gene (SMN1). The centromeric copy (SMN2) is the disease-modifying gene with milder cases having more copies.

In type 1, onset of weakness is before 6 months of age; most patients do not achieve sitting. In type 2, onset is between 6–18 months; most patients can sit but never walk. In type 3, onset is after 18 months and such patients may be difficult to diagnose and confused with limb-girdle muscular dystrophy.

In spinal muscular atrophy (SMA), there is presence of proximal more than distal weakness and despite of intrauterine hypotonia, arthrogryposis is not present. Electromyography study reveals fibrillations and fasciculations.

Once the genetic testing confirms SMA, the same should be performed in chorionic villi biopsy sample for prenatal diagnosis.

Congenital Muscular Dystrophy

This group is classified into syndromic and, nonsyndromic forms. The nonsyndromic form may have merosin deficient congenital muscular dystrophy (CMD) or merosin positive CMD.

Delayed motor milestones, hypotonia, contractures, and high creatine phosphokinase (CPK) values help to diagnose this condition. In merosin deficient CMD, MRI brain shows abnormal T2 hyperintensity giving an impression of leucodystrophy (Fig. 2).

Syndromic congenital muscular dystrophy is characterized by anomalies of cortical migration, ocular abnormalities like cataract, and muscle disease with high CPK.

Congenital Myotonic Dystrophy

Prominent clinical feature of this autosomal dominant disorder include facial diplegia; significant neonatal feeding

TABLE 1: Differential diagnosis of peripheral hypotonia depending on the component of motor unit involved

Motor neuron	Nerve	Neuromuscular junction	Muscle
• Spinal muscular atrophy	• Congenital hypomyelinating neuropathy • Hereditary motor sensory neuropathy-familial dysautonomia	• Congenital and transient myasthenia	• Congenital myotonic dystrophy • Congenital muscular dystrophy • Pompe's disease • Congenital myopathy

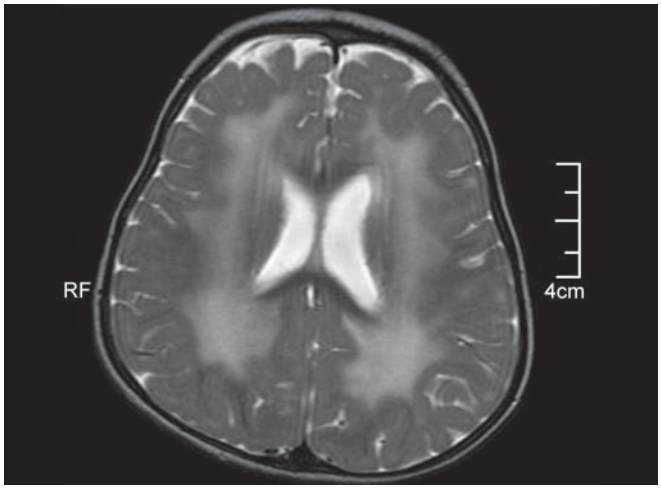


Fig. 2: T2 weighted axial sections of magnetic resonance imaging of brain in a patient with merosin deficient congenital muscular dystrophy

difficulty; and mental retardation. The mother is usually the affected parent when a child has the disease. There is unstable trinucleotide expansion with 300–1000 CTG repeats and hence genetic anticipation is common in myotonic dystrophy type 1. Cardiac dysrhythmias and cataract may also be present.

Pompe's Disease

Hypotonia in Pompe's disease is the result of glycogen storage in brain, spinal cord, and skeletal muscles. The presence of cardiomegaly with abnormal electrocardiogram is highly suggestive of alpha glucosidase deficiency.

After establishing the diagnosis with the help of enzyme analysis, patient should be offered enzyme-replacement therapy which is available at certain centers in India.

Myasthenic Syndromes

Transitory neonatal myasthenia usually presents as hypotonia and feeding difficulty; the cry of such an infant is weak and there is lack of facial expression. Antiacetylcholine receptor (AChR) antibody is high and such newborns respond to neostigmine.

Familial infantile myasthenia with prominent respiratory and feeding difficulty at birth and congenital myasthenia with predominant ocular findings are genetic myasthenic syndromes with negative anti AChR antibodies. These patients may have episodic apneas which could be life threatening.

Clinical Pearl

- A very high creatine phosphokinase value usually points toward a muscular dystrophy.

NEONATAL HYPOTONIA

Hypotonia is a manifestation of many acute neonatal injuries.

The profile of disorders presenting with neonatal hypotonia to the neonatal intensive care unit was studied in an 11-year retrospective cohort of neonates admitted to the Neonatal Intensive Care Unit at the Montreal Children's Hospital (Montreal, Québec). Of the 50 neonates, who met the inclusion criteria, hypotonia was classified as central in 33 patients (66%) and peripheral in 17 (34%). Hypoxic-ischemic encephalopathy (n = 13), Prader-Willi syndrome (n = 6), myotonic dystrophy (n = 6), other muscle disorders (n = 6), chromosomal disorders (n = 4), and peripheral nerve disorders (n = 3) were the most common diagnoses. The genetic tests of highest yield were FISH and DNA methylation studies for PWS, trinucleotide repeat testing for myotonic dystrophy, and karyotype analysis (Richer et al. 2001).

KEY POINTS

- ☞ Differentiating between central and peripheral hypotonia is the first step
- ☞ Targeted investigations will yield better results
- ☞ Many of the diseases are inherited, hence genetic counseling is important
- ☞ Neonatal hypotonia can be specially challenging to investigate.

SUGGESTED READINGS

1. Bodensteiner JB. The evaluation of the hypotonic infant. Semin in Pediatr Neurol. 2008;15:10-20.
2. Fenichel Gerald. Clinical Pediatric Neurology: A Signs and Symptoms Approach, 5th ed. Philadelphia: Elsevier; 2005. pp. 149-69.
3. Prasad AN, Prasad C. Genetic evaluation of the floppy infant. Semin Fetal Neonatal Med. 2011;16:99-108.
4. Peredo DE, Hannibal MC. The floppy infant: evaluation of hypotonia. Pedaitr in Review. 2009;30(9):66-76.

CHAPTER 90

Approach to Ataxia

Jayakumar Vaikundam

INTRODUCTION

Ataxia is a common symptom manifesting as unsteady gait, frequent falls, and clumsiness in walking or in using the hands due to derangement in posture control, movement, and co-ordination.

Ataxia can occur as a result of:

- Cerebellar dysfunction
- Posterior column dysfunction
- Vestibular dysfunction

Hence, as a first step one should be able to identify which is the main structure that is affected to result in ataxia. Table 1 will help in the differentiation.

SENSORY ATAXIA

The most common cause of sensory ataxia in children is vitamin B12 deficiency. It is more commonly seen in vegetarians. Apart from the dietary insufficiency and malabsorptive state, lack of intrinsic factor can also lead to vitamin B12 deficiency state.

It is clinically characterized by anemia, lethargy, poor cognitive performance, hypotonia, sensory ataxia, and involuntary movements especially in infants. Neurological examination will reveal hyporeflexia, posterior column involvement, and bilateral extensor plantar response due to additional pyramidal tract involvement.

TABLE 1: Differentiating features of different structures involved in the causation of ataxia

Features	Posterior column	Vestibular	Cerebellar
Headache/vomiting	–	+/–	+/–
Tinnitus/vertigo	–	Often present	+/–
Speech	Normal	Normal	Slurring/Scanning/Staccato
Titubation	–	–	+/–
Nystagmus	–	• Seen in primary position often with rotary component with direction of the fast phase away from the side of lesion • Positional nystagmus is common	• Usually not seen in primary position Gaze evoked (fast component to the direction of gaze) • Rebound nystagmus is also a sign of intrinsic cerebellar lesion • Positional nystagmus is not common
Clumsiness and in-coordination of upper limb	–	–	Common
Hypotonia	+/–	–	Often seen in acute lesions
Romberg sign	+	–	–
Gait	Sensory ataxia more prominent on eye closure or in darkness	Tendency to lurch to one side	Wide based, staggering, lurching, and drunken ataxia
Other signs	Other signs of peripheral nerve or cord involvement	Positional vertigo and blocking feeling in the ear	Dysdiadochokinesia, dyssynergia, and dysmetria

One important clinical clue for vitamin B12 deficiency state is the presence of hyperpigmentation over the dorsum of interphalangeal joints, knuckles, palmar creases, intertriginous areas, and recent scars. The mechanism for hyperpigmentation is not known and it is reversible disappearing with treatment.

Peripheral smear studies will show macrocytic anemia, hypersegmented polymorphs, bone marrow showing megaloblastic reaction. Serum vitamin B12 level is low. Magnetic resonance imaging studies usually show the picture of subacute combined degeneration causing increased signal intensity in T2W images in the posterior columns of cervical and thoracic spinal cord. Treatment may reverse these changes.

Clinical Pearl

- Hyperpigmentation over the knuckles, interphalangeal joints in an ataxic child should suggest the possibility of vitamin B12 deficiency which is eminently treatable.

VESTIBULAR ATAXIA

Recurrent attacks of vertigo with unsteadiness, nystagmus, and vomiting sometimes can occur in infants and preschool children as a part of benign paroxysmal vertigo. The episode lasts for few minutes and may recur irregularly.

It is often considered as a variant of migraine and nearly one-fourth of them subsequently develop migraine. There is often a family history of migraine.

CEREBELLAR ATAXIA

Cerebellar dysfunction appears to be the most common cause for ataxia and is characterized by the following clinical features which will help to some extent to identify which portion of the cerebellum is the most affected, although there is a considerable overlap.

- Ataxia:
  - Vermis lesions produce truncal ataxia and titubation
  - Hemispherical lesions produce limb ataxia with a tendency to lurch to the side of lesion
  - Anterior lobe lesions produce gait ataxia
- Kinetic tremor and incoordination: seen in hemispherical lesions involving dentate nucleus
- Hypotonia: seen mostly in acute lesions than in chronic
- Nystagmus and eye movement abnormalities: seen commonly in flocculonodular lobe and vermis lesions
- Dysarthria: slurring, scanning, and staccato speech are commonly in left cerebellar hemispherical lesions.

Clinical Pearls

- Nystagmus, dysarthria, incoordination suggest cerebellar ataxia
- Hypotonia is usually seen in acute lesions than in chronic.

Table 2 describes the localizing features of different signs.

TABLE 2: Cerebellar ataxia: localizing features

Site of involvement	Clinical features
• Midline: ○ Upper vermis lesion ○ Lower vermis lesion ○ Fastigial nuclear lesion	• Abnormal stance, truncal ataxia, titubation abnormal head-posture and eye-movement abnormalities ○ Abasia, gait ataxia are prominent ○ Nystagmus is prominent ○ Abasia (difficulty in maintaining the stance)
• Intermediate (lesions affecting interposed nuclei)	• Rebound response, titubation, dysdiadochokinesia, finger nose, heel-knee shin incoordination, kinetic tremor, proximal limb oscillation of outstretched arms
• Lateral hemispherical (lesions affecting dentate nuclei)	• Cerebellar dysarthria (especially in left-sided lesions), limb ataxia, hypotonia, kinetic tremor and eye-movement abnormalities

Clinical Pearls

- Nystagmus is a sign of flocculonodular lobe lesion
- Truncal ataxia is a sign of vermis lesion
- Limb incoordination is a sign of cerebellar hemispherical lesion
- Gait ataxia is a sign of involvement of anterior lobe of cerebellum.

Clinical Approach to Cerebellar Ataxia

Cerebellar ataxia can be acute, intermittent/episodic or chronic. Algorithm 1 describes the different causes.

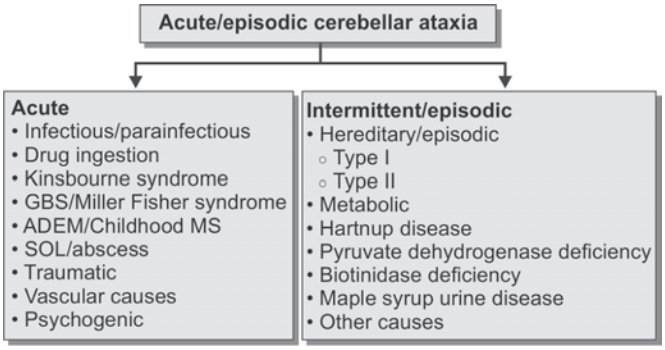
Acute Cerebellar Ataxias

Acute cerebellar ataxias due to infective/parainfective causes

- Often occur following infections with varicella, mumps, and other viral infections

ALGORITHM 1

Approach to an ataxic child (acute/episodic intermittent cerebellar ataxia)



SOL, space occupying lesion; GBS, Guillain-Barré syndrome; ADEM, acute disseminated encephalomyelitis, MS, multiple sclerosis.

- Occur either immediately following fever or within 6 weeks, characterized by headache, vomiting, a severe gait disturbance, nystagmus, and behavioral changes with increased cerebrospinal fluid (CSF) cell count in viral cerebellitis and normal cell count in postinfectious ataxia along with mild increase in proteins
- Although there is no specific therapy, most of them respond well to antiviral (acyclovir) drugs, steroids, and intravenous immunoglobulin therapy.

Ataxia due to drugs

- Overdose of phenytoin, phenobarbitone, carbamazepine, phenothiazines, benzodiazepines, and sometimes anthelmintic drugs like piperazine; antihistamine are well-known to produce acute ataxias
- Some helpful clues are drowsiness, vomiting, or nystagmus which is less prominent on downward gaze and absence of fever
- Electroencephalogram in some of these patients may show diffuse fast activity, indicative of sedative drug overdose
- The treatment depends on the identification of the specific causative drug. In certain life-threatening situations, dialysis and vital support function may be required.

Kinsbourne syndrome (opsoclonus myoclonus syndrome)

It is characterized by:

- Acute or subacute onset of peculiar dancing eye movements in different directions and planes (opsoclonus) due to unwanted spontaneous saccades. Opsoclonus may persist during sleep
- Myoclonic jerking of the trunk and limbs which may be stimulus sensitive and may increase with action
- Child is often irritable and ataxic and may require support with hands and may be even afraid of standing or sitting without support
- Nearly about 50% of the children with opsoclonus-myoclonus may have occult neuroblastoma and these symptoms can precede the diagnosis of the tumor
- May need abdominal ultrasonogram; urinary vanillyl-mandelic acid and homovanillic acid estimation; and in some cases computed tomography chest, abdomen; metaiodobenzylguanidine; or Dotatoc scan may be required
- Injection adrenocorticotropic hormone is useful in some patients.

Guillain-Barre syndrome/Miller Fisher syndrome

- Early stages of Guillain-Barre syndrome (GBS) can present with ataxia and subsequently patient may develop weakness
- A variant of GBS—viz. Miller Fisher syndrome characterized by acute ataxia, ophthalmoplegia, and areflexia can present with acute ataxia
- Ophthalmoplegia in Miller Fisher syndrome starts initially with upward gaze restriction followed by lateral gaze and finally down gaze restriction
- Intravenous immunoglobulin therapy is useful.

Acute disseminated encephalomyelitis

- Acute disseminated encephalomyelitis is usually a monophasic illness following a viral infection, immunization or vaccination usually after an afebrile period following the initial febrile illness
- Usually characterized by altered mental status, irritability and lethargy, seizures, and focal neurological deficits
- Some children may present with brainstem signs, limb ataxia, nystagmus, and bilateral optic neuritis (in multiple sclerosis the optic neuritis is unilateral)
- In MRI, T2W/FLAIR images will show multiple subcortical lesions (usually at the junction of deep cortical gray and subcortical white matter) with smudging of edges (in contrast the multiple sclerosis lesions will have sharp clear margins)
- Treatment involves mainly intravenous methyl prednisolone and in some cases intravenous immunoglobulin.

Childhood multiple sclerosis

- Around 4–5% of them can occur in children (mostly around 10–15 years of age)
- Visual disturbances are common apart from brainstem, cerebellar, and long tract disturbances
- In contrast to adult type of multiple sclerosis, seizures and mental status changes are common in children
- Magnetic resonance imaging typically shows hyperintense T2W lesions in cerebellum, brainstem, periventricular, and pericallosal white matter
- Evoked potentials studies and CSF immunoglobulin G index and CSF analysis for oligoclonal bands are useful
- Treatment involves intravenous methyl prednisolone.

Psychogenic

The following clues help in the diagnosis of acute psychogenic ataxia:

- Ataxia occurs immediately on standing
- Bizarre and gross
- Absence of wide based stance
- Tendency to move from one object to another in a room to get a support
- Absence of other neurological signs.

Other causes

- Space-occupying-lesions—cerebellar abscess
- Traumatic
- Vascular—cerebellar hemorrhage, infarct, or arterial dissection
- Basilar migraine.

Clinical Pearls

- Drug-induced ataxia should always be considered first in acute ataxia
- Past history of chicken pox should always be asked
- Guillain-Barré syndrome should be considered when there is ataxia with absent deep tendon reflexes
- In a febrile ataxic child with history of chronic suppurative otitis media, always rule out cerebellar abscess
- Past history of similar episode could suggest the possibility of episodic ataxias.

TABLE 3: Hereditary episodic ataxias

Features	Type I	Type II
Age	5–7 years	School going/adolescents
Precipitating factors	Exercise, fever, sudden movement, carbohydrate meal	–
Duration	Few seconds to minutes	Few minutes to few days
Frequency	Several times per day	1 to 3 times per month
Attacks	Mainly ataxia	Ataxia, dysarthria, diplopia, vertigo
Useful clinical clue in between the attacks	Myokymia (seen in periorbital, facial, and hand muscles)	Nystagmus
Ion channel involved	Potassium channel gene KCNA1 linked to chromosome 12p13	Calcium channel CACNA1A in Chromosome 19p
Treatment	Acetazolamide, phenytoin	Acetazolamide, flunarazine, 4-aminopyridine

Episodic/Recurrent/Intermittent Ataxias

Recurrent attacks of ataxia can occur either as a form of hereditary episodic ataxia or due to some metabolic disorders.

Hereditary episodic ataxia

Although there are four types of hereditary ataxias Type I and Type II are more common and their differentiating features are outlined in the table 3.

Metabolic disorders producing intermittent ataxia

The usual clues are—lethargy, vomiting and occasional ICT. The following metabolic disorders can present with intermittent ataxia.

- Hartnup disease
- Pyruvate dehydrogenase deficiency
- Biotidinase deficiency
- Maple syrup urine disease
- Certain urea cycle—ornithine transcarbamylase deficiency

Other causes of intermittent ataxia

Children with Down syndrome can present with ataxia, transient weakness of the limbs, especially after sudden flexion of the neck usually after vigorous towelling of the head after head bath due to recurrent atlanto-axial subluxation.

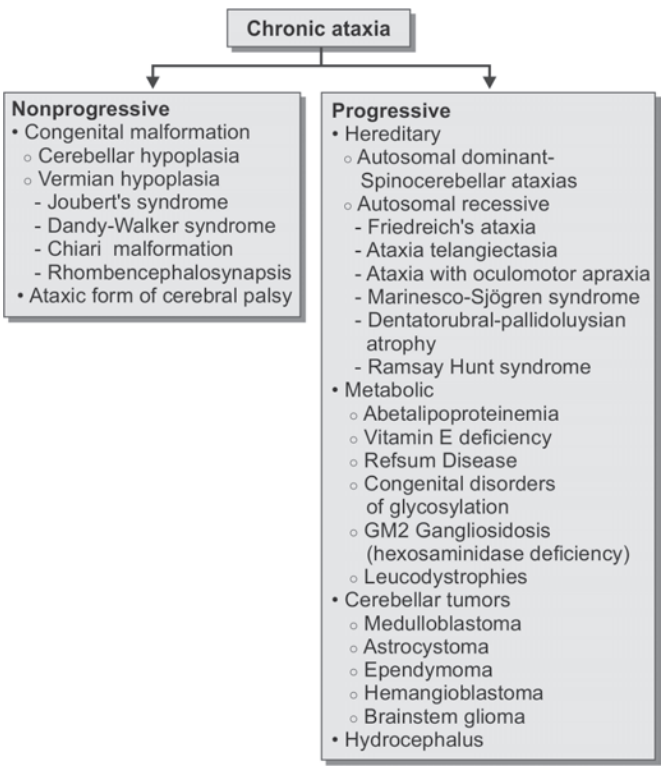
Clinical Pearls

- Pellagra like pigmentation suggest the possibility of Hartnup Disease
- Increased blood pyruvate and lactate suggest pyruvate dehydrogenase deficiency
- Alopecia, dermatitis, and deafness suggest biotinidase deficiency
- Acetazolamide is useful for Type I and Type II hereditary episodic ataxias
- Always rule-out atlanto-axial subluxation in an ataxic Down syndrome child.

Chronic Ataxias

Chronic ataxia can be nonprogressive or progressive and the various causes are outlined in the algorithm 2.

ALGORITHM 2



Chronic nonprogressive cerebellar ataxias

There are two major conditions which can cause nonprogressive cerebellar ataxias, viz.

1. Congenital malformations of the brain
2. Ataxic form of cerebral palsy.

Congenital malformations of the brain

The following malformations often cause nonprogressive cerebellar ataxia:

- Cerebellar hypoplasia
- Vermian hypoplasia:
  - Joubert's syndrome
  - Dandy-Walker syndrome

- Chiari malformation
- Rhombencephalosynapsis

- Congenital cerebellar hypoplasia:
  - Autosomal recessive disorder
  - Characterized by hypotonia, ataxia, nystagmus
  - Magnetic resonance imaging (MRI) of brain will show mainly cerebellar hemispherical atrophy
  - It should be differentiated from other progressive conditions by serial MRI and involvement of brainstem and other neurological findings.
- Cerebellar vermian hypoplasia: The vermis of the cerebellum is maximally involved in the following conditions:
  - Joubert's syndrome:
    - Autosomal recessive disorder with partial or total agenesis or hypoplasia of the vermis
    - Characteristic facies, squint, ataxia, oculomotor apraxia, and breathing abnormalities are typical
    - MRI brain will show the following characteristic findings:
      - Molar tooth appearance of the brainstem
      - Bullet-shaped upper-fourth ventricle
      - Horizontal superior cerebellar peduncle
      - Bat-wing appearance of the lower fourth ventricle.
  - Dandy-Walker malformation:
    - Clinically patients present with hydrocephalus and large posterior fossa
    - Vermian hypoplasia (mainly caudal vermis) and cystic dilatation of the fourth ventricle are characteristic imaging findings
  - Chiari malformation:
    - Clinically patients present with vague pain in the neck, suboccipital headache, and ataxia
    - The characteristic clinical clues are presence of down beat nystagmus, oscillopsia
    - May be associated with syrinx, lower cranial nerves palsy and skeletal abnormalities
    - Magnetic resonance imaging of craniovertebral junction will show downward displacement of the cerebellar tonsil which is peg shaped. Coexistent syrinx may be seen
    - Treatment involves surgical decompression.

Ataxic form of cerebral palsy

- Accounts for 5–10% of all forms of cerebral palsy
- 50% of them are autosomal recessively inherited
- History of birth asphyxia, mild spasticity, brisk reflexes, and ataxia
- Lack of correlation between imaging and clinical findings
- Recent gene mapping to chromosome 9p12-q12 is useful to differentiate this from other conditions.

Clinical Pearls

- Most of the congenital cerebellar malformations cause non-progressive ataxias
- Brisk deep tendon reflexes in a child with nonprogressive ataxia suggest the possibility of ataxic form of cerebral palsy
- Imaging findings do not correlate with clinical picture in ataxic cerebral palsy.

Chronic Progressive Cerebellar Ataxias

Chronic progressive cerebellar ataxias could be due to:

- Hereditary ataxias which could be autosomal dominant or autosomal recessively inherited
- Metabolic disorders
- Cerebellar tumors
- Chronic hydrocephalus.
- Hereditary ataxias:
  - Autosomal dominant variety is mostly seen in adults
  - Autosomal recessive disorders include:
    - Friedreich's ataxia
    - Ataxia telangiectasia
    - Ataxia with oculomotor apraxia
    - Abetalipoproteinemia
    - Vitamin E deficiency
    - Congenital disorder of glycosylation
    - Refsum disease
    - Marinesco-Sjogren syndrome.
  - Autosomal Recessive hereditary ataxias:
    - Friedreich's ataxia:
      - Autosomal recessive disorder due to defective expression of "frataxin" encoded by X25 gene at chromosome 9
      - Onset around puberty
      - Pes cavus, loss of deep tendon reflexes; extensor plantar and posterior column sensory loss, apart from cerebellar signs are the cardinal features
      - In 25% of them deep-tendon reflexes may be normal
      - Magnetic resonance imaging brain will show atrophy of cerebellum, cervical cord and abnormal signals in the posterior and lateral columns
      - Nerve conduction and somatosensory evoked potentials studies may show abnormality
      - Cardiomyopathy is seen in 50% and diabetes in 10%
      - Idebenone has been found to be useful for cardiac dysfunction
      - Diagnosis is confirmed by genetic testing showing GAA trinucleotide repeats in the range of 600–900 repeats

Clinical Pearl

- Deep tendon reflexes can be normal in 25% of patients with Friedreich's ataxia.

    - Ataxia telangiectasia:
      - Autosomal recessive disorder affecting nervous and immune system due to deficiency of ataxia-telangiectasia mutated (ATM) protein
      - Mutation in the large ATM gene linked to chromosome 11q22-23
      - Choreoathetosis followed by ataxia and dysarthria occur early
      - Oculomotor apraxia is seen in 90% of patients.
      - Telangiectasia:
        - Develops after 2–10 years of age

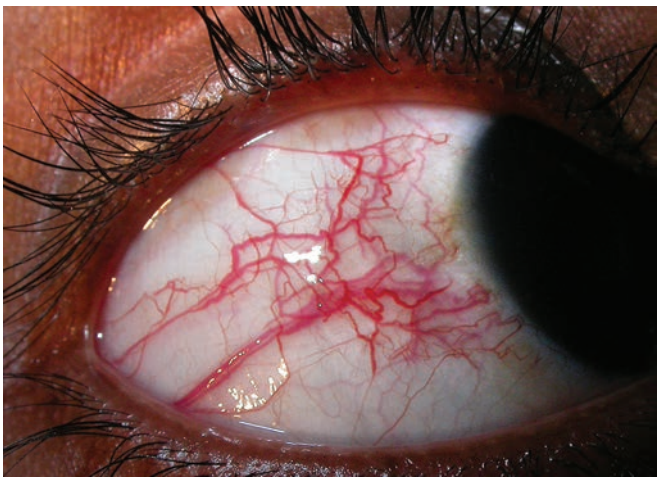


Fig. 1: Bulbar conjunctival telangiectasia

- Seen in bulbar conjunctiva, upper ears, forearm, and face (Fig. 1)
- Exacerbated by exposure to sunlight
- Tends to grow with advancing age

- Recurrent sinopulmonary infection and prone for lymphoma and leukemia (38%)
- Serum α-fetoprotein and carcinoembryonic antigen are elevated
- Serum IgG, IgA are reduced and IgM elevated
- Betamethasone 0.1 mg/kg/day divided every 12 hours for 4 weeks has been found to be useful in some patients.

Clinical Pearls

- Conjunctival telangiectasia develops later usually after 2 years of age
- Telangiectasia tends to grow with age
- Telangiectasia becomes more prominent after exposure to sunlight for some time
- Oculomotor apraxia is seen in Joubert's syndrome, ataxia telangiectasia, ataxia with oculomotor apraxia without telangiectasia, and in Gaucher's disease
- Serum albumin testing is important.

– Ataxia with oculomotor apraxia (Table 4):
  - Autosomal recessive disorder often mistaken for ataxia telangiectasia
  - No conjunctival telangiectasia and linked to chromosome 9p14

TABLE 4: Types of ataxia with oculomotor apraxia

Features	Type I	Type II
Age of onset	Early age	Adolescence
Gait ataxia	+	+
Oculomotor apraxia	Common and prominent	Less common
Serum albumin	Reduced	Normal

  - Two types are described.
– Others:
  - GM2 Gangliosidosis—low α and β hexosaminidase A in fibroblasts
  - Ramsay-Hunt syndrome is characterized by progressive myoclonus and ataxia
  - Marinesco-Sjogren syndrome is characterized by congenital cataract, skeletal abnormalities, mental retardation, and ataxia
  - Dentato rubro-pallidoluysian atrophy seen mostly among Japanese.

- Metabolic Disorders causing progressive ataxias:
  - Abetalipoproteinemia (Bassen-Kornzweig Disease):
    – Autosomal recessive disorder
    – Due to absence of microsomal triglycerides transfer protein, linked to chromosome 4q22-q24 causing absence of apolipoprotein B which results in deficiency of vitamins A, D, E, and K
    – Failure to thrive, steatorrhea, vomiting, ataxia, areflexia, and proprioceptive disturbance are the common clinical features
    – Retinitis pigmentosa is a constant feature usually seen before 10 years of age
    – Peripheral smear will reveal acanthocytosis
    – Plasma cholesterol and triglycerides are low (due to low apolipoprotein B)
    – Nerve conduction studies may show abnormalities
    – Treatment includes restriction of fat, and large doses of vitamin E (100 mg/kg/day).
  - Vitamin E deficiency:
    – Autosomal recessive disorder linked to chromosome 8q13
    – No malabsorption only isolated deficiency of vitamin E
    – Ataxia and peripheral neuropathy
    – Resembles Friedreich's ataxia
    – Diagnosed by low vitamin E level and normal vitamin E absorption
    – Treatment includes 800–900 IU of vitamin E.

Clinical Pearl

- Isolated vitamin E deficiency can resemble Friedreich's ataxia. Hence, when in doubt, it is always better to give a therapeutic trial with vitamin E

  - Refsum disease:
    – Autosomal recessive disorder due to deficiency of phytanic acid oxidase
    – Clinical features include:
      - Cerebellar ataxia
      - Deafness
      - Retinitis pigmentosa
      - Thickened nerves
      - Chronic demyelinating sensory motor neuropathy
      - Increased CSF proteins
      - Serum phytanic acid level increased
        - Plasma exchange is useful apart from restriction of dietary phytanic acid.

- Congenital disorder of glycosylation (carbohydrate deficient glycoprotein syndrome):
  - Autosomal recessive disorder linked to chromosome 16p13 affecting glycoprotein synthesis as a result of abnormal glycosylation
  - Clinically characterized by multisystem involvement:
    - Neurological: psychomotor retardation, hypotonia ataxia, cerebellar hypoplasia, squint, stroke-like-episodes, sometimes seizures, and peripheral nerve involvement
    - Dysmorphism: almond shaped eyes, large forehead, and inverted nipples
    - Lipocutaneous anomalies: peau d' orange skin, and infiltration with fat over the thighs and buttocks producing pads of fat
    - Hepatodigestive: hepatic cytolysis, and hepatic fibrosis
    - Cardiac: pericarditis and cardiomyopathy
  - Diagnosis: isoelectrofocusing of serum transferrin
  - Treatment consists of use of ketogenic diet, mannose, aspirin, and bisphosphonates.

Clinical Pearl

- Suspect congenital disorder of glycosylation in a child with ataxia with inverted nipples, supragluteal pads of fat and peau d' orange skin.

- Cerebellar tumors:
  - Medulloblastoma
  - Cerebellar astrocytoma
  - Ependymoma
  - Cerebellar hemangioblastoma (von Hippel-Lindau disease)
  - Brainstem glioma.

Clinical Pearls

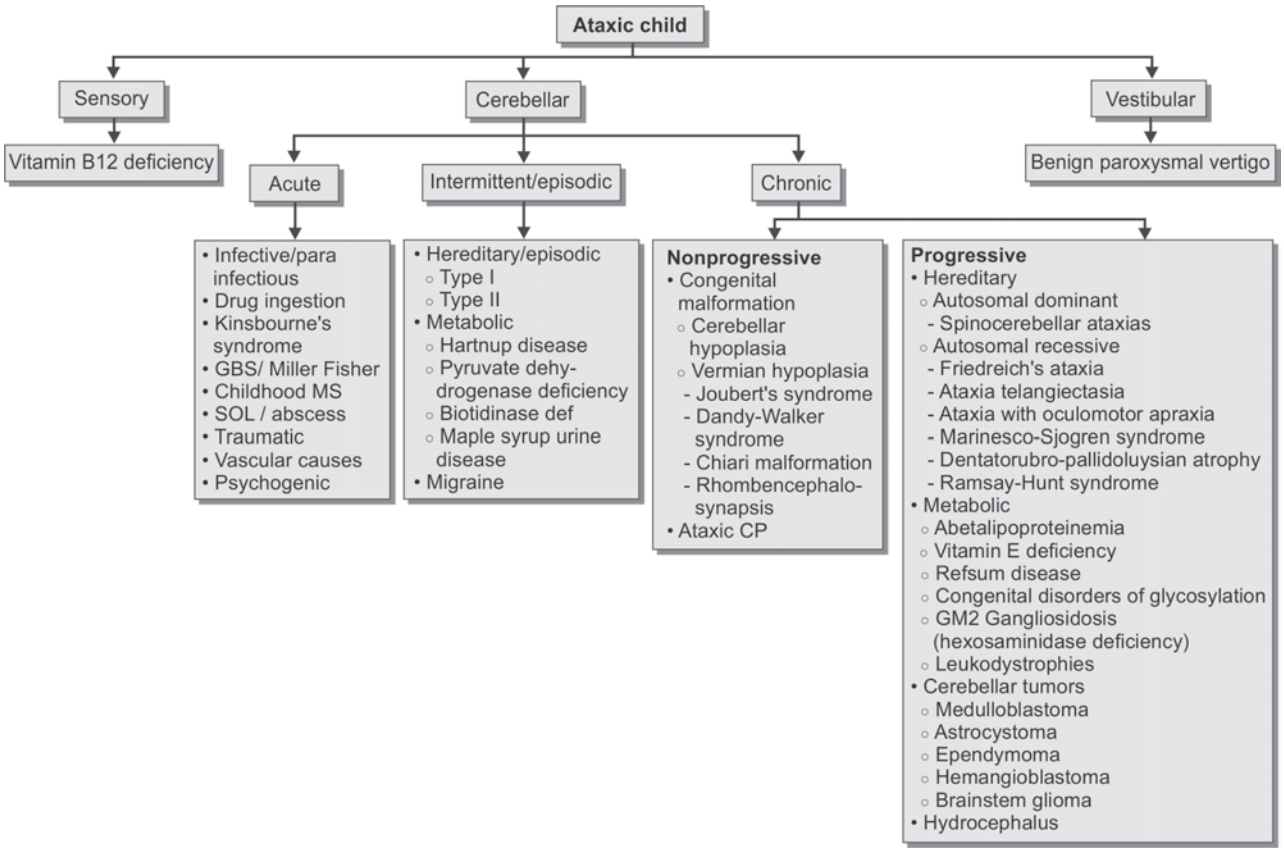
- Vomiting, nystagmus, truncal ataxia and torticollis in a preschool child suggest the possibility of medulloblastoma
- Unilateral cerebellar signs with features of increased intracranial pressure (ICP) in a 5–10 years old child think of the possibility of cerebellar astrocytoma which has a good prognosis
- Ependymoma of the floor of the fourth ventricle can present with only intractable vomiting
- Presence of retinal angioma in an ataxic child suggests the possibility of von Hippel-Lindau disease
- Ataxia with multiple lower cranial nerve palsies (6th and 7th) suggest the possibility of brainstem glioma where symptoms of ICP manifest late.

- Hydrocephalus: Hydrocephalus due to any cause can present with gait ataxia and symptoms of raised ICT.

Algorithm 3 gives the summary of approach to ataxias in children.

ALGORITHM 3

Summary of approach to ataxias in children



GBS; Guillain-Barre syndrome; MS, multiple sclerosis.

KEY POINTS

- ☞ First evaluate whether ataxia is due to cerebellar, vestibular or sensory involvement
- ☞ Vitamin B12 deficiency should be suspected when there is predominant sensory ataxia with hyperpigmentation over the knuckles, interphalangeal joints
- ☞ In cerebellar ataxias ascertain which part of cerebellum is maximally involved by looking at the appropriate clinical signs
- ☞ Acute ataxias are commonly due to drugs, infectious and post-infectious causes, acute disseminated encephalomyelitis, cerebellar abscess and early stages of Guillain-Barre syndrome
- ☞ Episodic ataxias often respond to acetazolamide
- ☞ Down syndrome with atlantoaxial subluxation can also present with intermittent ataxia in addition to some inborn errors of metabolism
- ☞ Nonprogressive cerebellar ataxias are often due to congenital cerebellar malformations and ataxic form of cerebral palsy
- ☞ Chronic hereditary cerebellar ataxias in children are often due to autosomal recessively inherited conditions
- ☞ Eye signs like oculomotor apraxia, bulbar conjunctival telangiectasia are important to look for (ataxia telangiectasia)
- ☞ Vitamin E deficiency induced ataxia may resemble Friedreich's ataxia. Hence a therapeutic trial of vitamin E is worth
- ☞ Cerebellar tumors and hydrocephalus can present as chronic progressive cerebellar ataxia
- ☞ Always look for treatable causes of cerebellar ataxia before making the diagnosis of cerebellar degeneration.

SUGGESTED READINGS

1. Brazis PW, Masdeu JC, Biller, J. Localization in clinical Neurology, 5th ed. (Indian reprint). Philadelphia: Lippincott Williams & Wilkins; 2007. pp. 374.
2. Facchini SA, Jami MM, Neuberg RW, Sorrell AD. A treatable cause of ataxia in children., Pediatr Neurol. 2001;24(2):135-8.
3. Ghezzi A, Deplano V, Faroni J, Grasso MG, Liguori M, Marrosu G, et al. Multiple sclerosis in childhood: clinical features of 149 cases. Mult Scler. 1997;3(1):43-6.
4. Jayaram S, Soman A, Tarvade S, Londhe V. Cerebellar Ataxia due to isolated vitamin E deficiency., Indian J Med Sci. 2005;59(1):20-3.
5. McHale DP, Jackson AP, Campbell, -Levene MI, Corry P, Woods CG, et al. A gene for ataxic cerebral palsy maps to chromosome 9p12q12. Eur J Hum Genet. 2000;8(4):267-72.
6. Neeraj Srivastava N, Chand S, Bansal M, Srivastava K, Singh Set al., Reversible hyperpigmentation as the first manifestation of dietary vitamin B12 deficiency. Indian J Dermatol Venereol Leprol. 2006;72(5):389-90.
7. Pandolfo M. Friedreichs ataxia: clinical aspects and pathogenesis. Semin Neurol. 1999;19:311-21.
8. Peter H. Berman PH., Ataxia in children., International Pediatrics. 1999;14(1): 44-7.
9. Sabrina Buoni, S, Zannolli R, Sorrentino L, Fois A. Betamethasone and improvement of neurological symptoms in ataxia-telangiectasia., Arch Neurol. 2006;63:1479-1482.
10. Schols, L, Bauer P, Schmidt T, et al. Autosomal dominant cerebellar ataxias; clinical features, genetics and pathogeneses. The Lancet Neurology. 2004;3: 291-304.
11. Singhvi JP, Prbhakar S, Singh P. Episodic ataxia: a case report and review of literature. Neurol India. 2000;48;78-80.
12. Stephanie Grunewald S, Gert Mathuus G, and Jaak Jaeken J., Congenital disorders of glycosylation. Pediatric Research. 2002;52: 618-624.
13. Jayakumar V. Childhood ataxias. Reviews in Neurology. 2008;14:339-372.

CHAPTER 91

Acute Hemiplegia in Children: An Algorithm for Diagnosis and Treatment

Viraj V Sanghi

INTRODUCTION

Hemiplegia is defined as complete paralysis of one-half of the body with or without facial involvement. The term hemiparesis refers to partial weakness of one-half of the body. The etiology of hemiplegia is vast and varied. The age of onset plays a vital role in determining the etiology.

HEMIPLEGIA IN INFANTS

Infantile hemiplegia is most commonly seen as a result of perinatal hypoxic or vascular events, infantile acquired cerebral infections, and the hemiconvulsion-hemiplegia-epilepsy syndrome.

Perinatal Stroke

The rate of arterial infarction in neonates is as high as the annual incidence of large-vessel ischemic stroke in adults. The incidence of perinatal stroke has been estimated at 1 in 1,600–5,000 births. Neonatal cerebral infarction accounts for 10–15% of the total number of neonates with seizures and is the main identified cause of congenital hemiplegia. Most perinatal strokes involve the middle cerebral artery and are caused by thromboembolism from an intracranial or extracranial vessel, the heart, or the placenta. Various risk factors have been associated with perinatal stroke. Maternal risk factors associated with fetal stroke include prothrombotic disorders, cocaine abuse, and placental complications such as chorioamnionitis and placental vasculopathy. During delivery, cervical arterial dissection may occur which leads to stroke. In the neonatal period, prothrombotic disorders, congenital heart disease, meningitis, and systemic infection can all lead to perinatal stroke (Box 1).

Box 1: Maternal risk factors associated with stroke

- Prothrombotic disorders
- Chorioamnionitis
- Placental vasculopathy
- Substance abuse

Clinical Pearl

- Focal clonic seizure in the newborn period is the most common clinical presentation of perinatal arterial ischemic stroke.

The majority of newborns do not go onto develop epilepsy. About 40% of patients do not have specific symptoms in the neonatal period and may be asymptomatic until months later when the infant is first noted to have pathological handedness. Hemiparesis is then noticed on clinical examination in later stages of infancy. Neuroimaging in these infants then leads to a retrospective diagnosis of perinatal arterial ischemic stroke (AIS). The recurrence rate after perinatal stroke is very low (Fig. 1) .

Hemiconvulsion-hemiplegia-epilepsy Syndrome

Hemiconvulsion-hemiplegia-epilepsy syndrome is an uncommon outcome of prolonged focal status epilepticus in childhood. The prolonged focal motor seizure usually occurs during the course of a febrile illness and is followed by hemiplegia, ipsilateral to the side of convulsions. A prolonged febrile seizure results in inflammation which may worsen the level of cell injury. Inflammation and prolonged ictal activity act on blood-brain-barrier permeability. There may also be predisposing factors facilitating prolonged seizure such as genetic factors or focal epileptogenic lesion (Fig. 2).

HEMIPLEGIA IN OLDER CHILDREN

In older children, the etiology differs from that of infantile hemiplegia. The causes of acute hemiplegia are varied (Box 2). Extensive clinical, radiological, and laboratory workup is essential to arrive at a diagnosis before commencing treatment.

Childhood Stroke

Childhood stroke has been considered to be a rare disorder. The reported incidence for ischemic stroke has increased

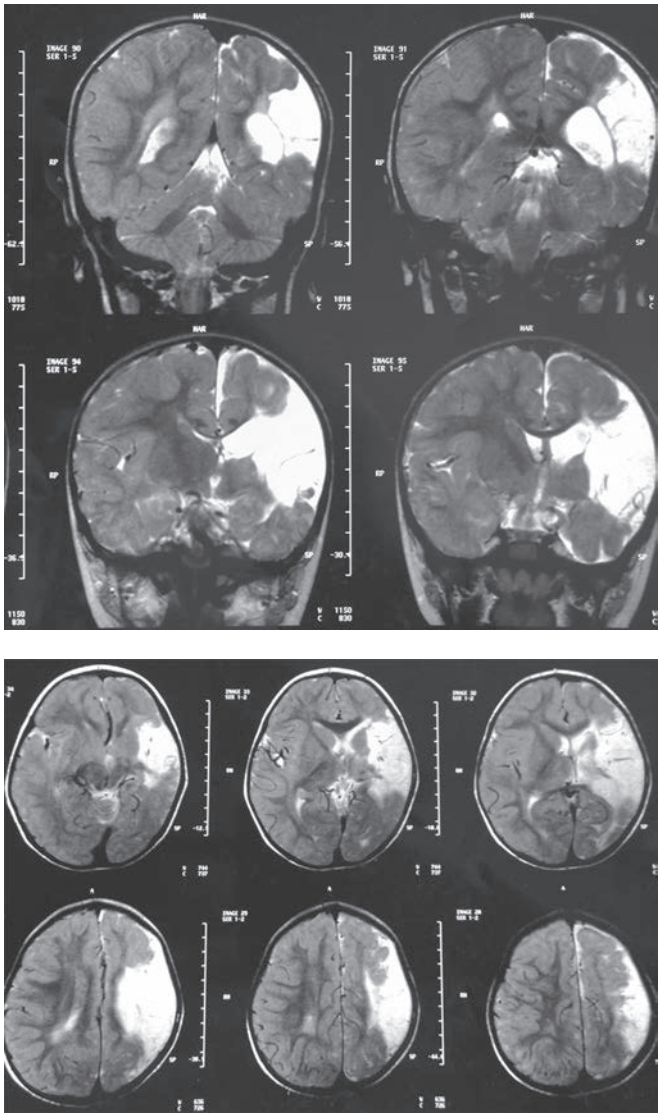


Fig. 1: T2 weighted coronal and axial magnetic resonance imaging: large cystic encephalomalacic lesion in left hemisphere due to perinatal stroke

during the past two decades. The recent reported incidence rates are between three and eight per 100,000 children per year. The major syndromes comprising ischemic stroke in childhood consist of AIS and sinovenous thrombosis (SVT). Arterial ischemic strokes constitute 80% of cases.

Toddlers with AIS more frequently present with abrupt onset of a hemiparesis, with facial droop, difficulty using one hand, or dragging of one leg. In school age or teenage child, other symptoms such as speech or visual disturbance; headache, or focal sensory deficits may be seen in addition to hemiparesis. Seizures accompany the stroke in approximately 50% of children (Box 3) .

In SVT, a clinical picture indistinguishable from "pseudotumor cerebri" is the most frequent presentation, characterized by prominent headache, papilledema and occasionally sixth nerve palsy. Visual disturbances including

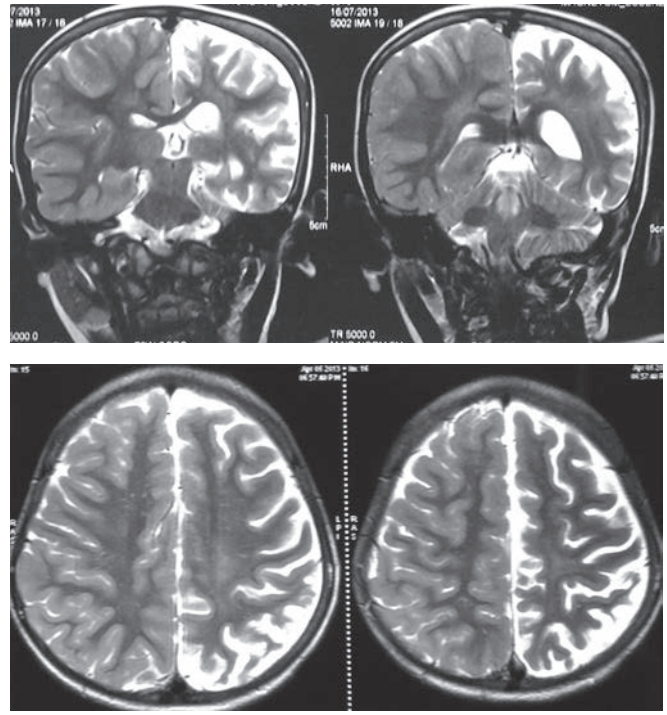


Fig. 2: T2 weighted magnetic resonance imaging of brain: left hemispheric atrophy in chronic stage of hemiconvulsion-hemiplegia-epilepsy syndrome

Box 2: Causes of acute hemiplegia in children

- Stroke (ischemic and hemorrhagic)
- Infections (bacterial abscess, tuberculosis, viral encephalitis, parasitic)
- Demyelination (acute disseminated encephalomyelitis, multiple sclerosis, neuromyelitis optica); autoimmune encephalitis (anti N-methyl-D-aspartate receptor/anti voltage gated potassium channel receptor encephalitis)
- Metabolic (hypoglycemia, diabetic ketoacidosis, hyponatremia, mitochondrial)
- Migraine and familial hemiplegic migraine; alternating hemiplegia of childhood
- Postseizure hemiparesis (Todd's paralysis)
- Tumors
- Trauma

Box 3: Clinical presentation of arterial ischemic stroke

- Toddlers:
  - Facial droop
  - Difficulty using one hand
  - Dragging of one leg
- Older children:
  - Hemiparesis
  - Speech disturbances
  - Visual disturbances
  - Headache
  - Focal sensory deficits
  - Seizures

an increased central scotoma or diplopia are present in 18% of children with SVT. Hemiparesis and other focal signs are present in 35–45%. Seizures occur at presentation in 48% of older infants and children (Box 4).

Box 4: Clinical presentation of sinus venous thrombosis

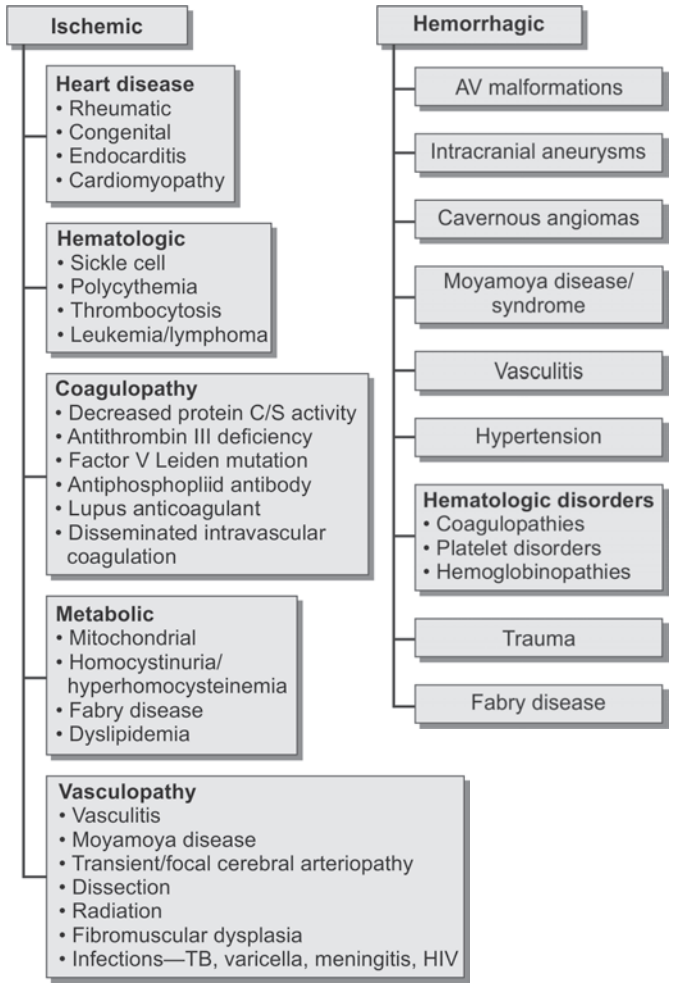
- Headache, papilledema, and 6th nerve palsy
- Hemiparesis
- Visual disturbances
- Seizures

A wide range of risk factors/causes associated with childhood AIS (Box 3). These include cardiac disorders, sickle-cell disease, prothrombotic disorders, trauma, and major infections such as meningitis, sepsis, and encephalitis. However, in the majority of the children, no underlying systemic disease is found. With advances in neuroimaging, cerebral arteriopathies are increasingly recognized as one of the major causes of childhood stroke, in otherwise healthy children. Some arteriopathies are due to well-recognized causes such as arterial dissection, moyamoya syndrome or disease, connective tissue disorders, and sickle-cell disease. Late effects of radiation to the head and neck in childhood cancer survivors have also been associated with stroke due to cerebrovascular disease, and children with neurofibromatosis can have complications of a cerebral arteriopathy. However, in up to 30% of children presenting with a first AIS, a focal arterial stenosis is identified but none of the classic underlying causes are discovered.

Transient Cerebral Arteriopathy (TCA), the most common type of arteriopathy identified in pediatric stroke, is a monophasic arterial disease characterized by a unilateral focal or segmental stenosis involving the distal part of the internal carotid and the initial segments and branches of the anterior and/or middle cerebral artery followed by complete or partial resolution. The pathophysiology of TCA is uncertain. 44% of TCA cases are associated with varicella zoster infection in the 12 months prior to AIS causing postvaricella arteriopathy. Varicella virus invades the arterial wall causing an acute vasculitis. Other frequent infectious agents such as parvovirus B19, cytomegalovirus, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, enterovirus, human immunodeficiency virus and *Helicobacter pylori* might be responsible for TCA (Algorithm 1).

ALGORITHM 1

Causes of stroke in children



TB, tuberculosis; HIV, human immunodeficiency virus; AV, arteriovenous.

Treatment

Acute treatment of children with stroke includes:

- Maintenance of respiratory and cardiovascular status
- Aggressive treatment of infection, seizures, and fever
- Maintenance of normoglycemia and normovolemia
- Adequate blood pressure should be maintained
- Intracranial hypertension may require mannitol and hyperventilation to prevent cerebral herniation.

Anticoagulation with heparin can be considered in some children with AIS, particularly those with arterial dissection or progressive neurologic deficits believed to be a result of recurrent emboli or thrombosis. Anticoagulation in cardiac embolism is controversial. Aspirin is the most commonly used antiplatelet agent. The recommended dosage is 3–5 mg/kg/day. Treatment of children with AIS using tissue plasminogen activator (t-PA) is limited due to delayed diagnosis and lack of safety and efficacy studies and is not currently recommended as standard treatment protocol. Moyamoya disease can be treated surgically with revascularization.

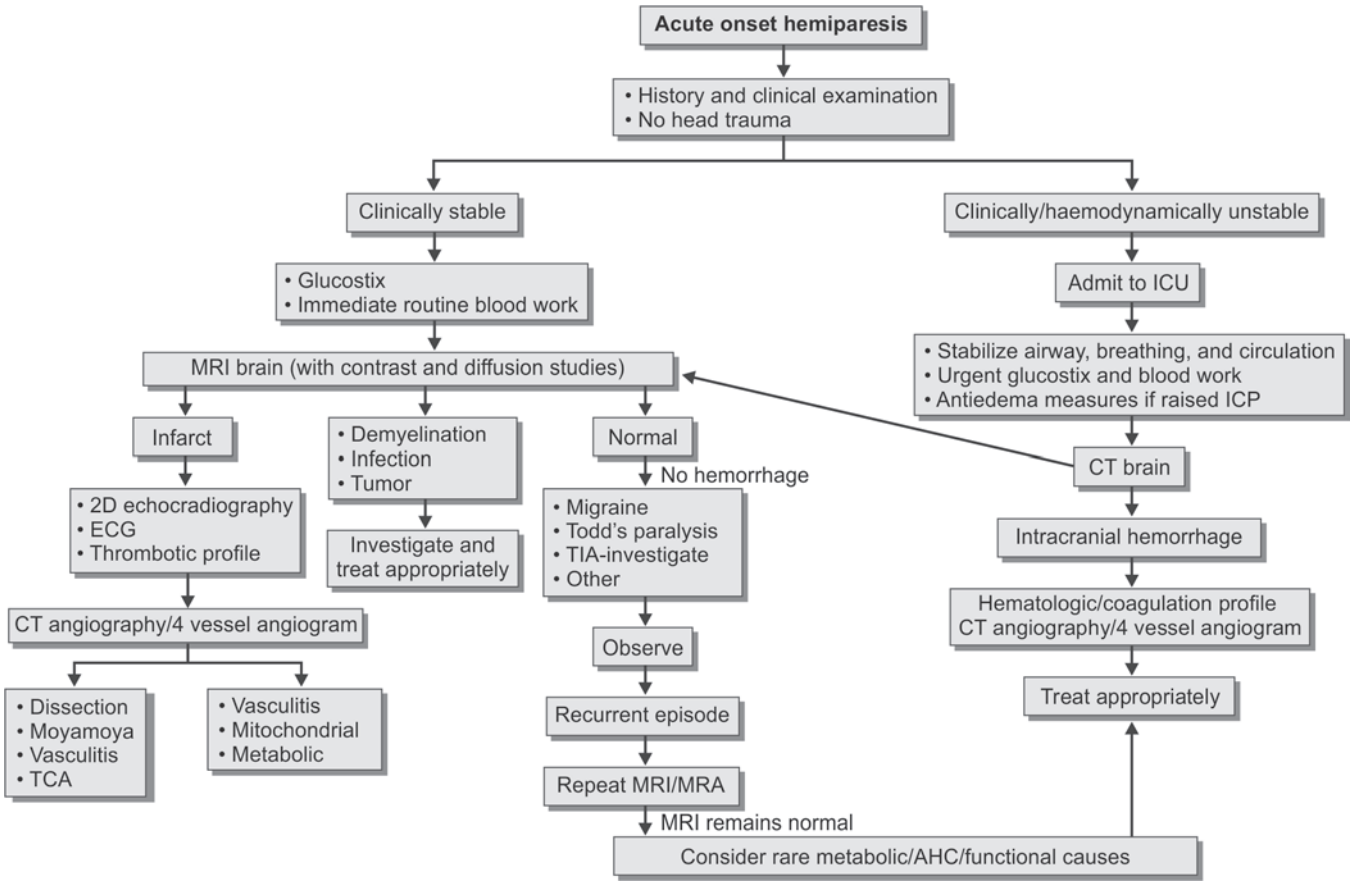
Demyelination in Children

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory and demyelinating disorder of the central nervous system, commonly preceded by an infection. It principally involves the white matter tracts of the cerebral hemispheres, brainstem, optic nerves, and spinal cord. Acute disseminated encephalomyelitis mainly affects children. Clinically, patients present with multifocal neurologic abnormalities that reflects the widespread involvement in central nervous system. Cerebrospinal fluid may be normal or may show a mild pleocytosis with or without elevated protein levels. Magnetic resonance image shows multiple demyelinating lesions. The diagnosis of ADEM requires both multifocal involvement and encephalopathy by consensus criteria. Acute disseminated encephalomyelitis typically has a monophasic course with a favorable prognosis.

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating syndrome of the central nervous system.

ALGORITHM 2

Management of acute hemiplegia in children



ICU, intensive care unit; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; CT, computed tomography; TIA, transient ischemic attack; AHC, alternating hemiplegia of childhood; ICP, intracranial pressure; TCA, transient cerebral arteriopathy.

Consensus criteria have been proposed by the International Paediatric Multiple Sclerosis Study Group. Acute attacks are managed with intravenous methylprednisolone (10–30 mg/kg/dose) for 3–5 days. This may be followed by a tapering course of oral prednisone (starting dose of 1–2 mg/kg/day). Immunomodulatory therapies are introduced early in the course of disease with the aim of reducing disability and cerebral atrophy. First line agents include interferon-β and glatiramer acetate. Disease modifying therapy should be offered to any patient with MS after a second attack of demyelination.

Recurrent Hemiplegia in Children

- Demyelination: relapsing ADEM, MS, and neuromyelitis optica
- Ischemic stroke: cardioembolic, vasculitis, and moyamoya vasculopathy
- Metabolic: mitochondrial
- Migraine and familial hemiplegic migraine
- Alternating hemiplegia of childhood
- Todd's paralysis.

KEY POINTS

- ☞ Detailed clinical history and examination are essential in establishing a diagnosis
- ☞ Focal clonic seizure in the newborn period is the most common clinical presentation of perinatal arterial ischemic stroke
- ☞ The most common cause of infantile hemiplegia is perinatal stroke; risk of recurrence is extremely low
- ☞ Pediatric stroke is not uncommon. The diagnosis is often delayed and early recognition is vital
- ☞ In previously healthy children, the most common cause of stroke is an arteriopathy. Imaging with computed tomography angiography or conventional 4-vessel angiography is essential
- ☞ Transient (Focal) cerebral arteriopathy is an important cause of stroke in children. Preceding history of varicella infection (up to 12 months prior) must be sought as it is a major cause of transient cerebral arteriopathy
- ☞ Acute episodes of demyelination must be treated with intravenous steroids (3–5 days). Differentiating acute disseminated encephalomyelitis from multiple sclerosis in children using current criteria is essential for long-term therapy and prognosis.

SUGGESTED READINGS

1. Alper G. Acute disseminated encephalomyelitis. J Child Neurol. 2012;27(11): 1408-25.
2. Amlie-Lefond C, Bernard TJ, Sebire G, Friedman NR, Heyer GL, Lerner NB, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. Circulation. 2009;119: 1417-23.
3. Armstrong-Wells J, Ferriero DM. Diagnosis and acute management of perinatal arterial ischemic stroke. Neurol Clin Pract. 2014;4(5):378-85.
4. Auvin S, Bellavoine V, Merdariu D, Delanoë C, Elmaleh-Bergés M, Gressens P, et al. Hemiconvulsion-hemiplegia-epilepsy syndrome: current understandings. Eur J Paediatr Neurol. 2012;16(5):413-21.
5. Chabrier S, Husson B, Dinomais M, Landrieu P, Nguyen The Tich S. New insights (and new interrogations) in perinatal arterial ischemic stroke. Thrombosis Research. 2011;127:13-22.
6. deVeber G, Andrew M, the Canadian Pediatric Ischemic Stroke Study Group. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345: 417-23.
7. deVeber G, The Canadian Pediatric Ischemic Stroke Study Group. Canadian paediatric ischemic stroke registry: analysis of children with arterial ischemic stroke. Ann Neurol. 2000;48:526.
8. deVeber G. Stroke and the child's brain: an overview of epidemiology, syndromes and risk factors. Current Opinion in Neurology. 2002;15:133-8.
9. Fox CK, Fullerton HJ. Recent advances in childhood arterial ischemic stroke. Curr Atheroscler Rep. 2010;12:217-24.
10. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007;119:495-501.
11. Hirano K, Aiba H, Yano M, Watanabe S, Okumura Y, Takahashi Y. Effect of tacrolimus in a case of autoimmune encephalitis. No To Hattatsu. 2007;39(6):436-9.
12. Johnston J, So TY. First-line disease-modifying therapies in paediatric multiple sclerosis: a comprehensive overview. Drugs. 2012;72(9):1195-211.
13. Kirkham F, Sebire G, Steinlin M, Sträter R. Arterial ischemic stroke in children. Thromb Haemost. 2004;92:697-706.
14. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013;19(10):1261-7.
15. Lynch JK, Nelson KB. Epidemiology of perinatal stroke. Curr Opin Pediatr. 2001;13(6):499-505.
16. Lynch JK. Epidemiology and classification of perinatal stroke. Semin Fetal Neonatal Med. 2009;14(5):245-9.
17. Pediatric Stroke Working Group. Stroke in childhood: clinical guidelines for diagnosis, management and rehabilitation. 2004.
18. Sebire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case-control study. Ann Neurol. 1999;45:679-80.
19. Sebire G. Transient cerebral arteriopathy in childhood. Lancet. 2006;368:8-10.
20. Tenney JR, Schapiro MB. Child neurology: hemiconvulsion-hemiplegia-epilepsy syndrome. Neurology. 2012;79(1):e1-4.
21. Wu YW, Lynch JK, Nelson KB. Perinatal arterial stroke: understanding mechanisms and outcomes. Semin Neurol. 2005;25(4):424-34.

CHAPTER 92

Approach to a Child with Spastic Paraplegia

Arun G Roy, Vinayan KP

INTRODUCTION

Paraplegia is defined as partial or complete weakness of both legs sparing the upper limbs. This can be due to upper motor neuron (UMN) or lower motor neuron (LMN) pathology. The UMN lesion should be above L1 segment involving the pyramidal tract (thoracic or cervical) of spinal cord or rarely in cerebral cortex involving the leg area (parasagittal) or subcortical regions affecting the fibers to legs to cause spastic paraplegia. Lower motor neuron lesion of paraplegia is secondary to intramedullary lesion affecting the lumbar and sacral spinal segments of legs (L1–5 and S1–3), multiple root involvement (L1–5 and S1–3), multiple peripheral nerve involvement, and rarely anterior horn cell disease. In this chapter we are describing paraplegia secondary to spinal lesions. The most common cause of cerebral paraplegia in children is cerebral palsy, which is not discussed in this chapter.

Clinical Pearl

- The first step of diagnosis is to localize whether it is primarily upper motor neuron or lower motor neuron lesion as it helps to narrow down the localization and avoid over investigating the patient. Hence, a detailed history and examination is vital.

CLINICAL FEATURES OF UPPER MOTOR AND LOWER MOTOR NEURON LESIONS

A child refusing to stand or walk or bear weight is the most common complaint in acute causes, while dragging of legs, tripping of toes while walking may favor spasticity of legs in chronic disorders. Parents may describe the limb as flaccid or stiff on handling. In an acute UMN lesion, muscle tone is flaccid with hyporeflexia before the appearance of spasticity. The pyramidal distribution of weakness has specific pattern in limbs which is seen when weakness is not severe. In lower limbs, weakness is most marked in flexors and internal rotators of hip, knee flexors, and toe and ankle dorsiflexors. The spasticity is most marked in extensors of lower limbs which is best elicited on flexion movements of leg. Deep tendon reflexes (DTR) are exaggerated with extensor plantars in UMN lesion.

Clinical Pearl

- By rule, upper motor neuron (UMN) lesions cause spastic paraplegia and lower motor neuron lesions result in flaccid paraplegia with exemption of acute spinal shock where lesion is UMN but paraplegia is flaccid

In LMN lesion, the weakness is in distribution of spinal segment, root, nerve, anterior horn cell, or muscle depending on site of involvement with hypotonia in weak muscles. Wasting of muscles is another feature noted. The DTRs are hyporeflexic with flexor plantars (Table 1).

Primary sensations, pain, and temperature are carried by lateral spinothalamic tract while vibration, joint-position sensations, and fine touch are by posterior column and crude touch by anterior spinothalamic tract. An older child can complain of burning pain, tingling, numbness of legs, or loss of sensations which can indicate a sensory involvement. The distribution of sensory level depends on site of lesion. In spinal cord, there can be differential involvement of tracts and sensation will be lost below the level of lesion. Since posterior column crosses at level of medulla, spinal cord lesion causes

TABLE 1: Clinical features to differentiate upper motor neuron and lower motor neuron

Features	Upper motor neuron	Lower motor neuron
Weakness	Pyramidal pattern	Depending on site of lesion
Atrophy	Late disuse atrophy	Prominent, early feature
Tone	Spasticity	Flaccid
DTR	Exaggerated	Sluggish/Absent
Plantar reflex	Extensor	Flexor

DTR, deep tendon seflexes.

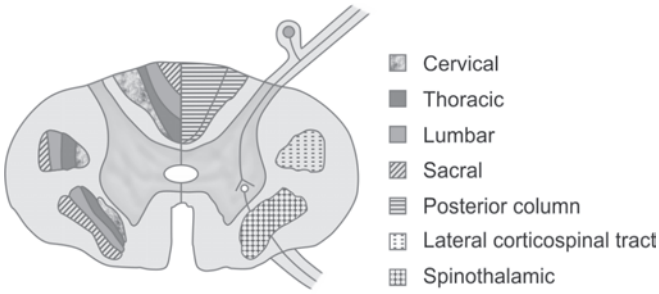


Fig. 1: Transection of spinal cord

TABLE 2: Major tracts of the spinal cord-location and functions

Tracts	Location in spinal segment	Function
Posterior column	Posterior cord	Vibration, joint position, Fine touch
Lateral spino-thalamic tract	Lateral cord	Pain and temperature
Anterior spino-thalamic ract	Anterior cord	Crude touch

loss of sensation ipsilaterally, while spinothalamic tract crossing occurs at spinal level, hence, the loss of sensation will be contralateral to site of lesion while transection of cord will cause sensation loss of all tracts bilaterally (Fig 1). In cortex and subcortical region, sensory loss is contralateral to site of lesion (Table 2).

Normal bladder and bowel control depends on segmental reflexes involving both autonomic and somatic motor neurons, as well as descending and ascending tracts of the spinal cord. Hence, bladder and bowel function may be impaired after an injury to any segmental level of the spinal cord. Bladder involvement can be retention of urine or incontinence of urine (urge or over flow). Urge incontinence is seen in UMN bladder, where lesion is above S2–S4 segments, while retention and overflow incontinence favors LMN bladder (S2–S4 segments or roots). A palpable bladder indicates retention of urine. Injuries to the spinal cord that result in paraplegia from a lesion above T6 may also impair autonomic control and result in episodes of severe hypertension or hypotension. This is due to excessive and uncontrolled sympathetic output from the spinal cord. Common triggers include bladder distension, constipation, rectal fissures, joint injury and urinary tract infection.

Clinical Pearls

- Cortical lesions: spastic paraparesis is usually accompanied by upper motor neuron (UMN) cranial nerve palsies, UMN bladder
- Brainstem lesions: spastic paraparesis is accompanied by cranial nerve palsies—UMN or lower motor neuron depending on the site of lesion (mid brain, pons, medulla), UMN bladder ± sensory tracts
- Spinal cord lesions: spastic paraparesis with sensory tract involvement, sensory level and UMN bladder, there is no cranial nerve involvement.

TYPES OF SPINAL CORD DISORDERS

Spinal cord disorders can be extramedullary or intramedullary (Fig. 2 and 3). The clinical features can vary in extramedullary and intramedullary spinal disease (Table 3). This is because of the lamination of tracts in the cord and type of compression of these tracts. Extramedullary means the lesion is outside the cord and can be intradural or extradural. Intradural lesions involve predominantly dura and root (examples: neurofibroma, meningioma), while extradural lesions are in vertebrae and surrounding structures (example: Pott's spine). Radicular pain, giibbus, vertebral pain, and spine tenderness are features of extramedullary disorders.

Spinal Cord Syndromes (Table 4)

These depend on the extent of lesion. (1) hemisection of the cord (Brown Sequard syndrome), (2) complete spinal cord syndrome, (3) central cord syndrome (Box 1), (4) Combined

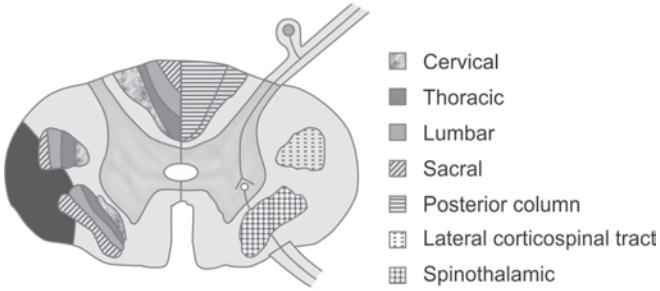


Fig. 2: Extramedullary compression

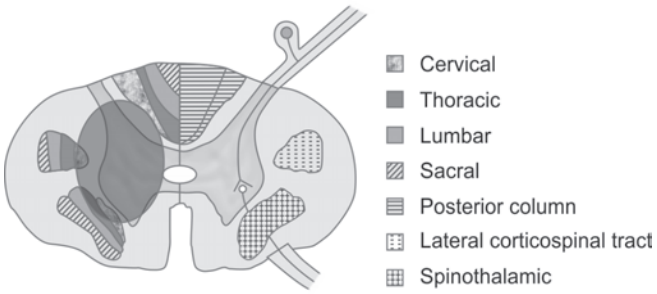


Fig. 3: Intramedullary compression

TABLE 3: Clinical features of extramedullary and intramedullary spinal cord disorders

Clinical features	Extramedullary	Intramedullary
Radicular pain	Common	Rare
Funicular or tract pain	Rare	Common
Sensory loss	Ascending type	Descending type
Band of hyperesthesia	At the site of lesion	Rare
Lower motor neuron signs	At the site of compression	Depends on extent of lesion
Upper motor neuron signs	Below the level of lesion and early	Late and less severe

TABLE 4: Clinical features of various spinal cord syndromes

Spinal cord syndrome	Motor deficit	Spinothalamic tract involvement	Posterior columns involvement
Brown Sequard syndrome (hemisection of cord)	Ipsilateral UMN weakness below the lesion	Contralateral loss of pain and temperature sensation	Ipsilateral loss of touch, position, and vibratory sensation
Complete transection of cord	Bilateral UMN weakness below lesion	Bilateral loss of pain and temperature	Bilateral loss of touch, position, and vibratory sensation
Anterior cord syndrome	Bilateral UMN weakness	Bilateral loss of pain and temperature	Sparing of touch, position, and vibration sensation
Posterior lateral column syndrome	UMN weakness	Sparing of pain and temperature sensation	Loss of touch, position, and vibratory sensation

UMN, upper motor neuron; LMN, lower motor neuron.

Box 1: Central cord syndrome

- This is not a classical cause for paraplegia. Lesion in cervical cord resulting in upper limb weakness more than leg weakness. Another classical feature is suspended sensory loss for pain and temperature due to involvement of decussating fibers carrying these sensations.

posterior and lateral column disease, (5) anterior spinal artery disease.

At the site of lesion, there can be LMN weakness, band of hyperesthesia, and loss of all sensations due to radicular involvement.

CAUSES OF SPASTIC PARAPLEGIA

Depending on presentation and duration it can be acute or chronic. Etiology varies depending on presentation, hence onset is important. Family history should be asked regarding similar illness, which helps in diagnosing inherited causes of spastic paraplegia like hereditary spastic paraplegia and leukodystrophy. Etiology can be broadly classified into compressive and noncompressive myelopathy (Table 5 and 6). In compressive myelopathy, there is definite sensory level, radicular symptoms at site of compression with asymmetric involvement of tracts while in non compressive myelopathies, radicular symptoms and definite sensory level are not seen and there is selective sparing of tracts and findings are usually symmetric.

TABLE 5: Causes of acute myelopathy

Compressive myelopathy	
Traumatic	Vertebral body fracture, or direct injury
Hemorrhage	Epidural or subdural hematoma
Infective	Epidural or subdural abscess, Pott's spine
Noncompressive myelopathy	
Vascular	Embolism, dural arteriovenous fistula, APLA syndrome
Inflammatory	Demyelinating disorders (MS, ADEM, NMO)
Infective	Viral, bacterial, tuberculosis

APLA, antiphospholipid antibody; MS, multiple sclerosis; ADEM, acute disseminated encephalomyelitis; NMO, neuromyelitis optica.

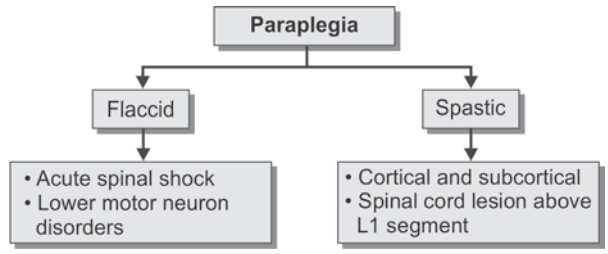
TABLE 6: Causes of chronic myelopathy

Compressive myelopathy	
Neoplasm	Neurofibroma, meningioma
Infective	Pott's spine
Congenital disorders	Dermoid cyst, arachnoid cyst
Noncompressive myelopathy	
Demyelinating disorders	MS, NMO
Infections	HIV, neurosyphilis, TB
Vascular	Ischemia due to AVM
Nutritional	Vitamin B12 deficiency
Toxic	Radiation and chemotherapeutic agents
Congenital disorders	Tethered cord syndrome

MS, multiple sclerosis; NMO, neuromyelitis optica; HIV, human immunodeficiency virus; AVM, arteriovenous malformation; TB, tuberculosis.

ALGORITHM 1

Approach to paraplegia



Pott's Spine

One of the leading causes of compressive myelopathy in children. This can have an acute or a chronic presentation and is due to cord compression secondary to vertebral destruction and wedging. Local spine tenderness and Gibbus are features of Pott's spine. Gentle tapping over vertebra with finger is best and safe way to elicit tenderness. Direct spinal cord involvement due to tuberculosis infection is seen but less compared to Pott's spine. Magnetic resonance imaging (MRI) is the investigation of choice as it shows involvement of disk, vertebra, and the extension of disease into soft tissues. Treatment is with

antitubercular drugs and surgical intervention is indicated in acute and severe paraparesis secondary to compression and unstable spine.

Acute Transverse Myelitis

Transverse myelitis is a segmental spinal cord injury caused by acute inflammation. The inflammation of TM is generally restricted to one or two segments, usually in the thoracic cord. The deficits are usually bilateral, producing weakness and multimodality sensory disturbance below the level of the lesion. Majority of cases are idiopathic but other causes are infections, autoimmune disorders, demyelinating disorders like multiple sclerosis (MS) and neuromyelitis optica. Cerebrospinal fluid can be normal or may show a moderate lymphocytosis (typically <100/mm^3) and an elevated protein level (usually 100–120 mg/dL). Glucose levels are normal. Magnetic resonance imaging is the investigation of choice and can show local enlargement of the spinal cord and increased signal intensity on T2 weighted images which can extend few segments of cord. In MS, the extent is two or less than two segments. Contrast enhancement may or may not be there.

Intramedullary Spinal Arteriovenous Malformations

Twenty percent of the lesions are diagnosed in children under 16 years of age. Myelopathy is produced by the mass effect of the lesion or by ischemia or hemorrhage into the cord.

Adrenomyeloneuropathy

A variant of adrenoleukodystrophy, an X-linked recessive disorder, is characterized by a slowly progressive spastic paraparesis and mild polyneuropathy. Sensory and sphincter disturbances are typically absent. There may be mild adrenal insufficiency.

Hereditary Spastic Paraplegia

Inherited disorders, in which the prominent feature is a progressive spastic paraparesis. Hereditary spastic paraplegia is classified according to the mode of inheritance, and the spastic paraplegia syndrome occurs alone or is accompanied by additional neurologic or systemic abnormalities ("pure" versus "complicated"). Hereditary spastic paraplegia is a clinical diagnosis, based in large part on the family history. Magnetic resonance imaging spine may be normal or show cord atrophy.

Spinal Cord Tumors

This is a rare diagnosis in the pediatric population. The types of tumors seen in children tend to be different than the adult types. Intramedullary tumors are most common type in children. In children with intramedullary tumors, astrocytomas represent around 60% of tumors, ependymomas 30%, developmental tumors 4%, and then a group of other less frequently identified types.

Deficiency of Vitamin B12

Deficiency of vitamin B12 leads to degeneration of the dorsal and lateral white matter of the spinal cord, producing a slowly progressive weakness, sensory ataxia, and paresthesias, and ultimately spasticity, paraplegia, and incontinence.

Tethered Cord Syndrome

Classically tethered cord syndrome has been defined as a spectrum of congenital anomalies resulting in an abnormally low position of the conus medullaris. Motor deficits are due to UMN and LMN features, since there is involvement of pyramidal tracts and lumbosacral roots. Children can present with delayed gait development, spasticity, hyperreflexia, hyporeflexia, and muscular atrophy. Sensory deficits, when present, are due to tract or root involvement and children can present with painless ulcers in leg. Neurogenic bladder dysfunction can be incontinence, urgency, or with recurrent urinary tract infections. Magnetic resonance imaging is the modality of choice in visualizing the level of the conus medullaris and for identifying terminal filum.

KEY POINTS

- Paraplegia is weakness of lower limb sparing upper limbs; it can be flaccid or spastic
- Involvement of sensory tracts and bladder with sparing of the cranial nerves and cognition localizes the lesion to spinal cord
- The causes can be compressive and noncompressive, extramedullary and intramedullary which can be differentiated by history and clinical findings
- History of systemic illness, family history, trauma, onset and progression of disease can give clue to etiology.

SUGGESTED READINGS

1. Blackmer J. Rehabilitation medicine: 1. autonomic dysreflexia. CMAJ. 2003; 169(9):931-5.
2. Brinar VV, Habek M, Brinar M, Malojcić B, Boban M. The differential diagnosis of acute transverse myelitis. Clin Neurol Neurosurg. 2006;108:278-83.
3. Bui CJ, Tubbs RS, Oakes WJ. Tethered cord syndrome in children: a review. Neurosurg Focus. 2007;23(2):E2.
4. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008;9(6)453-66.
5. Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 1988;318:1720-8.
6. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nat Clin Pract Neurol. 2007;3:140-51.
7. Pidcock FS, Krishnan C, Crawford TO, Salorio CF, Trovato M, Kerr DA. Acute transverse myelitis in childhood: center-based analysis of 47 cases. Neurology. 2007;68:1474-80.
8. Raghavan N, Barkovich AJ, Edwards M, Norman D. MR imaging in the tethered spinal cord syndrome. AJR Am J Roentgenol. 1989;152(4):843-52.
9. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. Lancet Neurol. 2008;7:1127-38.
10. Schick U, Marquardt G. Pediatric spinal tumors. Pediatr Neurosurg. 2001;35: 120-7.
11. Yasargil MG, Symon L, Teddy PG. Arteriovenous malformations of the spinal cord. In: Symon L (Ed). Advances and Technical Standards in Neurosurgery. Wien: Springer; 1984. p. 61.

CHAPTER 93

Acute Febrile Encephalopathy

Rashmi Kumar

INTRODUCTION

The term acute febrile encephalopathy (AFE) literally means acute onset of fever with encephalopathy (or altered consciousness). This presentation is a very important cause of hospital admissions in children in India. In 2006, World Health Organization coined the term acute encephalitis syndrome (AES) to include "a person of any age at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures)". Basically these two terms mean the same thing and for the sake of uniformity the term "acute encephalitis syndrome" is used.

CAUSES

Causes of AFE/AES are varied. Most commonly this presentation is caused by actual invasion of the brain by an infectious agent. The important causes of AFE are given in box 1.

Examination should be focused and should be looked for (Box 2).

Although the etiology is varied, common causes may predominate depending on the region. For example, Japanese encephalitis (JE) is very common in large parts of east and south India. Cerebral malaria is important in areas endemic for *Plasmodium falciparum*. Dengue encephalopathy, rickettsiae, leptospirosis, etc. are also reported from different parts of India. The age, seasonal and rural-urban distribution, and other epidemiologic clues may be helpful in suspecting specific infections. Box 3 gives some epidemiological and clinical clues to etiology.

In practice, the diagnosis of encephalitis is presumptive, based on clinical assessment and exclusion of other possibilities. Specific virological investigations are complex, time consuming, and expensive. Even in advanced centers, etiological diagnosis is possible in only a small proportion of clinically suspected cases (Algorithm 1).

WORKUP

A pragmatic investigative workup can be planned according to common etiology of the region (Box 4).

Clinical Pearl

- Acute febrile encephalopathy/acute encephalopathy syndrome can be divided into illnesses which are purely neurological as in japanese encephalitis, herpes simplex virus and rabies; or into neurological plus systemic type as in dengue, malaria, enteric and other non-viral agents like leptospirosis and rickettsioses.

Encephalopathies versus Meningoencephalitis

The term encephalopathy, besides meaning altered sensorium also refers to a diffuse disturbance of cerebral function due to a noninflammatory cause. Metabolic or toxic encephalopathy can produce a picture of AFE. Examples of such metabolic/toxic causes include Reye's syndrome, dyselectrolytemia, diabetic, uremic or hepatic coma, poisoning, and heat stroke. Clues must be sought to differentiate encephalopathy from encephalitis, but the distinction is not always possible on clinical grounds. General features of encephalopathies are shown in box 5.

TREATMENT (BOX 6)

Supportive treatment is the mainstay of therapy. A severe case should be managed in an intensive care unit. Measures include maintenance of airways, breathing, and circulation; hydration; electrolyte status; and control of pyrexia and convulsions. It is prudent to use appropriate parenteral antibiotics to cover for meningitis. Raised intracranial tension should be controlled with mannitol infusion (0.25–1.0 g/kg every 4–6 hours), hypertonic saline infusion, intravenous furosemide or intermittent positive pressure ventilation to keep arterial CO_2 tension between 25–30 mmHg. Proper nursing care must

Box 1: Causes of acute febrile encephalopathy/acute encephalopathy syndrome (AFE/AES)

Neuroinfections

- Viruses
  - Arbo or "arthropod borne" viruses: examples, Western equine, Eastern equine, Venezuelan equine, Japanese, St Louis, West Nile, Dengue, Murray valley encephalitis viruses. These viruses are naturally transmitted between insects and vertebrate animals that decide the geographical habitat and seasonal occurrence of the infection
  - Herpesviruses: Herpes simplex 1 and 2, Varicella zoster, Epstein-Barr, *Cytomegalovirus*, *Human Herpesvirus-6*, B virus
  - Enteroviruses: Polioviruses, Coxsackie, Echo, Enteroviruses 70 and 71
  - Orthomyxoviruses: Influenza viruses
  - Paramyxoviruses: Measles, Mumps, parainfluenza, Nipah virus
  - Adenoviruses
  - Rhabdoviruses: Rabies, chandipura
  - Parvoviruses
- Nonviral agents
  - Bacteria:
    - Pyogenic and tuberculous meningitis
    - *Mycoplasma pneumoniae*
    - *Listeria monocytogenes*
    - Spirochetes: syphilis, Leptospirosis, Lyme disease
    - Brucellosis
    - Legionella
    - *Salmonella typhi*
    - Cat scratch disease (Bartonellosis)
  - Rickettsia
  - Fungi: Cryptococcus, histoplasma, *Aspergillus*, mucormycosis, *Candida*, coccidioidomycosis
  - Protozoa: *Plasmodium*, *Trypanosoma*, *Naegleria*, *Acanthamoeba*, *Toxoplasma gondii*, schistosomiasis, *Echinococcus granulosus*
  - Metazoa: Trichinosis, *Echinococcus*, cysticercus, *Schistosoma*.

Noninfectious inflammation

- Acute disseminated encephalomyelitis
- Autoimmune encephalitis

Infectious encephalopathy

- Cerebral malaria
- Dengue encephalopathy
- Virus associated encephalopathy, e.g., influenza
- Enteric encephalopathy
- Sepsis
- Shigella encephalopathy

Structural coma with fever due to another cause

- Structural causes of coma like tumors, vascular events, etc. if associated with fever due to any other cause may present as AFE/AES

Functional coma with fever due to another cause

- Many causes of coma such as toxic and metabolic disorders, poisoning, inborn errors, etc. if associated with fever due to another cause may present as AFE/AES

Box 2: Clinical assessment

Epidemiology

- Age
- Location
- Rural/urban
- Season of year

History

- Fever
- Headache
- Vomiting
- Seizures
- Altered sensorium
- Altered behavior
- Personality changes
- Prodromal flu-like symptoms
- Rash, bleeding from any site
- Animal contact or dog bite
- Drug or toxin exposure
- Recent travel or immunization
- Trauma
- Recurrent episodes of encephalopathy
- Jaundice
- Premorbid medical condition such as diabetes or renal impairment

Examination

- Depth of coma
- Bleeding manifestations
- Features of shock
- Hepatosplenomegaly
- Rash
- Signs of raised intracranial tension
- Meningeal signs
- Focal neurological deficits
- Muscle tone
- Extrapyramidal features
- If in deep coma, signs of brainstem death

Box 3: Epidemiological and clinical clues

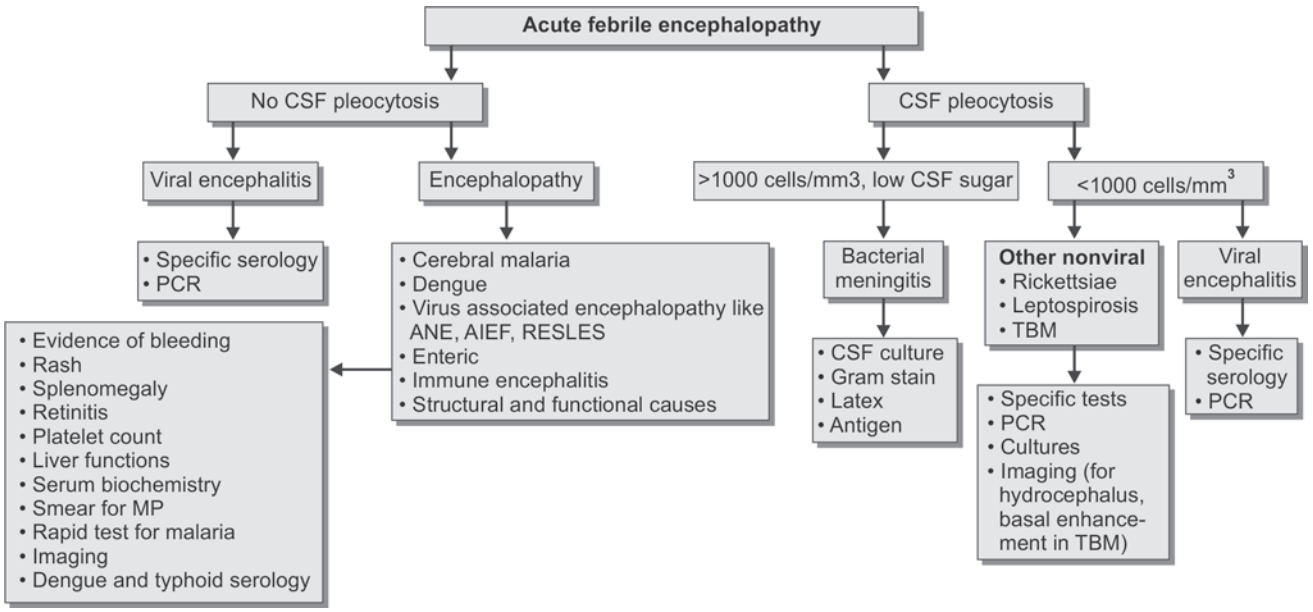
- Monsoon and postmonsoon season, rural, older child, endemic area—Japanese encephalitis
- *Plasmodium falciparum* endemic area—cerebral malaria
- Prominent extrapyramidal features—Japanese encephalitis
- Sudden onset high fever with chills and rigors, multisystem involvement with anemia, acidosis, blackwater fever, and bilateral upper motor neuron signs—cerebral malaria
- Rash, bleeding, hepatic involvement, nonpitting edema—dengue encephalopathy
- History of exposure to animal urine, and liver and kidney involvement—leptospirosis
- Prominent meningeal signs—bacterial meningitis
- Focal neurological deficits, personality change, fulminant course—herpes encephalitis
- History of animal bite, fatal course—rabies
- Rash, eschar

be given. The role of steroids in acute viral encephalitis is debatable. Theoretic arguments exist for and against their use. A study that evaluated high-dose dexamethasone in JE found no benefit of steroid therapy.

Specific therapy is recommended in encephalitis caused by herpes group of viruses. Acyclovir in a dose of 10 mg/kg administered as an intravenous infusion over 1 hour every

ALGORITHM 1

Approach to diagnosis in acute febrile encephalopathy



CSF, cerebrospinal fluid; PCR, polymerase chain reaction; MP, malarial parasite; TBM, tuberculous meningitis; ANE, acute necrotizing encephalopathy

Box 4: Suggested workup for acute febrile encephalopathy/ acute encephalopathy syndrome

Workup

- Blood counts including platelets and packed cell volume
- Rapid malaria test and smear for malarial parasite/dengue
- Cerebrospinal fluid (CSF) examination: this is an essential investigation but should be done only when considered safe. CSF should be examined for total and differential cell count, protein and sugar, bacterial culture and Gram stain; viral PCRs and serology
- Virology: samples for viral culture from respiratory secretions, throat swab, CSF, blood, urine, and stool taken as early as possible in the illness should be collected in appropriate transport media and sent to the reference laboratory
- Serological investigations in acute serum for specific immunoglobulin M (IgM) antibody level. JE is commonly diagnosed by the antibody capture ELISA for IgM antibody in acute phase serum and CSF
- Polymerase chain reaction is being developed to provide a rapid, and accurate diagnostic tool for a host of pathogens and is the mainstay of diagnosis. This is widely used for diagnosis of HSE with high sensitivity (>90%) and specificity (100%)
- Neuroimaging should be done whenever possible. As far as possible, magnetic resonance imaging should be insisted on. It can show nonspecific features of encephalitis or specific features suggestive of JE, Herpes simplex encephalitis or acute disseminated encephalomyelitis. Imaging may also occasionally reveal structural cause of coma (Figs 1 and 2)
- Blood chemistry: a routine blood chemistry may reveal a metabolic cause of encephalopathy. Blood glucose, urea, creatinine, electrolytes and liver function tests should be done.
- Blood culture: should be done in every case
- Other investigations may be done according to clinical clues

JE, Japanese encephalitis; HSE, herpes simplex encephalitis; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

Box 5: Features of encephalopathies (diffuse cerebral disturbance without inflammation)

Features of encephalopathies

- Absence of fever or meningeal signs
- Absence of focal neurologic signs or focal seizures
- No peripheral leukocytosis
- Normal cerebrospinal fluid
- Diffuse slowing on electroencephalography
- Normal imaging studies

Box 6: Treatment of AFE/AES

Initial rapid assessment and stabilization

- Establish and maintain airway: Intubate if GCS ≤8, impaired airway reflexes, abnormal respiratory pattern, signs of raised ICP, oxygen saturation <92% despite high flow oxygen, fluid refractory shock
- Ventilation, oxygenation
- Circulation:
  - Establish IV access, take samples (CBC, Blood sugar, KFT, LFT, electrolytes, blood gas, lactate, PS and RDT for malarial parasite, serology for viruses),
  - Fluid bolus if in circulatory failure (20 mL/kg NS), inotropes if required
- Identify signs of cerebral herniation or raised intracranial pressure
- Temperature: treat fever and hypothermia
- Treat ongoing Seizures: Benzodiazepine, followed by phenytoin loading

Empirical treatment must be started if CSF examination cannot be done or report will take time and patient is sick:

- Ceftriaxone
- Acyclovir (treat in all suspected sporadic viral encephalitis)
- Artesunate (stop if peripheral smear and rapid malaria test are negative)

Continued

Continued

Supportive care and treatment

- Maintain euglycemia, control fever, maintain hydration
- Treat raised intracranial pressure, mild head end elevation—15–30°
- Treat seizures. Give anticonvulsant if history of seizures or if GCS <8, or child has features of raised ICT
- Steroids—Pulse steroids (methylprednisolone or dexamethasone) must be given in children with suspected ADEM

Prevention/treatment of complications and rehabilitation

- Physiotherapy, posture change, prevent bed sores and exposure keratitis
- Complications—aspiration pneumonia, nosocomial infections, coagulation disturbances
- Nutrition—early feeding
- Psychological support to patient and family

GCS, glasgow coma scale; ICP, intracranial pressure; IV, intravenous; CBC, complete blood count; KFT, kidney function test; LFT, liver function test; PS, peripheral smear; CSF, cerebrospinal fluid; ADEM, acute disseminated encephalomyelitis; RDT, rapid diagnostic test; ICT, intracranial tension.

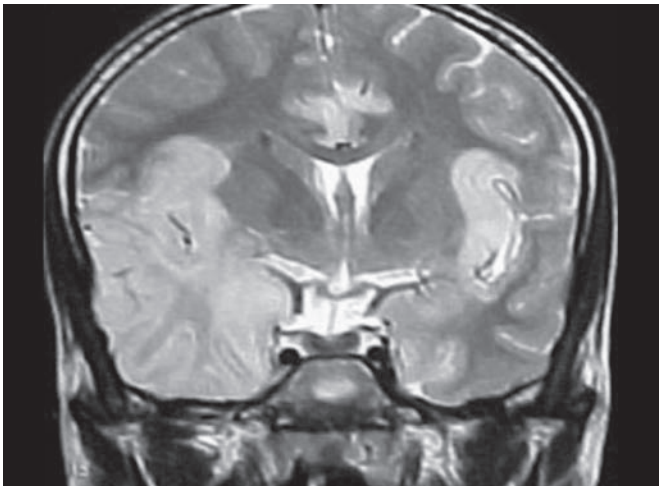


Fig. 1: Magnetic resonance imaging brain showing temporal lobe changes in herpes encephalitis

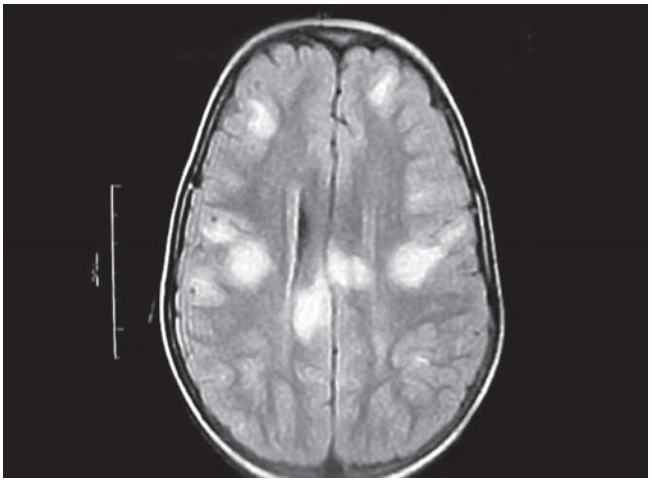


Fig. 2: Magnetic resonance imaging brain showing changes of acute disseminated encephalomyelitis

8 hours for 14 days (21 days in immunocompromised) is indicated in herpes simplex encephalitis. Success of antiviral therapy depends on early institution of therapy. Acyclovir is also recommended for varicella-zoster encephalitis. Oseltamivir can be considered for influenza encephalitis. Trials with α-interferon and nasogastric ribavirin in JE in children have revealed no benefit. Specific antimalarial therapy may also be indicated if suspicion of cerebral malaria exists.

Minocycline is a semisynthetic penicillin which has neuroprotective properties. It has excellent penetration in the cerebrospinal fluid. Besides its direct effects on non-viral pathogens, it has been shown to have antiviral, anti-apoptotic and anti-inflammatory actions with significant benefit in animal models of viral encephalitis. There may be a role of minocycline in AES even of undetermined etiology and human trials with this agent are underway.

Clinical Pearl

- Tuberculous meningitis (TMB) usually has a subacute onset. Here the prodromal stage with nonspecific symptoms will be longer than a week. If the child is comatose and computed tomography scan does not show hydrocephalus it is unlikely to be TBM; presence of basal exudates and/or granulomas is suggestive of TBM while subdural collections are suggestive of bacterial meningitis. Cerebral malaria is a multisystem illness with acute onset of high fever, chills and rigors, bilateral upper motor neurone signs, anemia, hemoglobinuria and normal cerebrospinal fluid.

KEY POINTS

- ☞ Acute febrile encephalopathy is a common cause of intensive care admissions in pediatrics
- ☞ Etiology is varied with both infectious and non infectious causes
- ☞ A good history along with targetted investigations like Magnetic resonance imaging brain, infection screen and Cerebrospinal fluid analysis help in reaching diagnosis in majority
- ☞ Pending investigations, empirical ceftriaxone, acyclovir and artesunate could be started in Indian scenario
- ☞ A subset of patients may be undiagnosed despite extensive investigations. Autoimmune or inflammatory causes should be suspected in these.

SUGGESTED READINGS

1. Bale JF. Viral encephalitis. Med Clin North America. 1993;77(1):25-41.
2. Cherry JD. Encephalitis. In: Behrman RE, Kleigman RM (Eds). Nelson Textbook of Pediatrics, 14th edition. Pennsylvania: WB Saunders Co; 1993. pp. 666-9.
3. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clinical Infect Dis. 2006;43:1565-77.
4. Kalra V. Acute febrile encephalopathy. In: Gupta V, Gupta D (Eds). Practical Paediatric Neurology, 2nd edition. Avichal Publishing Co. (Arya Publication). 2008. p. 112.
5. Kumar R. Viral encephalitis and encephalopathies in Medical Emergencies in Children Ed M Singh.
6. Sharma S, Mishra D, Aneja S, Kumar R, Jain A, Vashishth VM. Evaluation and Management of Suspected Acute Viral Encephalitis in Children in India. Indian Pediatrics. 2012;49:897-903.

CHAPTER 94

Approach to Pediatric Movement Disorders

PA M Kunju, Anoop K Verma

INTRODUCTION

Movement disorders are characterized by abnormal or excessive involuntary movements that may result in abnormalities in posture, tone, balance, or fine motor control. It is often used synonymously with basal ganglia or extrapyramidal disease but it does not adequately describe all the movement disorders.

Basically movement disorders are characterized as akinetic rigid syndrome and hyperkinetic or dyskinetic syndrome. In akinetic syndrome there, is slowness or paucity of movement, for example, parkinsonism, (this particular disorder is rare in pediatric age group). In dyskinetic syndrome, there is excessive movement, e.g., chorea, athetosis, ballismus, tremor, dystonia, tics, and other stereotypic behavior.

How They Differ in Children

Movement disorders in childhood are a heterogeneous group of diseases with presentations that vary according to etiopathogenesis and age of onset. Involuntary movements can represent the sole disease manifestation, or they may be one of many symptoms and signs of other systemic disorder. While sharing certain characteristics with the conditions that affect adults, they also have unique features that are determined by the metabolic, physiological, and environmental distinctiveness of the developing brain. So they show some particular characteristics:

- An increased occurrence of hyperkinetic movements, rather than bradykinesia or rigidity
- A higher frequency of transient motor phenomena in the first year of life
- A higher prevalence of paroxysmal movement disorders
- A major primary etiology for chronic motor dysfunction being residue of static encephalopathy
- A greater likelihood that symptoms are secondary to hereditary metabolic disorders
- An evolving pattern of movements associated with metabolic disorders.

Some of the common benign movement disorders that have to be ruled out in infancy are:

- Benign neonatal sleep myoclonus
- Benign myoclonus of infancy
- Jitteriness
- Shuddering attacks
- Paroxysmal tonic upgaze of infancy
- Spasmus nutans
- Benign paroxysmal torticollis
- Benign idiopathic dystonia of infancy.

CATEGORIZATION OF MOVEMENT DISORDER

If we categorize the movement disorder according to the level of involvement at the brain, it can be summarized as per the following algorithm 1.

The structures responsible for motor control are upper motor neuron (UMN), lower motor neuron (LMN), cerebellar circuitry, basal ganglia circuitry, motor activation cortex, and sensory cortex. Virtually the entire nervous system is engaged in motor control.

The basal ganglia consist of five large subcortical nuclei that are the caudate nucleus, putamen, globus pallidus, substantia nigra, and subthalamic nuclei. Bradykinesia is related to insult at substantia nigra, ballismus to subthalamic nucleus, dystonia to putamen, and chorea to caudate nucleus, but overlaps are also seen.

Clinical Pearls

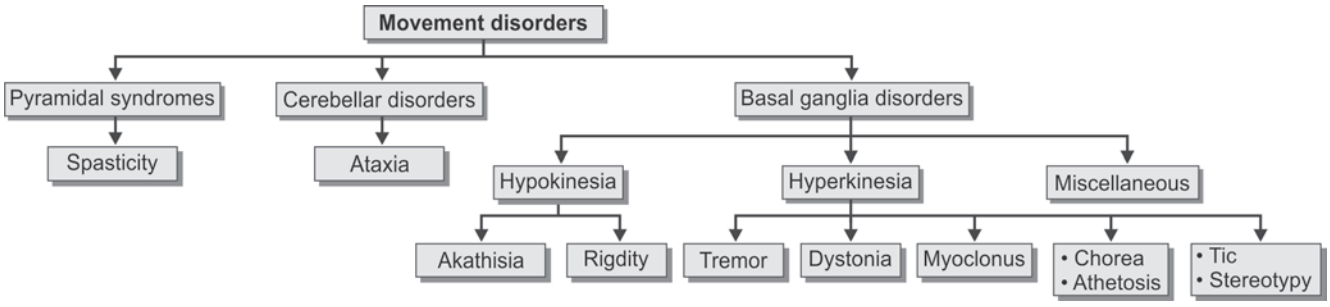
- Movement disorder and seizures can be differentiated by the preservation of consciousness
- Except ballism movement disorders stop during sleep
- Video recording using mobile phones will help in identifying the type of abnormal movements.

PHENOMENOLOGY OF MOVEMENT DISORDERS

Phenomenology refers to the clinically observable aspects of movement disorder, and one must be able to identify, the

ALGORITHM 1

Categorization of movement disorders



characteristic of each movement disorder as each of them has a different character (Table 1).

Clinical Pearl

- Movement disorders can be grouped according to the speed of movement
- Fastest being myoclonus, slightly slower will be ballism, then chorea, then athetosis, and slowest dystonia.

TABLE 1: Charecteristics of movement disorders

Movement disorder	Brief description
Chorea	Chorea is rapid jerky, large amplitude involuntary movements of proximal more than distal muscles
Athetosis	Slower writhing irregular movements predominantly in the hands and wrist
Dyskinesia	General term for abnormal movement; however, commonly denotes movements of mouth and face, usually drug induced (orofacial dyskinesia)
Dystonia	Cocontraction of agonist and antagonist, which lead to an intermittent or persistent maintenance of abnormal posture
Hemiballismus	Violent flinging movements, which are irregular affecting one side
Myoclonus	Sudden shock-like contraction of a muscle or a group of muscle leading to involuntary purposeless jerk of affected limb
Ataxia	Ataxia is inability to control movements and typically is caused by cerebellar dysfunction
Tics	Tics are rapid, complex, nonvoluntary, repetitive segmental movements. Simple tics last less than 6 months. Chronic tics last longer than 6 months
Tourette syndrome	There are motor tics and vocalizations lasting longer than 12 months, start between 2 and 10 years of age, and may fluctuate in severity over time
Tremor	Rhythmic oscillation about a certain point or position involving one or more body part
Stereotypies	Stereotypies are repetitive, patterned involuntary movements that have no apparent function

GENERAL APPROACH TO MOVEMENT DISORDERS

Evaluation of movement disorders, like all neurologic symptoms, begins with a comprehensive history:

- Patient's gestation, detailed birth history, early development, previous illnesses, drug history, exposure to potential toxins, and social and family history, are often essential for proper classification
- The key questions to be asked are as follows:
  - What is the distribution? (e.g., orofacial—chorea)
  - Is it unilateral or generalized? (e.g., Hemidystonia associated with structural lesion)
  - What is the speed of movement—fast (excessive movement, hyperkinetic) or slow (paucity of movement, hypokinetic)?
  - Is it rhythmic or is it jerky? (e.g., rhythmic—tremor; palatal myoclonus)
  - Is it present at rest? With action? Is there any relation to certain postures or positions? (e.g., rest tremor-parkinsonism; action tremor—familial essential tremor)
  - Is there any task specificity? (e.g., kinesigenic choreoathetosis)
  - Is patient able to suppress it? (e.g., tics)
  - Is it stereotyped? (e.g., Tics/Stereotypy)
  - Is movement disorder continuous or intermittent or occurring in discrete episodes? (e.g., paroxysmal dyskinesia)
  - Is there an association with an urge? (e.g., tics)
  - Is it related to sleep? (e.g., hemiballism/restless leg syndrome; seizure)
  - Is it associated with functional motor impairment?
  - Are there any aggravating/alleviating factors?

Clinical Pearl

- Video of abnormal movement is important which can supplement witnessing the real-time abnormal movement of the patient.

A critical feature is determining whether the presenting signs/symptoms are an isolated disorder, associated with other neurologic findings, part of a static condition, or

appearing in conjunction with a loss of other previously acquired skills.

A comprehensive general examination is further required for properly defining the movement and identifying clues indicating a systemic problem. The category of movement assists in localizing the pathologic process, whereas the onset, age and degree of abnormal motor activity and associated neurologic findings help organize the investigation. Correct classification of the type of movement disorder forms the basis for the subsequent diagnostic process.

The features of movement disorders are discussed in table 2.

Thus, compiling the important pieces of information from history and examination, the strategy is to reach the diagnosis from recognizing the patterns based on phenomenology and then focus on the causes as possible etiologies for acute, subacute onset and acquired causes.

TABLE 2: Features of movement disorders

Features	Category	Examples
Speed	• Hyperkinetic • Hypokinetic	• Tremor, chorea, myoclonus, tics, restless legs syndrome, dystonia • Apraxia, Parkinson bradykinesia
Region	• Whole body • Hemibody • Segmental • Multifocal • Focal • Proximal • Distal • Oral	• Generalized dystonia • Hemidystonia, hemichorea • Segmental myoclonus • Polyminimyoclonus • Writer's cramp • Rubral tremor • Athetosis • Tardive dyskinesia
Character	**Rhythm**	
	• Rhythmic	• Tremor, dystonic tremor, periodic movements in sleep
	• Arrhythmic	• Akathitic movements, athetosis, ballism, chorea, dystonia, hemifacial spasm, hyperekplexia, arrhythmic myoclonus, stereotypy, tics
	Frequency	
	• Fast • Slow	• Chorea, tics, minipolymyoclonus • Ballism
	Amplitude	
	• Large • Fine	• Ballism • Tremor, minipolymyoclonus
	At Rest	
	• At rest and continues with action • With action	• Ballism, chorea, dystonia, postural tremor • Action tremor, ataxia
	Force	
	• Powerful	• Stiff-man syndrome
Trigger	• Action • Position	• Writer's cramp • Orthostatic tremor
Intentionality	• Voluntary • Involuntary	• Tics • Tardive dyskinesia
Relieving factor	• Sleep	• Dystonia, tremor
Psychiatric		Huntington disease

CAUSES OF MOVEMENT DISORDERS

The causes of movement disorders can be summarized as in algorithm 2.

Clinical Pearl

- Hemidystonia may indicate a structural abnormality and generalized dystonia may indicate a possible idiopathic disorder.

Drug-induced Movement Disorders

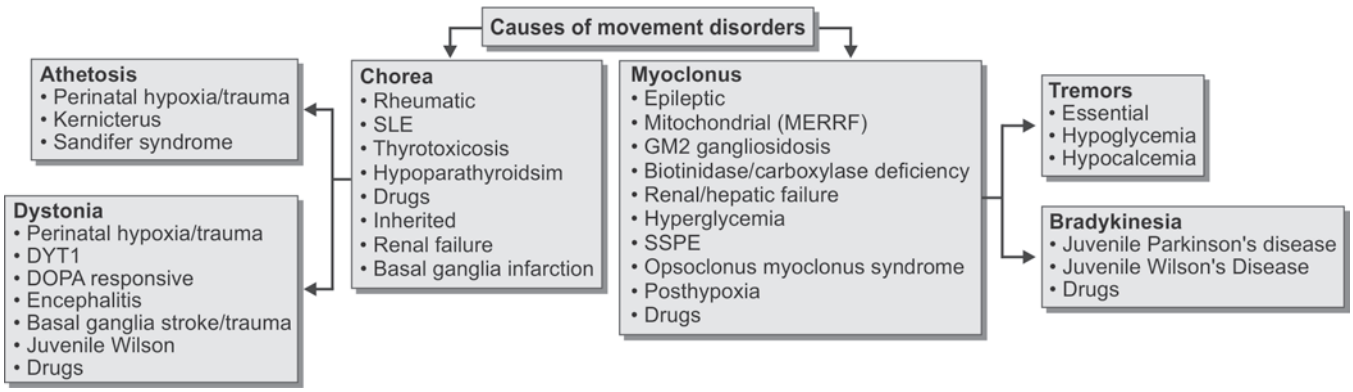
There are various movement disorders which are caused due to adverse effects of medications or drugs. They are summarized in table 3.

Before discussing the individual movement disorders, it would be prudent to take a look at the inherited disorders causing movement disorders (Table 4).

Clinical Pearl

- Three generations pedigree, including cousins and siblings of parents and grandparents can give a clue to the hereditary causes of movement disorders.

ALGORITHM 2



SLE, systemic lupus erythematosus; MERRF, myoclonic epilepsy with ragged red fibers; SSPE, subacute sclerosing panencephalitis; DOPA, dopamine.

TABLE 3: Drug-induced movement disorders

Type of movement disorder	Drugs	Presence in sleep
Bradykinesia	Typical neuroleptics and atypical antipsychotic	No
Chorea/athetosis	Phenytoin, carbamazepin, valproic acid, dopamine receptor blocking agent, tricyclic antidepressant, theophylline, oral contraceptives, steroids, and stimulants	No
Dystonia	Typical neuroleptics, antipsychotics, metoclopramide	No
Myoclonus	Epileptic myoclonus can be aggravated by some antiepileptics	Yes
Tremor	Tricyclic antidepressant, valproic acid, phenytoin, carbamazepine, theophylline	No
Tics	Lamotrigine, stimulants, levodopa, neuroleptics	Yes

TABLE 4: Inherited condition causing movement disorders

Etiology	Age at onset	Clinical signs	EEG and Imaging	Lab finding and genetic testing
Glutaric aciduria Type 1	5–10 months	Acute encephalopathy followed by dystonia, motor impairment, macrocephaly	CT/MRI: Frontotemporal atrophy	Organic acid in urine, enzyme assay
Glucose transporter 1 deficiency syndrome	Infancy	Seizures, developmental delay, complex movement disorder	EEG improves postprandially	Low-glucose concentration in CSF
Lesch-Nyhan syndrome	3–13 months	Self-mutilation, facial grimacing, involuntary writhing repetitive movement of arm	Development of kidney stone	Hyperuricemia
Leigh's disease	Birth to first year	Diffuse encephalopathy, dysphagia, dystonia, myoclonus, hypotonia central respiratory insufficiency	MRI: PVL, hyperintense T2 signal in the basal ganglia and thalami	High serum/CSF lactate
PKAN	1st decade	Delayed motor and language, later choreoathetosis, dystonia, dysarthria, dysphasia, spasticity retinopathy	MRI: Eye of the tiger sign	Noncontributing
Wilson's disease	1st and 2nd decade	Dysarthria, gait disturbances, risus sardonicus, dystonia, rigidity, tremor, dysphagia	MRI: High signal in basal ganglia, dentate nuclei and cerebellum on T2	KF ring, low-serum ceruloplasmin
Huntingtons disease	2nd decade	Neurological and psychiatric symptoms, chorea, rigidity, hypokinesia	MRI: Nonspecific generalized or striatal atrophy	Noncontributing
Early onset torsion dystonia	Between 3 and 26 years	Ashkenazi Jews, dystonia affecting first one arm or leg progressing to generalized or multifocal	Noncontributing	Noncontributing

PKAN, pantothenate kinase-associated neurodegeneration; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalography; KF ring, Kayser–Fleischer ring; PVL, periventricular leukomalacia.

The category of movement assists in localizing the pathologic process, whereas the onset, age and degree of abnormal motor activity and associated neurologic findings help to organize the investigation. Correct classification of the type of movement disorder forms the basis for the subsequent diagnostic process.

No specific biological marker is available:

- Many diagnostic tests are available but these are often expensive, time-consuming or invasive
- The diagnostic value of these tests is often limited, especially in early stages of the disease.

The investigational workup can be greatly simplified once the type of movement disorder has been defined properly.

INVESTIGATIONS

The investigations in movement disorders can be divided under different headings of neuroimaging, hematological, immunological, or other investigations as applicable. Magnetic resonance imaging (MRI) brain is the neuroimaging modality of choice in pediatric movement disorders and the following algorithm 3 proves a good guide to diagnosis.

Clinical Pearl

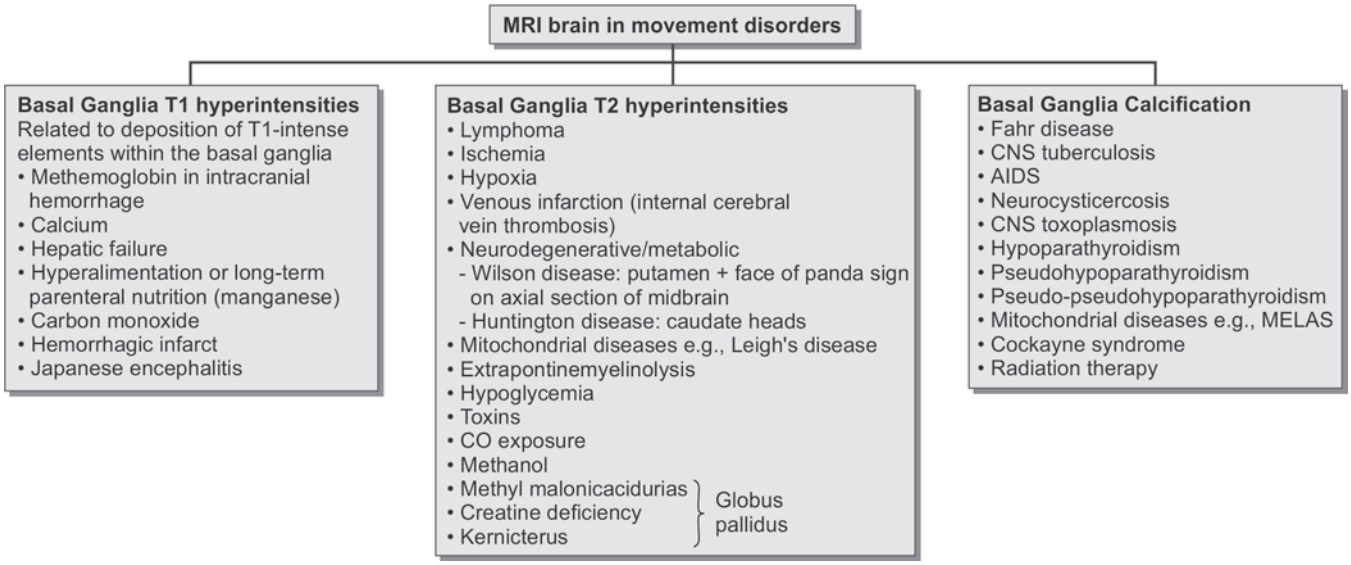
- Magnetic resonance imaging will help in identifying various disorders. Basal ganglia calcification can be due to Fahr syndrome or pseudohypoparathyroidism and basal ganglia hyperintensity can be commonly due to Wilson disease (caudate) and kernicterus (globus pallidus)

TREATMENT

Although the treatment of movement disorders is varied and multidisciplinary according to the type, the common

ALGORITHM 3

Brain MRI changes in movement disorders



MRI, magnetic resonance imaging; CNS, central nervous system; AIDS, acquired immunodeficiency syndrome; CO, carbon monoxide; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

TABLE 5: Drugs used in movement disorders

Drugs	Doses	Precautions	Indications in movement disorders
Pimozide	1–2 mg/day (2–6 mg, if required)	Prolong QT interval Cardiac arrhythmias	Gilles de tourette syndrome
Haloperidol	20–50 μg/kg initially; maximum to 10 mg/day	Liver, kidney disease epilepsy, thyrotoxicosis	Choreiform movement, rheumatic chorea, hemiballismus Gilles de tourette syndrome
Tetrabenazine	12.5 mg BID; increment of 12.5 mg every 3–4 day to a maximum of 3 mg/kg/day	Pregnancy, lactation depression, patient on levodopa, reserpine	Chorea, hemiballismus, myoclonus, buccolingual dyskinesia, in certain dystonia
Trihexyphenidyl	1 mg first day, 2 mg second day, then increase to 2 mg every 3–5 day; maintenance usually 6–16 mg/day	Glaucoma, sick sinus syndrome, cardiac failure, tachycardia	Dystonia, myoclonus, drug induced movement disorders, torticollis
Levodopa-carbidopa	Up to 5 mg/kg/day	–	Dopa responsive dystonia, dystonia and Parkinson state
Carbamazepine	<6 years: 5 mg/kg/24 hours orally; may increase every 5–7 day by 5 mg/kg/day 6–12 years: initially 10 mg/kg/day; increase by 5/mg/day at weekly intervals Usual dose—800–1200 mg/24 h	Porphyria, hepatic failure, MAO inhibitors	Chorea, Athetosis, Ballismus, Paroxysmal kinesigenic dyskinesia
Sodium valproate	Below 20 kg: 20 mg/kg/day Above 20 kg: 400 mg/day	Liver disease, SLE, porphyria	Chorea
Clonazepam	Initial 0.01–0.03 mg/kg/24 h in 2–3 divided doses; increase 0.25–0.5 mg/24 h every 3–5 days; maximum dose 0.3 mg/kg/24 h	Hypersensitivity to benzodiazepine	Dystonia, torticollis, myoclonus, startle syndrome

SLE, systemic lupus erythematosus; MAO, monoamine oxidase; BID twice a day.

drugs used to treat and their dosages are given in table 5. The drugs are thereafter mentioned briefly when describing the individual movement disorders.

INDIVIDUAL MOVEMENT DISORDERS

Following is a short discussion of movement disorders.

Dystonia

Though dystonia is a common symptom in neurology, it is being recognized less frequently by pediatricians.

Definition

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal (often repetitive) movements, postures, or both. The factor which distinguishes myoclonus, chorea, athetosis, and dystonia would be the variable speed of movement; fastest being myoclonus, 50–100 ms and slowest one being dystonia, which may last at least a second.

Dystonia evolves in a focal manner and during voluntary activity—"action dystonia".

Pathophysiology

Dystonia is a circuit disorder, historically thought to arise from basal ganglia but now recognized to result from injury or malfunction in any of the several nodes within the motor cortex.

Classification

The dystonias are classified according to their distribution, age of onset, type of onset, and etiology.

Distribution

- Focal
  - When dystonia is confined to anyone single region:
    - Ocular muscles: Blepharospasm
    - Tongue: Lingual dystonia
    - Vocal cord: Dystonic dysphonia
    - Mouth: Oromandibular dystonia
    - Neck: Torticollis
    - Hand: Writer's cramp (Fig. 1)
- Segmental
  - When focal dystonia spreads to contiguous area:
    - Cranial: Face and neck
    - Axial: Neck and trunk
    - Brachial: Arm and trunk
    - Crural: One leg and trunk; both legs with or without trunk
- Generalized—Crural
  - With any other segmental involvement.
  - Focal or segmental dystonia may progress and become generalized if:
    - Childhood or adolescent onset
    - Beginning in the lower limbs
- Hemidystonia: when one side of the body is involved.

Type of Onset

It is broadly divided in to four groups:

1 Acute dystonia
2 Tardive dystonia
3 Paroxysmal dystonia
4 Chronic nonprogressive/progressive dystonia.

Acute dystonia

Acute dystonia arise from neuroleptic drugs, exposure to toxins, infections, and certain familial disorders. Acute reactions can appear soon after starting treatment with phenothiazine, or even promethazine. Manifestations include bizarre postures of face (sustained grimacing), eyes (oculogyric crisis), jaw (trismus, mandibular dystonia), tongue (lingual dystonia), neck (torticollis), trunk (scoliosis, lordosis, kyphosis, and opisthotonos) and limbs (torsion spasm). These may be confused with seizure, tetany or encephalitis if a proper history of drug ingestion is not obtained.

The acute dystonic reactions may be the result of excess dopaminergic activity. Response to treatment of acute dystonia is often dramatic. Anticholinergic drugs like diphenhydramine or promethazine will reverse the acute dystonia within minutes. We have seen transient dyskinesia in asthmatic patients receiving theophylline. Interaction of theophylline and hypoxemia with other factors may induce this.

Fig. 1: Writers cramps—before and after Botox injection

Clinical Pearl

Acute dystonias can be remembered by VITS:

- V—Vascular (infarct; hemorrhage, etc.)
- I—Infection and post-infectious, e.g., Japanese encephalitis; autoimmune encephalitis
- T—Toxin (drugs like phenothiazine toxicity)
- S—Space occupying lesion (subacute)

Tardive dystonia

It is a separate entity from acute dystonic reactions in that it is persistent, does not show response to intravenous diphenhydramine or anticholinergics. Another striking feature is the distribution of dystonic movement. Generalized dystonia is more in younger individuals whereas in older subjects it has a more restricted distribution.

Paroxysmal dystonia

A group of interesting disorders which may be confused with seizures:

- Familial paroxysmal dystonic choreoathetosis: This rare bizarre paroxysmal movements occurring in an autosomal dominant manner. Each attack is characterized by (a) painful spasm of affected musculature, (b) choreoathetosis and (c) return to normality
- Paroxysmal kinesigenic dystonia: Sudden movement or startle and stress will precipitate an attack. These patients can avert an attack by avoiding abrupt movement and sensory stimuli
- Exercise induced paroxysmal dystonia: A paroxysmal dystonic choreoathetosis, which is seen after continued exercise or by sensory stimuli but not after a sudden movement
- Paroxysmal hypnogenic dystonia: Certain varieties of dystonia may be brought on by sleep. In addition to the idiopathic variety, we have seen paroxysmal dystonias due to intracranial tumor, hyperthyroidism and transient ischemic attacks.

Recently following genetic associations are found with paroxysmal movement disorders. Paroxysmal kinesigenic dyskinesia due to *PRRT2* mutations (DYT10); paroxysmal nonkinesigenic dyskinesias (DYT8) with mutations in the *PNKD* (also known as *MR-1*) gene; and exertion-induced dyskinesia (DYT18) with *SLC2A1* mutations.

Clinical Pearl

- Paroxysmal movement disorders (PD) may resemble seizures but will respond to antiepileptic drugs like phenytoin, carbamazepine (kinesgenic PD), or clonazepam (nonkinesegenic PD)

Treatment: Paroxysmal *kinesigenic choreoathetosis* responds to phenytoin. Other varieties may respond to clonazepam, L-tryptophan and carbamazepine.

Chronic nonprogressive/progressive dystonias

Etiology: Dystonias are divided into two types on the basis of etiology as follows:

1. Primary dystonia
2. Secondary dystonia.

Primary dystonia

In the past 20 years, monogenic defects have been found to underlie many forms of dystonia. Monogenic forms of isolated dystonia are referred to as DYTs.

- Idiopathic torsion dystonia (ITD)/Dystonia musculorum deformans (DMD): Autosomal dominant dystonia gene is found to be located on chromosome 9q34. The usual age of onset is 5–15 years with dystonia of legs and within 5–10 years disease reach to maximum level of disability. At that time they are twisted axially with contorted oromandibular, neck, trunk, and limb musculature.
- Dopa-responsive dystonia: This group of patients with dystonia respond dramatically to a very low dosage of levodopa. Features include onset of dystonia before the age of 16, onset in the legs or with gait, and often having features of parkinsonism. Inheritance is autosomal dominant. Since the demonstration of dopa-sensitive dystonic states, levodopa has been tried in some of the cases of the congenital cerebral palsy where choreoathetotic rigidity is seen.
- Diurnal dystonia (Segawa syndrome): Relatively free of dystonic movements and postures in the morning and be afflicted severely in the late afternoon. Segawa had described this type of dystonia and we have seen many with similar involvement and who showed dramatic response to levodopa. . The disease is caused by a GTP cyclohydrolase 1 (GCH) deficiency. Genetic mutations in the tetrahydrobiopterin synthetic pathway, specifically the GCH1 gene (DYT 5) in the autosomal-dominant variant, and the TH gene in the autosomal recessive form, are responsible for the condition.

Clinical Pearls

- Common cause of nonprogressive dystonia is dyskinetic cerebral palsy due to kernicterus or birth asphyxia (Fig. 2)
- However, in such cases a dose of levodopamine must be tried to rule-out diurnal dystonia (Segawa syndrome), which is an eminently treatable condition.

Secondary dystonias

Secondary dystonia can be due to congenital, hereditary, metabolic, vascular, infection, degeneration, demyelination, tumor, drugs, toxins, etc.

Useful clinical pointers to suggest a secondary dystonia:

- History to suggest involvement of other organ systems, e.g., liver (Wilson's disease), multiple system (systemic lupus erythematosus)
- Coexistent neurological signs indicating involvement of higher mental, retinal, pyramidal, or LMN function
- History of exposure to antipsychotic drugs, toxins, injury, or cerebrovascular disorders.

Treatment

Treatable dystonic conditions like Wilson's disease, tardive dystonias, etc. have to be considered first.

Fig. 2: A child with dystonic choreoathetosis

- Drugs: Trihexyphenidyl, dopamine agonists, baclofen, clonazepam, carbamazepine and clonidine)
- Local administration of botulinum toxin for focal dystonias (Fig. 2)
- Surgical methods
- Psychological methods.

Clinical Pearl

- Dopa-responsive dystonia (DYT5, Segawa disease) is the most important cause of primary dystonia with childhood onset, responds dramatically to low doses of levodopa

Chorea

Involuntary, purposeless/quasi purposive, jerky, dance-like movements.

Athetosis: Now described as a slow, writhing form of chorea.

Ballism: Forceful, flinging form of chorea; proximal more than distal, typically unilateral, and often coexistent with chorea.

Pathophysiology of Chorea

Injury to basal ganglia, especially the striatal indirect pathway, is a common anatomic precipitant for many forms. The neurophysiology underlying chorea is still poorly understood.

Causes of Chorea

- Structural:
  - Ischemic stroke—acute/subacute—unilateral chorea; localizing neurologic signs
  - Tumor—subacute—symptoms of raised intracranial pressure
  - Moyamoya disease—Subacute, multifocal seizures.
- Metabolic/Endocrine:
  - Hypernatremia/hyponatremia; hypomagnesemia—altered biochemical status
  - Hyperparathryoidism/hypoparathryoidism, pseudohypoparathyroidism—Basal ganglia calcification.
- Autoimmune:
  - Autoimmune encephalitis—underlying ovarian teratoma/positive N-methyl-D-aspartate receptor antibody
  - Systemic lupus erythematosus—signs of systemic erythematosus
  - Sydenham's chorea—preceding streptoccal infection
  - Antiphospholipid antibody syndrome—focal signs stroke; hypercoagulable state.
- Genetic
  - Chorea-acanthocytosis syndrome—obsessive compulsive behaviors, orolingual dystonia, peripheral neuropathy, seizures
  - Wilson's disease—tremor, dystonia typical, psychiatric features
  - Huntington's disease—in children more of rigid dystonia
  - Ataxia-telangiectasia—ataxia, oculomotor apraxia, increased sinopulmonary infection
  - Spinocerebellar ataxia 1, 2, 3, 17—ataxia, peripheral neuropathy, abnormal movements
  - Lesch–Nyhan syndrome—self mutilation
  - Leigh's syndrome—dystonia, spasticity, myoclonus, lactic acidosis
  - Pantothenate Kinase-Associated Neurodegeneration—progressive dystonia, dysarthria, rigidity, ballism, choreoathetosis, spasticity, dementia and pigmentary retinal degeneration; MRI shows the characteristic "eye of the tiger" sign within globus pallidus interna (Figs 3 and 4)
  - Fahr's disease—second decade of life, microcephaly, hypertonia, and choreoathetosis
  - Basal ganglia and cerebellar nuclei calcification and also punctate calcifications in thalamus (Fig. 5).

Tremor

Definition

Regular rhythmic repetitive to and fro oscillatory movements.

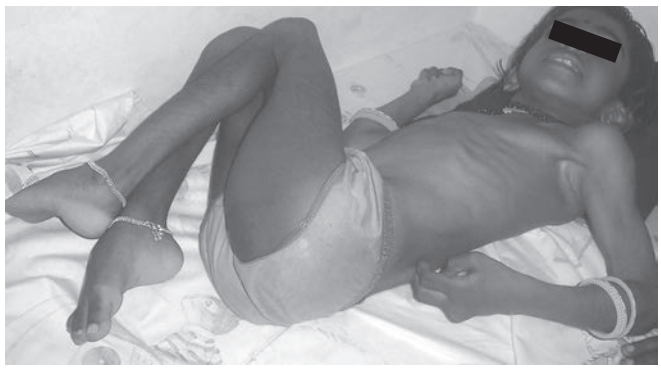


Fig. 3: Pantothenate kinase-associated neurodegeneration—severe dystonia

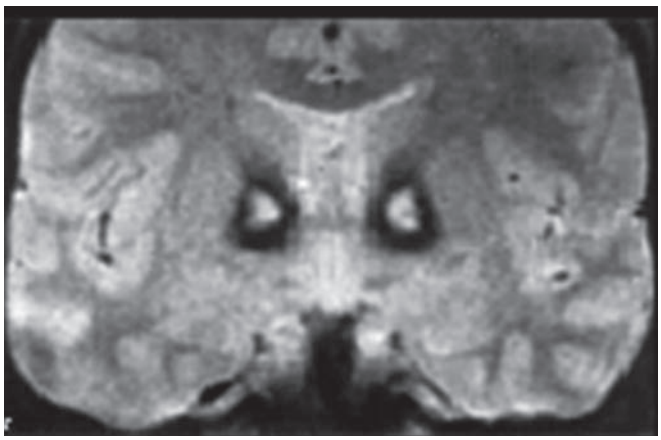


Fig. 4: Eye of the tiger sign in coronal magnetic resonance imaging

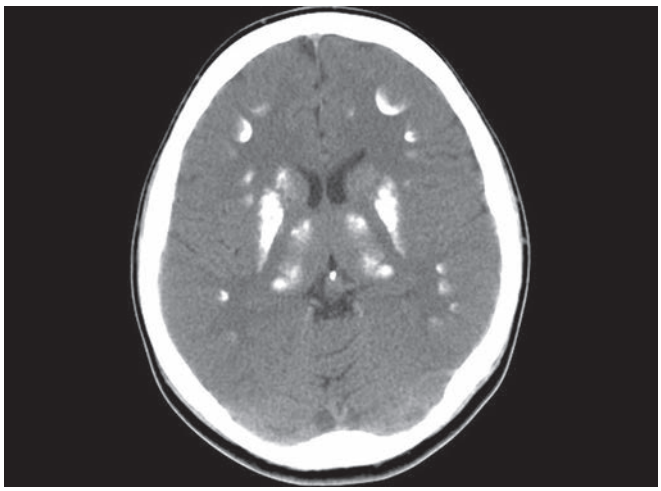


Fig. 5: Computer tomography scan-basal ganglia calcification—Pseudohypoparathyroidism

Pathophysiology

Can arise from cortex, basal ganglia, brainstem, cerebellum, or periphery—each location associated with distinct tremor characteristics.

Types

- Resting tremor—decreases or resolves with movement. Worsens with agitation or inattention
- Action tremor—elicited by initiating movement or increasing force generated. Four subtypes can be postural tremor, intention tremor kinetic, or isometric tremor
- Physiologic tremor—seen with particular situational challenges, e.g., stress, caffeine, fatigue
- Rubral tremor—coarse, jerky, irregular, large amplitude and low frequency (Holmes tremor or midbrain tumor)
- Psychogenic tremor—variability in tremor frequency, amplitude, distribution, and direction. Usually acute in onset but non progressive
- Drug-induced tremors—seen with medications (bronchodilators, thyroid hormone, stimulants, steroids, etc.).

Rigidity

A form of hypertonia in which resistance to passive movement is present at low speeds, does not depend on the speed and does not exhibit a speed or threshold angle.

Hallmarks of Rigidity

Associated with diseases with a primary failure of dopamine production:

- Juvenile Parkinson's disease—rigidity, bradykinesia (no tremor in children)
- Dopa-responsive dystonia
- Dystonic cerebral palsy.

Tics

Definition

Rapid, arrthymic, repetitive movements or sounds that wax and wane over weeks/months to involve other body parts and actions.

Types

- Simple—e.g., blinking or sniffing.
- Complex—e.g., gesticulating or uttering
- Transient tics—less than 12 months
- Chronic motor or vocal tics—last at least 1 year.

Tourette syndrome

Criteria requires the (a) combination of motor and vocal tics, (b) duration of at least 1 year, (c) onset before the age of 18; exclusion of other causes [direct physiologic effects of a substance (e.g., stimulant drugs) or a general medical condition (e.g., Huntington disease or postviral encephalitis)]. Associated with other comorbid disorders like obsessive compulsive disorders, attention deficit hyperactivity disorder or behavioral problems.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

Now regarded as a controversial diagnosis. Abrupt onset of tics or obsessive compulsive disorders after infection with group A β-hemolytic streptococcus in prepubertal children, with motoric hyperactivity and adventitious movements but not frank chorea.

Treatment of Tics

- 1st tier drugs: α2-agonists (clonidine, guanfacine)
- 2nd tier drugs: Atypical antipsychotics (risperidone, olanzapine, etc.)
- 3rd tier drugs: Typical antipsychotics (haloperidol, pimozide, fluphenazine)
- Others: Tetrabenazine, botulinum toxin (for single site bothersome tics).

Clinical Pearl

Tics "rule of three",

- One-third disappears
- One-third are better
- One-third continue.

Stereotypy

Described as repeated, purposeless movements
Divided into two groups:

1. *Primary,* indicating a physiologic basis, and
2. *Secondary,* for those associated with other neuro-developmental problems like:
   - Pervasive developmental disability—Autism spectrum disorders, Rett syndrome
   - Intellectual retardation
   - Sensory deprivation—congenital blindness/deafness
   - Inborn errors of metabolism—Lesch-Nyhan syndrome
   - Genetic—Neuroacanthocytosis.

Tics are different from stereotypies which can be reproduced voluntarily and the patient has partial control. They do not interfere with voluntary activity.

Myoclonus

Definition

It is an involuntary muscle jerk which cannot be suppressed and generally with no premonitory features. It can be isolated though uncommon in children or a symptom of other disorders. In children it should be evaluated for epileptic myoclonus.

Types

Myoclonus can be subdivided according to the anatomic origin:

- Cortical: Originates from the sensorimotor cortex. Seen as focal, distal and arrthymic movement usually seen in the arms or trunk. It can be spontaneous or induced by action. Examples: progressive myoclonic epilepsies, Angelman's syndrome, Huntington's disease, Rett's syndrome, etc.
- Subcortical: Seen with injury to thalamus or brainstem. Examples: palatal myoclonus, hyperekplexia, etc.
- Spinal: Duration is longer and more variable than cortical or subcortical myoclonus. Examples: post-trauma, ischemic myelopathy, etc.
- Peripheral: Peripheral nerves lesions where sensory input is affected. They are typically arrthymic and non-stimulus sensitive. Example: hemifacial spasm.

Physiological myoclonus is much more common and should be differentiated from pathological causes. The common types of physiological myoclonus include benign neonatal sleep myoclonus and benign myoclonus of infancy.

Opsoclonus-myoclonus-ataxia Syndrome ("Dancing Eyes, Dancing Feet")

It is a rare but a dramatic, autoimmune disorder most commonly seen between 1 and 5 years.

Etiology

In children, 50% are associated with neuroblastoma and majority of nonneoplastic remain idiopathic but presumed postinfectious.

Clinical presentation

Presents with robust myoclonus and opsoclonus seen as multidirectional, darting, chaotic, conjugate eye movements. Excessive irritability, sleep disturbances, and mutism are common.

Diagnosis

It is essentially a clinical diagnosis but neuroblastoma screening is mandatory.

Prognosis and treatment

Neurologic outcome is unfavorable and a significant affected are left with motor and cognitive sequelae. Treatment includes immunosuppression and supportive medication for sleep and behavior disruption.

KEY POINTS

- ☞ Establishing phenomenology is key to diagnosis to movement disorder
- ☞ Every type of MD has its own characteristic, and combinations of them are also not rare, try to find the dominant one and existence of others also
- ☞ Presence of neurological and non-neurological causes of abnormal movements, epilepsy and epilepsy mimics should be also considered
- ☞ After having reached to clinical based movement disorder type, proceed for diagnostic workup to locate the cause behind and accordingly plan for treatment
- ☞ Keep your camcorder ready; patient never gives you second chance.

SUGGESTED READINGS

1. Albanese A, Bhatia K, Bressman S, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.
2. Butler IJ. Movement disorders of children. Pediatr Clin North Am. 1992;39:727-42.
3. Emilio Fernandez-Alvarez. Movement disorders in children: recent advances in management. Indian Journal of Pediatrics. 2009;76:531-6.
4. Fenichel GM. Movement disorders. Clinical Pediatric Neurology, 4th edition. 2001. p. 281.
5. Fuchs T, Ozelius LJ. Genetics of dystonia. Semin Neurol. 2011;31:(5):441-8.
6. Grosset KA, Grosset DG. Prescribed drugs and neurological complication. Journal of Neurology, Neurosurgery, and Psychiatry. 2004;75(Suppl 3):iii2-8.
7. Jarman PR, Wood NW. Genetics of movement disorders and ataxia. Journal of Neurology Neurosurgery and Psychiatry. 2002;73:ii22.
8. Kennards C (Ed). Recent Advance in Clinical Neurology. Edinburgh: Churchill Livingstone; 1988. pp. 175-200.
9. Korn-Lubetzki I, Stelner I. Common movement disorders in children: diagnosis, pathogenesis and management. Neuroscience & Medicine. 2012;3:90-100.
10. Kunju PAM. Extrapyramidal disorders. In: Gupte S (Ed). Recent Advances in Pediatrics. New Delhi: Jaypee Brothers Medical Publishers; 1994. pp. 140-66.
11. Lees AJ. Odd and unusual movement disorders. Journal of Neurology Neurosurgery and Psychiatry. 2002;72:i17-21.
12. Nygaad TG, Wooten GF. Dopa-responsive dystonia: some pieces of puzzle are still missing. Neurology. 1998;50:853-5.
13. Rojahn J. Self-injurious and stereotypic behavior of non institutionalized mentally retarded people: prevalence and classification [published erratum appears in Am J Ment Defic. 1987;91(6):619]. Am J Ment Defic 1986;91(3):268-76 [Medline].
14. Singer HS, Mink JW, Gilbert DL, Jankovik J. Movement disorders in Childhood, 1st edition. Saunders Elsevier, 2010.
15. Thyagarajan D. Recent advances. J Clin Neuroscience. 1999;6:1-8.

CHAPTER 95

Afebrile Encephalopathy: Bedside Approach to Diagnosis and Management

Lokesh Lingappa, Sirisharani Siddaiahgari

INTRODUCTION

Encephalopathy sets in with diffuse cerebral involvement, bilateral thalamic or ascending reticular activating system pathology. In children, diffuse cerebral involvement is the most common pathology leading to altered sensorium. A study by the California Encephalitis Project on epidemiology and etiology of encephalitis found that 63% of the patients remained without an etiology after a battery of tests for 16 potential infectious agents. The situation is much more difficult in the developing world in view of limited viral testing facilities.

Any child with encephalopathy needs to be evaluated for presence of an infectious etiology. This can be because of direct infection by the organism or part of systemic inflammatory response syndrome. Once these possibilities are ruled out one needs to consider other etiologies. Absence of fever during an infection may be due to immunocompromised states (including acquired and inherited immunodeficiency state, drug induced immunosuppression), chronic kidney disease, chronic liver disease, etc.

Clinical Pearl

- Absence of fever does not negate the presence of infection, 10% of Herpes simplex encephalitis children may not have fever as presenting manifestation.

Approximately 30–70% of acute encephalopathies do not receive etiologic diagnoses. Many of them might have an autoimmune basis some easily diagnosable and some still challenging. Most of them present acutely in pediatric practice. They can be broadly classified as infective pathology; the noninfective pathology consists of a wide range of etiologies (Table 1).

TABLE 1: List of disorders known to present with afebrile encephalopathy

Categories	Disorders
Autoimmune	• NMDA receptor encephalitis, voltage gated potassium channel antibody encephalitis • Hashimoto encephalitis
Epilepsy	• Nonconvulsive status epilepticus, prolonged postictal state
Metabolic disorders—Inherited	• Mitochondrial disorders, urea cycle disorders, organic acidemias and fatty acid oxidation disorders
Metabolic disorders—Acquired	• Hepatic failure, uremia, hypoglycemia, hyponatremia/hypernatremia
Parainfectious/ systemic vasculitis	• Acute disseminated encephalomyelitis, SLE, antiphospholipid antibody syndrome, hemolytic uremic syndrome
Structural	• Acute hydrocephalus, intracranial space occupying lesion
Trauma	• Accidental, nonaccidental
Toxins	• Drugs of abuse, antiepileptic drugs, organophosporous/organochloride compounds
Vascular	• Posterior circulation stroke, cerebral sinovenous thrombosis, intracranial bleed, hypertensive encephalopathy

NMDA, N-methyl-D-aspartate; SLE, systemic lupus erythematosus.

Clinical Pearl

- History from parents or adult person present at onset of altered sensorium is very important to generate appropriate differential diagnoses (80% of diagnoses are suspected based on history).

VARIED ETIOLOGIES AND THEIR BRIEF PRESENTATION ALGORITHM 1

Metabolic

Inborn errors of metabolism: in infants and young children presenting with encephalopathy one of the important etiology would be inborn errors of metabolism. Most present before age of two years, except few organic acidurias which may present later on.

Small molecule diseases (amino acid disorders, fatty acid oxidation disorders, organic acidurias, and urea cycle disorders) present with encephalopathy, symmetric motor signs. They have presence of increased anion gap metabolic acidosis along with variable hypoglycemia, hyperammonemia, lactic acidemia, and ketones.

Presence of metabolic acidosis with variable lactic acidosis and hypoglycemia and ketosis would point toward organic acidurias. Evidence of bone marrow suppression with bicytopenia also is manifestation of org anic aciduria.

Child presenting with nonketotic hypoglycemia especially in early morning hours with or without hepatomegaly and anicteric hepatitis would strongly point toward the presence of underlying fatty acid oxidation disorder. Medium chain Acyl Co A dehydrogenase deficiency is the most common followed by carnitine palmitoyl 1A deficiency.

Clinical Pearl

- In fatty acid oxidation disorder hepatomegaly and elevation of liver enzymes may evolve over initial days and may not be seen at presentation.

Urea cycle disorder will have variable presentations including encephalopathy, recurrent vomiting in association with hyperammonemia. Newborn presentation with progressive encephalopathy and abnormalities on magnetic resonance imaging (MRI) brain with restricted diffusion on brainstem is suggestive of maple syrup urine disease.

Clinical Pearl

- Ammonia levels need to be processed immediately and to be transported on ice to the laboratory for accurate results. Borderline elevation of ammonia is usually due to delayed processing of samples

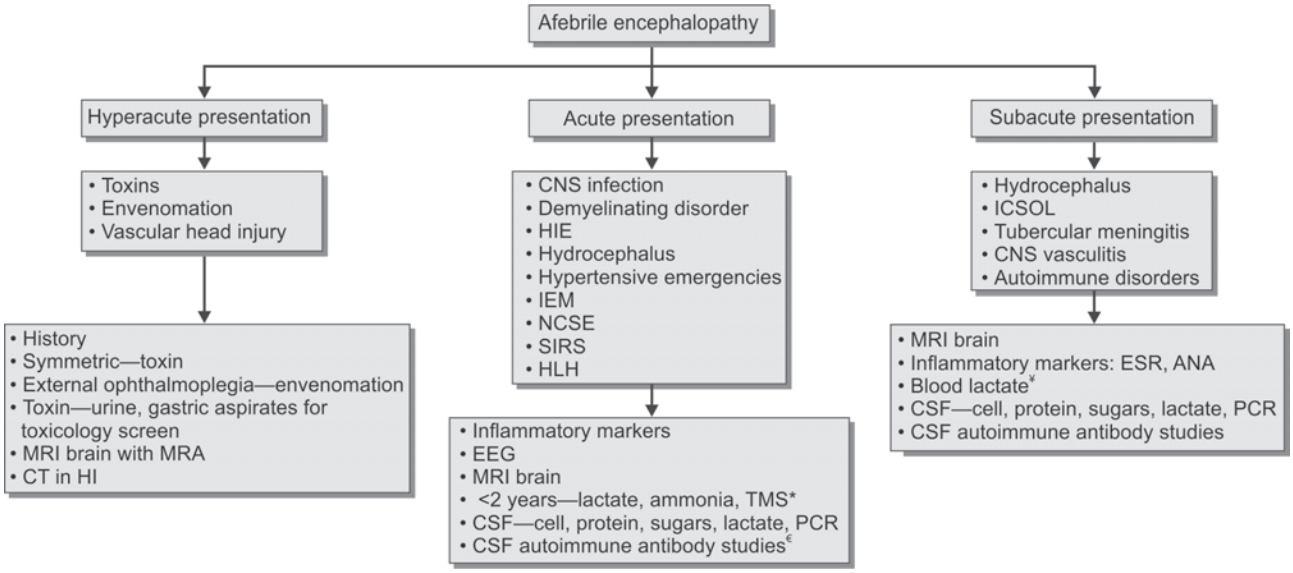
Stepwise decompensation in infancy with presence of breathing difficulty and lactic acidosis needs consideration of mitochondrial disorder. Neuroimaging demonstrating bilateral basal ganglia hypodensities on computed tomography of brain along with involvement of peri-aqueductal gray matter suggests Leigh's disease. Magnetic resonance imaging with MRI spectroscopy with elevated lactate and elevated cerebrospinal fluid (CSF) lactate further confirm the diagnoses.

Clinical Pearl

- It is imperative that in an infant or young child less than 3 years with unexplained encephalopathy with or without acidosis and hypoglycemia, samples (tandem mass spectroscopy, lactate and ammonia, urine for organic acids,) should be taken before starting vitamin cocktails

ALGORITHM 1

Diagnosis and investigations of acute encephalopathy based on presentation



*Children less then two years are at risk of presenting with encephalopathy due to inborn errors of metabolism.

€Autoimmune antibody associated encephalitis can be suspected within first one or two weeks of onset.

¥Mitochondrial disorders can have varied presentation and needs to be differential diagnoses in unexplained encephalopathies.

MRI, magnetic resonance imaging; MRA, magnetic resonance angiogram; CT, computed tomography; HI, head injury; CNS, central nervous system; HIE, hypoxic ischemic encephalopathy; IEM, inborn errors of metabolism; NCSE, nonconvulsive status epilepticus; SIRS, systemic inflammatory response syndrome; HLH, hemophagocytic lymphohistiocytosis EEG, electroencephalogram; TMS, tandem mass spectrometry; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; ICSOL, intracranial space occupying lesion; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody.

An EDTA sample should be stored in case of sudden death and further pregnancy counseling can be possible after performing appropriate genetic analysis.

Acquired: Hepatic/Uremic/Others

Hepatic Encephalopathy

Spectrum of neuropsychiatric abnormalities in patients with liver dysfunction are characterized by personality changes, intellectual impairment, and depressed level of consciousness. The diagnosis is usually given away by presence of icterus, significant elevation of liver enzymes, and in few children with history of pre-existing liver disease.

Uremic encephalopathy may be more challenging to diagnose. Hypertension would be an independent risk factor for encephalopathy. Short stature, anemia, hypertension, and features of rickets would be the systemic clues to chronic kidney disorders.

Clinical Pearl

- Early central visual impairment before losing consciousness would be a pointer toward hypertensive emergency causing posterior reversible leukoencephalopathy syndrome

Electrolyte Disturbances/ Hyperglycemia/Hypoglycemia

Children with acute gastroenteritis and endocrine disorders can present with altered sensorium. Severe gastroenteritis leads to sinovenous thrombosis with raised intracranial pressure. Slow correction of hyponatremia is essential. Hyperglycemia as first presentation or poor control of insulin dependent diabetes mellitus is associated with encephalopathic presentation.

Insulin dependent diabetes mellitus is associated with encephalopathic presentation.

Clinical Pearl

- Normal magnetic resonance imaging brain with symmetrical encephalopathy (encephalopathy with preserved eye movement without lateralizing neurological findings) points toward metabolic encephalopathy, systemic inflammatory response syndrome and toxins. Magnetic resonance imaging can be normal in early phases of acute disseminated encephalomyelitis.

Inflammatory/Vasculitis

Parainfectious/Postinfectious Demyelination

In children presenting with biphasic illness, neurological worsening with polyfocal symptoms and encephalopathy, acute disseminated encephalomyelitis (ADEM) is a relevant differential diagnoses. Magnetic resonance imaging brain performed early on may be normal; most will demonstrate changes by 5–7 days in subcortical white matter along with deep gray nuclei especially in poststreptococcal ADEM. N-methyl-D-aspartate receptor (NMDAR) encephalitis can also have similar presentation with minimal MRI changes.

Vasculitis/Hypertensive Encephalopathy/ Vascular Etiologies

Adolescent age group especially in girls presenting with multisystem involvement and focal neurological presentation or diffuse encephalopathy consider systemic vasculitis disorder. Neuroimaging might provide the directions for vasculitic pathology or elevated ESR might suggest the underlying etiologic process.

Autoimmune Pathologies

Children present with neurological syndromes associated with serum and/or CSF antibodies directed against ion channels, receptors and associated proteins are diagnosed as antibody-mediated encephalopathies. The clinical features of these disorders overlap and, in many cases, the etiology may not be apparent at presentation. Investigation and treatment needs to be ongoing in this clinical situation. Many patients present with fever, seizures, amnesia, confusion, and psychiatric features, and some develop encephalopathy with a movement disorder.

Clinical Pearl

- Presence of characteristic movement disorder with perioral dyskinesia and dystonia is the usual key to diagnoses of N-methyl-D-aspartate encephalitis with no diagnostic cerebrospinal fluid or magnetic resonance imaging brain findings.

In some the encephalopathy can be part of a paraneoplastic syndrome. Majority of children do not have detectable tumors except in adolescent girls who harbor ovarian teratoma.

Autoimmune encephalopathies are increasingly being diagnosed in children with antibodies to NMDAR, and rarely with antibodies to voltage-gated potassium channel (VGKC)-complex proteins or other central nervous system antigens such as glutamic acid decarboxylase. The clinical phenotypes associated with these conditions are increasingly recognized but some patients are negative for the available antibody tests.

Acquired Brain Injury

Accidental/nonaccidental injury

In onset of altered sensorium is immediate in significant head injury except in cases of epidural hematoma where symptoms can evolve over 24 hours. An inconsistent history from different family members and varied stages of injuries on neuroimaging or unexplained fractures would suggest nonaccidental injury (Tables 2 to 5).

TABLE 2: Course of illness as clue to diagnoses

Abrupt onset (onset within minutes to hours)	• Intracranial bleed • Posterior circulation stroke • Trauma—accidental/nonaccidental • Poisoning
Acute onset (hours to less than week)	• Central nervous system infection • Demyelinating disorder • Hypoxia ischemic event • Hydrocephalus • Hypertensive emergencies • Inborn errors of metabolism • Nonconvulsive status epilepticus • Septicemia with systemic inflammatory response syndrome • Hemophagocytic lymphohistiocytosis
Subacute progression (More than 1 week of symptoms)	• Intracranial space occupying lesion • Hydrocephalus • Tubercular meningitis (20% can present acutely in children) • Central nervous system vasculitis—primary/secondary (variable course)

TABLE 3: Clinical clues to diagnoses

General physical examination	• Short stature—Chronic renal failure • Icterus—Hepatic encephalopathy, rarely in FAOD • Hypertension—Hypertensive encephalopathy, raised ICP • Skin-rash—Vasculitis, HSP • Joint swelling—HSP, Rachitic features in chronic renal failure
Abdomen	• Hepatosplenomegaly—Hemophagocytic lymphohistiocytosis
Large head	• Hydrocephalus, glutaric aciduria type I (6 to 18 months)
Neurocutaneous markers	• Multiple cafe au lait spots—Moyamoya syndrome with stroke • Hypopigmented macules—TSC complex with nonconvulsive status epilepticus • Facial angioma—Stroke like episodes, status epilepticus in Sturge-Weber syndrome

FAOD, fatty acid oxidation disorder; ICP, intracranial pressure; HSP, Henoch-Schonlein purpura; TSC, tuberous sclerosis alliance.

TABLE 4: Investigations

Blood	• Markers of infection—CBC, CRP, procalcitonin, blood and urine cultures • PS for MP, Mycoplasma antibodies, Weil Felix test • ESR—elevation more than 100 mm/1st hour usually indicates either active systemic vasculitis/chronic infection or a malignancy • ANA, APLA, ANCA antibody studies • Thyroid function, antithyroid antibodies • IEM workup—blood lactate, ammonia, tandem mass spectroscopy
Neuroimaging	• CT brain—done in acute situation—is good for acute bleeding, head injuries, rule out a space occupying lesion • MRI brain—undiagnosed encephalopathy, stroke, demyelination, etc. • Caveat—normal MRI brain is seen in significant proportion of NMDAR encephalitis/ADEM in first week of illness • MR angiogram and venogram in appropriate clinical setting
EEG	• Continuous EEG monitoring will help to diagnose nonconvulsive status epilepticus
Cerebrospinal fluid Always preserve extra samples for later testing	• Opening pressure, cell count, protein, paired sugar and lactate, cultures • PCR for Herpes simplex infection and other viruses as appropriate • Anti-N-methyl-D-aspartate receptor antibodies and antivoltage gated potassium channel antibodies
Ophthalmological opinion	• Retinal haemorrhages—consider nonaccidental injury • Papilledema—Sinovenous thrombosis • Hypertensive changes • Whitening of vessels, papilledema and cotton wool spots in malaria
Urine	• Cultures, toxicology screen

CBC, complete blood count; CRP, C-reactive protein; PS, peripheral smear; ESR, erythrocyte sedimentation rate; MP, malarial parasite; ANA, antinuclear antibodies; APLA, antiphospholipid antibodies; ANCA, anti-neutrophil cytoplasmic antibody; IEM, inborn error of metabolism; CT, computed tomography; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; ADEM, acute disseminated encephalomyelitis.

TABLE 5: Bilateral basal ganglia lesions in context of acute encephalopathy

Metabolic	Toxins	Vascular
• Organic acidurias • Mitochondrial disorders • Thiamine deficiency • Hypoxic insult • Hypoglycemia • Hemolytic uremic syndrome • Osmotic myelinolysis	• Carbon monoxide • Methanol • Cyanide	• Deep venous thrombosis • Hypertensive encephalopathy • Basal meningitis

Clinical Pearls

- An inconsistent history from different family members and varied stage of injuries or unexplained fractures—suspect nonaccidental injury
- Documentation of anthropometry, blood pressure, heart rate, breathing pattern are important clues to etiologic diagnoses
- Detailed eye examination-pupils—eye movements, and fundus has great localizing and diagnostic value.

MANAGEMENT

Management of acute encephalopathy involves stabilization of airway, breathing, and circulation. Start treatment for infection with antibiotics and antiviral medications as appropriate. Symptomatic treatment of seizures and management of raised intracranial pressure is essential. Ongoing monitoring on vital parameters and end-organ functions are essential part of treating a child with encephalopathy. Once accurate etiology is established the management will have to focus and unwarranted medications can be withdrawn.

N-methyl-D-aspartate receptor encephalitis responds to immunomodulation and even the severe motor disability improves significantly. First-line immunotherapy includes steroids and intravenous immunoglobulin. If there is no response, rituximab once a week for 4 weeks improves the condition. It is imperative to monitor CD20 levels during therapy. Acute disseminated encephalopathy usually responds to methylprednisolone followed by oral steroids in most.

Outcomes are dependent on etiology and severity of pathology. Ongoing counseling of family and involving them in important decision-making will help to reduce the stress on the treating team and the family.

KEY POINTS

- ☞ Afebrile encephalopathy is a common clinical problem of varied etiologies and presentations
- ☞ Accurate history and comprehensive examination will provide clue to the etiologic diagnoses in many children
- ☞ Investigations are to be performed as per individual patient including appropriate neuroimaging
- ☞ Early identification of etiologic diagnoses helps in appropriate management and improved outcome.

SUGGESTED READINGS

1. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. J Child Neurol. 2012;27:1460-9.
2. Hegde AN, Mohan S, Lath N, Lim CC. Differential diagnosis for bilateral abnormalities of the basal ganglia and thalamus. Radiographics. 2011;31: 5-30.
3. Maguire S, Pickerd N, Farewell D, Mann M, Tempest V, Kemp AM. Which clinical features distinguish inflicted from non-inflicted brain injury? A systematic review. Arch Dis Child. 2009;94:860-7.
4. Plum and Posner's Diagnosis of Stupor and Coma, 4th edition. Oxford University Press, 2007.
5. Wong CP, Forsyth RJ, Kelly TP, Eyre JA. Incidence, aetiology, and outcome of non-traumatic coma: a population based study. Arch Dis Child. 2001;84:193-9.

CHAPTER 96

Approach to Rickets in Children

S Thangavelu, M Vijayakumar

INTRODUCTION

Rickets is caused by defective mineralization of growing bones resulting in bony deformities. Vitamin D deficiency is the most common cause of rickets. Rickets, like illness can occur in wide variety of other disorders like renal tubular disorders, chronic liver disease, and some metabolic disorders. Clinical appearance is similar, but after biochemical evaluation, one can differentiate one from the other.

Nutritional rickets being common in the past, the traditional practice consisted and still consists of treating every child having rickets with vitamin D, particularly stoss therapy using high dose of intramuscular D3. Then child is reevaluated clinically and radiologically after 6 weeks and 12 weeks. In a fair number of cases, the decision of non-nutritional rickets is made only after 12 weeks. Gradually this scenario has changed to complete evaluation to a specific diagnosis so as to decide on need for vitamin D. This is possible because of the availability of sophisticated investigations and subspecialty consults like pediatric nephrology, gastroenterology, and metabolic specialists. Here, the process is completed in a short time of 5–7 days. But in peripheral areas and in the absence of adequate laboratory and subspecialty facilities, the traditional method is still an ideal one. Specific management differs according to the underlying illness. Most of them present with symptomatology of delayed walking or bony deformities. Head to foot clinical examination may reveal following findings.

CLINICAL EXAMINATION

Head

Features include craniotabes, delayed closure of anterior fontanel, and frontal and parietal bossing leading to box-like appearance of head known as caput quadratum. Delayed eruption of primary teeth, enamel defects, and caries teeth are the dental abnormalities.

Thorax

Palpable and visible knobby enlargement of costochondral junctions are called rachitic rosary (Fig. 1A). Harrison's sulcus (Fig. 1B) is the horizontal depression along the lower part of chest corresponding to the costal attachment of diaphragm due to traction on the rib cage. This may also be associated with pectus carinatum or violin-shaped chest. In severe forms and untreated cases, spinal and pelvic deformities can occur.

Extremities

Palpable and visible knobby enlargement of long bones around wrists and ankles (double malleoli) are present. Weight bearing can lead to bow legs, knock knees, and anterior curving of legs, coxa vera, and greenstick fractures. Deformities of spine, pelvis, and leg results in short stature called "rachitic dwarfism" (Fig. 1C). Lower extremities are almost always more extensively involved than upper extremities in familial hypophosphatemic rickets (FHR), whereas upper limb involvement is more pronounced in hypocalcemic rickets.

General

Pot belly abdomen can be pressent (Fig. 1D). Motor symptoms are more common with hypocalcemic rickets whereas motor symptoms are usualy absent in predominantly hypophosphatemic rickets. One can approach rickets in children through the following algorithm (Algorithm 1).

METAPHYSEAL DYSPLASIA

Though there are many clinical findings, bony changes such as enlarged bony ends are the striking clinical features and they form the center point of clinical differentiation. Few conditions closely mimic rickets clinically as well as radiologically. They are (i) metaphyseal dysplasia, (ii) hypophosphatasia, and (iii) mucopolysaccharidosis.

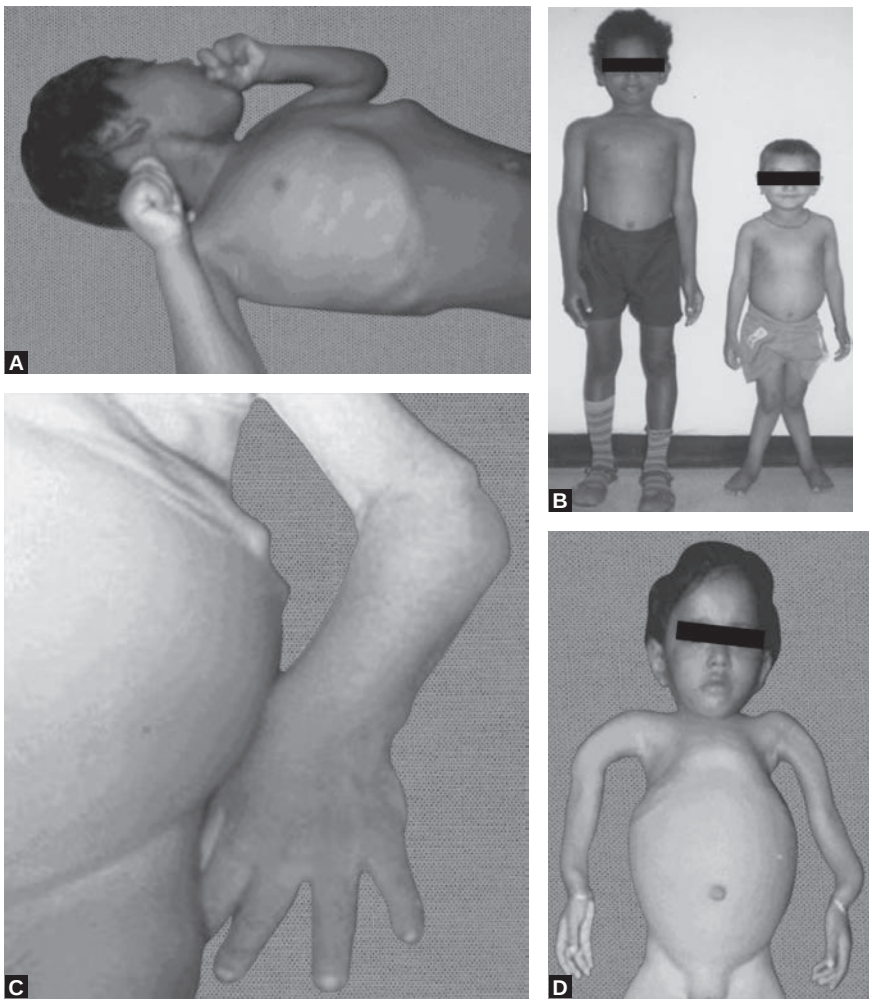
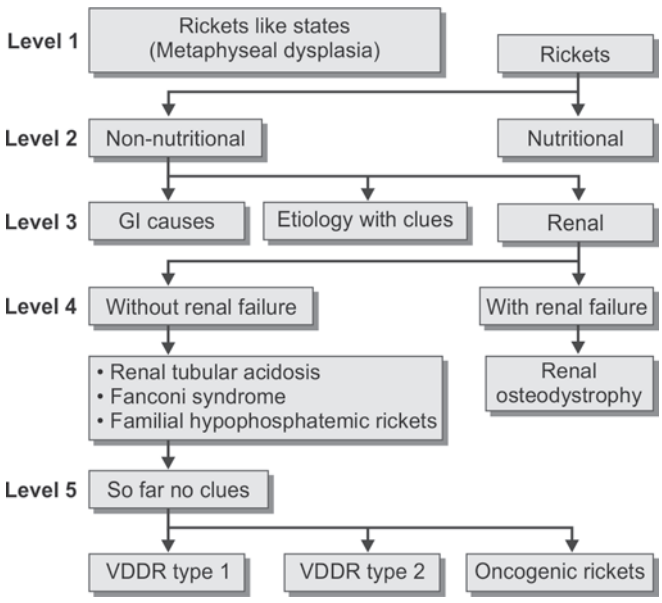


Fig 1: Clinical features of rickets. **A,** Rachitic rosary; **B,** Harrison's sulcus; **C,** Rachitic dwarfism; **D,** Pot belly

ALGORITHM 1

Algorithmic approach to rickets in children



GI, gastrointestinal; VDDR, vitamin D dependent rickets.

Do preliminary investigations like serum calcium, phosphorous, serum alkaline phosphatase (SAP), and have a close look at the X-rays. Though rickets like states such as hypophosphatasia (caution: not hypophosphatemia) and metaphyseal dysplasia are far rarer than rickets, it is wise to confirm the diagnosis of rickets before proceeding further. This will avoid unnecessary therapy with vitamin D.

Clinical Features and Radiological Signs Suggestive of Metaphyseal Dysplasia

Clinical and radiological signs are similar to rickets but with subtle difference. Here, growth plate is not wide with differential involvement of bones in a joint, e.g., femur shows radiological changes, but tibia is normal. Biochemical investigations, such as serum levels of calcium, phosphate and alkaline phosphatase, are normal.

Clinical Features and Radiological Signs Suggestive of Hypophosphatasia

Clinical signs of rickets are present but X-ray of long bones show tongue-like radiolucency projecting from growth plate

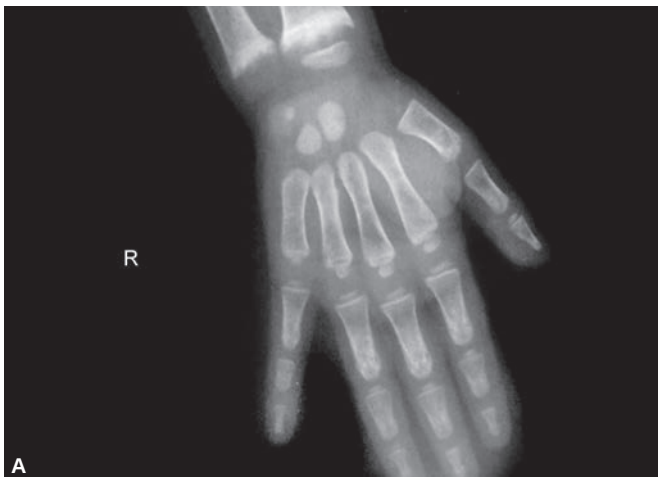
into metaphysis whereas in rickets growth plate is uniformly wide. Biochemical changes will be different from rickets as SAP levels are low and serum calcium and phosphate levels are normal.

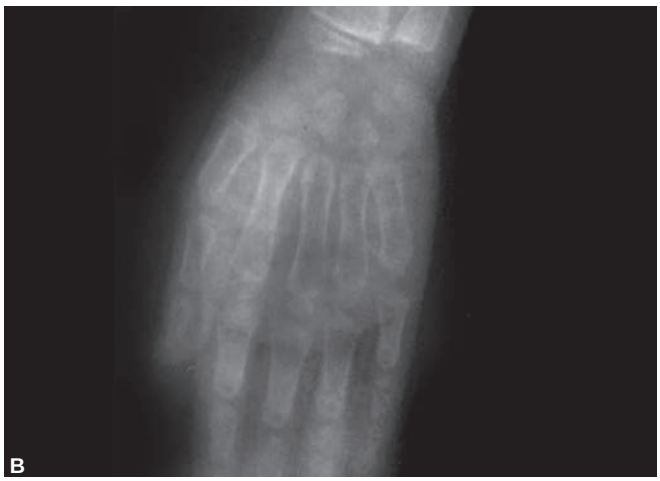
Clinical Pearl

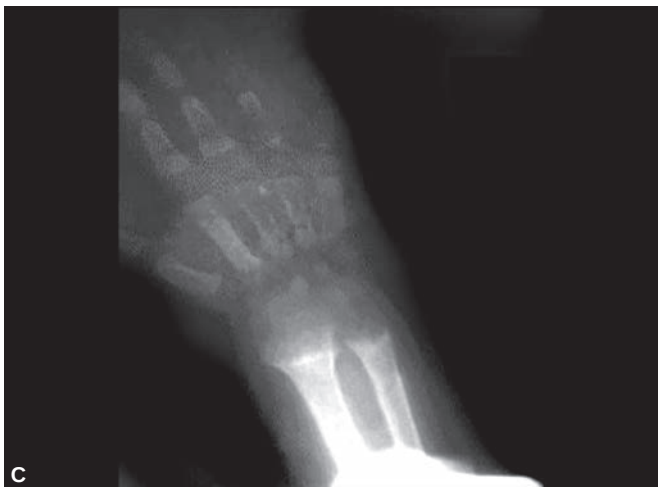
- Metaphyseal dysplasia and hypophosphatasia can be confused with rickets in children. In metaphyseal dysplasia, serum levels of calcium, phosphate, and alkaline phosphatase are normal and there will be differential involvement of bones in a joint. In hypophosphatasia, biochemical changes will be different from rickets as serum alkaline phosphate levels are low and serum calcium and phosphate levels are normal.

NUTRITIONAL RICKETS

Nutritional rickets is reappearing in large numbers all over the world. Inadequate exposure to sunlight, lack of dietary or vitamin supplements, and deficiency of vitamin D in breastfeeding mothers are important reasons. This being a disease of growing children, nutritional rickets usually appears between the age group of 6 months to 2 years. Any child presenting beyond this age group, involvement of more than one family member, and associated failure to thrive or failure of adequate vitamin D therapy to correct rickets indicates the diagnosis of non-nutritional rickets. Differentiation is important because non-nutritional rickets needs extensive biochemical evaluation and specialist's opinion. Diagnosis and management of nutritional rickets is straightforward, but in non-nutritional rickets, it is complicated and needs prolonged therapy. In nutritional rickets, 25-hydroxy vitamin D level will be low and other associated features include low serum calcium, phosphate, and high alkaline phosphatase with elevated serum levels of parathyroid hormone (PTH). Radiological changes are observed in ends of long bones such as knees or wrist. Classical radiological changes of rickets are absence of zone of provisional cartilaginous calcifications and widening, fraying and cupping (concavity) of the distal ends of shaft. But some studies indicate the lack of correlation between low serum levels of vitamin D and presence of radiological changes. Despite very low levels, no radiological changes are observed in some (Figs 2A to C).







Figs 2: A, Active rickets (before vitamin D); **B,** Healing rickets (after vitamin D); **C,** Nonhealing rickets

Clinical Pearl

- Vitamin D deficiency rickets previously called as nutritional rickets will show healing after adequate vitamin D therapy. Rickets without obvious clues definitely needs serum vitamin D level assessment at whatever age they are presenting to us. One should note that even before healing rickets is seen in the X-rays, the elevation of serum phosphate level from its original low level will give us clue that we are dealing with vitamin D deficiency rickets only.

NON-NUTRITIONAL RICKETS

Among the non-nutritional causes, three common causes are seen. Most commonly renal, next gastrointestinal, and third are miscellaneous causes. Sometimes obvious clues may be identified which will lead to the diagnosis of the underlying cause.

ETIOLOGY WITH CLUES

History of prematurity and lack of vitamin D supplementation, neonatal cholestasis, chronic renal failure, or child taking anticonvulsant therapy are obvious clues. One should look for leading points in the history and examination in a child with rickets like positive family history which is common in metabolic diseases and in renal tubular acidosis (RTA).

- Jaundice may be a clue toward hepatobiliary disease, metabolic disorders, and tyrosinemia
- Cataract and rickets are seen in galactosemia, Wilson's disease, and Lowe syndrome
- Mental retardation and seizures are seen in Lowe syndrome, galactosemia, and in primary central nervous system problem with drug-induced rickets.

At this stage, one should differentiate between two causes: (i) gastrointestinal including hepatobiliary and (ii) renal causes.

GASTROINTESTINAL CAUSES

Features Indicating Gastrointestinal Etiology (Particularly Malabsorption Disorders Leading to Rickets)

History: recurrent diarrhoea, oily stools, abdominal pain, and distention

Examination: anemia, hypoproteinemia, multiple vitamin and mineral deficiencies, and failure to thrive.

Laboratory features: vitamin D deficiency, low phosphate, calcium may be normal or low with raised PTH.

Features Indicating Hepatobiliary Disorder Leading to Rickets

Clinical features: jaundice, pale stools, oily stools, high colored urine and hepatomegaly,

Laboratory features: raised serum total and direct bilirubin, raised hepatic enzymes, low serum albumin, and prolonged prothrombin time.

RENAL CAUSES

Clinical and Laboratory Features Indicating Renal Etiology Leading to Rickets

Clinical features: recurrent vomiting, failure to thrive, lethargy, acidotic breathing, and presence of underlying renal disorders are indicative of renal etiology.

When renal cause is suspected, investigations play a major role in confirming or excluding them. Four renal diseases constitute the following causes: (i) RTA, (ii) hypophosphatemic rickets, (iii) Fanconi syndrome, and (iv) renal failure.

Among these four causes, chronic renal failure leading to renal osteodystrophy will have the following features.

Clinical and laboratory features: vomiting, lethargy, growth retardation, hypertension, anemia, with or without edema, features of obstructive uropathy, raised blood urea, and serum creatinine. Serum potassium may be normal or high. Abnormalities in abdominal ultrasonography (USG) showing renal anomalies, obstruction, and renomegaly or contracted kidney can be seen. Dimercaptosuccinic acid scan showing scars and micturiting cystourethrogram showing vesicoureteric reflux should be noted in specific situations.

If there is no renal failure, one of the other three renal problems are considered: RTA, Fanconi syndrome, or FHR.

History, examination, and laboratory features suggestive of RTA: recurrent vomiting and diarrhea with acidotic breathing associated with positive family history is common. Metabolic acidosis with low serum bicarbonate, low serum pH, normal serum anion gap, hypokalemia, and raised serum chloride are usually seen. Normal blood urea and serum creatinine with no proteinuria or glycosuria is noted.

History, examination, and laboratory features suggestive of Fanconi syndrome: clinically severe form of rickets with stunting and deformity and features mentioned in RTA are seen. Aminoaciduria, glycosuria, and phosphaturia are present. Usually normal blood urea and serum creatinine or minimally increased blood urea and serum creatinine can be seen. Features of underlying causes such as cystinosis and Wilson's disease may be present.

History, examination, and laboratory features suggestive of familial hypophosphatemic rickets: prominent lower limb deformity with stunted growth and often with family history is noted. Frequent dental abscess and early decay are common. Low serum phosphate and low tubular reabsorption of phosphate are documented.

If clinical, laboratory features are not suggestive of any one of the above-mentioned conditions leading to rickets, then one of the following diagnoses discussed in the next section is likely.

Clinical Pearl

- Renal osteodystrophy (ROD) is different from other forms of renal rickets though included in them, as it designates alteration in skeletal growth and remodeling that occurs in children with chronic renal disease, because of alteration in bone and mineral metabolism. Even treatment for ROD is not straight forward therapy for vitamin D defects alone.

VITAMIN D-DEPENDENT RICKETS TYPE 1

History, examination, and laboratory features suggestive of VDDR type 1: often presents in early infancy with afebrile seizures and hypocalcemic tetany with or without radiological changes. The differentiating feature from vitamin D deficiency is improvement with vitamin D therapy and recurrence of symptoms after stopping the therapy. In this situation, estimating vitamin D metabolites will be very useful. Here, serum 25-hydroxy vitamin D [25(OH) D] levels will be normal, unlike in vitamin D deficiency. But 1,25-dihydroxy vitamin D level is low despite normal or high 25(OH) D indicating that there is defective conversion. In vitamin D-dependent rickets type 1, the pathology is defect in 1 α-hydroxylation.

VITAMIN D-DEPENDENT RICKETS TYPE 2

History, examination, and laboratory features suggestive of VDDR type 2: these children may present with or without alopecia, in addition to features of florid rickets. Very often they would have received one or multiple doses of vitamin D3 as injection or in oral form, without any clinical or radiological response. In this receptor defect, 1, 25-dihydroxy vitamin D level is high in contrast to vitamin D-dependent rickets type 1 and this investigation is absolutely essential for differentiation.

ONCOGENIC RICKETS

History, examination, and laboratory features suggestive of oncogenous rickets: it is a rare disease, where phosphate loss in the urine associated with mesenchymal tumors like hemangioendothelioma or neurofibroma. They are commonly seen in hands, feet, and abdominal sheath. Sometimes they may be small and undetectable and rickets develops years before tumor is apparent. Phosphate loss is due to secretion of fibroblast growth factor. Phosphate replacement along with 1,25-dihydroxy vitamin D and tumor removal are the steps in the management.

INVESTIGATIONS DONE IN ANY CHILD WITH RICKETS

Investigations are done stepwise or at one stretch if clinical features warrant.

Basic Investigations to Confirm Rickets

Serum calcium, phosphorous, alkaline phosphatase, X-rays of ends of long bones such as knee or wrist are the basic investigations in any child with rickets.

Second Level Investigations

Blood urea, creatinine, electrolytes, arterial blood gas analysis, and tubular reabsorption of phosphate are second level investigations. Urine analysis for glucose, protein, specific gravity, and anion gap are needed. Liver function test, USG abdomen, investigation for malabsorption, and "inborn errors of metabolism" are done as per the clinical diagnosis suspected at this level. Parathyroid hormone level is elevated in rickets and is useful in determining certain forms of rickets.

Tertiary Level Investigations

Estimation of vitamin D metabolites (to differentiate VDDR type 1 from type 2), *in vitro* studies to assess receptor-vitamin D interaction (VDDR-type 2) and bone mineral content by bone densitometry are investigations done at this stage.

Clinical Pearl

- In modern era, vitamin D level estimation in the serum is readily available. 25-hydroxy vitamin D level should be tested to confirm vitamin D deficiency rickets and to rule out vitamin D deficiency itself. Even in renal osteodystrophy, estimation of 25-hydroxy vitamin D levels should not be ignored as treatment involves therapy with 25 hydroxy vitamin D as well. 1,25-dihydroxy vitamin D levels are essential to differentiate vitamin D-dependent rickets type 1 from type 2.

MANAGEMENT

Management of rickets becomes straight forward once the cause is found out. Table 1 outlines the management strategy for treatment of various types of rickets in children. While a large dose of vitamin D has been classically used to treat rickets/vitamin D deficiency, whether slow correction over 6–10 weeks is equally or more beneficial with lesser adverse effects is a matter of research and debate at present. The present recommendations are given in table 1.

TABLE 1: Guidelines in the treatment of rickets

Types of rickets	Treatment
Vitamin D deficiency rickets	• Traditional therapy: vitamin D 10,000 IU/kg IM is given and then X-ray repeated after 4–6 weeks. If radiological healing is seen, then switched to daily maintenance. If no improvement second stat dose may be needed • Recent guidelines for therapy: *Oral preparations preferred over IM. Though daily dose is preferred, for practical reasons, stoss therapy can be used ◦ < 3 months – large oral dose not recommended ◦ 3–12 months – one single oral dose 50,000 units ◦ 12 months to 12 years – 150,000 IU (50,000 weekly three doses) ◦ 12 years – 3,00,000 IU (50,000 weekly six doses)
VDDR type 1	• 1,25-dihydroxy vitamin D3 (0.25–1.0 μg/day orally)
VDDR type 2	• 1,25-dihydroxy vitamin D3 or 1 α-hydroxy vitamin D3 (6 μg/day or a total of 30–60 μg orally per day) with supplemental calcium
Renal tubular acidosis (RTA)	• Alkali therapy: 3–5 mEq/kg/day in distal RTA and 5–15 mEq/kg/day in proximal RTA • Supplements of potassium as per serum potassium levels

Continued

Continued

Types of rickets	Treatment
Fanconi syndrome	• Phosphate replacement (40 mg of elemental phosphorous/kg per day to start with, later increased to 250–500 mg and to maximum of 3,500 mg/day) either as sodium or potassium phosphate or as Joulie's solution • 1-α-hydroxy vitamin D3 or 1,25-dihydroxy vitamin D3 • Alkali therapy as for proximal RTA
Renal osteodystrophy	• 1-α-hydroxy vitamin D3 or 1,25-dihydroxy vitamin D3 • Phosphate binders • Alkali therapy • Renal replacement therapy • Cholecalciferol as per 25-hydroxy D3 levels
Familial hypophosphatemic rickets	• Phosphate replacement every 4–6 hour • 1-α-hydroxyvitamin D3 or 1,25-dihydroxy-vitamin D3
Rickets of prematurity	• Calcium 100 mg/kg/day • Phosphate 50 mg/kg/day for 3 month • Vitamin D in normal requirements

Note: Reassess the response to treatment to decide need for further therapy. Maintenance calcium 50 mg/kg/day in 3 divided doses.

IM, intramuscularly; VDDR, vitamin D-dependent rickets.

*Modified from Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016;101(2):394-415.

KEY POINTS

- ☞ Vitamin D deficiency rickets is clinically suspected first and then confirmed by laboratory investigations such as X-ray of long bones, serum calcium, phosphate, and alkaline phosphatase
- ☞ In rickets, mimicking conditions like metaphyseal dysplasia, biochemical investigations like serum calcium, phosphate, and alkaline phosphatase are normal, though radiological changes may be similar
- ☞ Estimating serum electrolytes, urea, creatinine, and arterial blood gas analysis will identify renal disorders like renal osteodystrophy, renal tubular acidosis, and hypophosphatemic rickets. Because in addition to radiological changes, each disorder will have its own biochemical features. In addition to this, abdominal ultrasonography and other renal imaging modalities like dimercaptosuccinin acid and voiding cystourethrography are necessary to confirm them
- ☞ In disorders of vitamin D metabolism, estimating the serum 25-hydroxy vitamin D and 1,25-dihydroxy vitamin levels are absolutely necessary. A low 25-hydroxy vitamin D level confirms vitamin D deficiency, but a low 1,25-dihydroxy vitamin D in the background of a raised 25-hydroxy vitamin D level confirms the diagnosis of vitamin D-dependent type 1 rickets. But in a child with clinical features of rickets and alopecia, raised 1,25-dihydroxy vitamin D level is diagnostic of vitamin D-dependent type 2 or end organ receptor defect
- ☞ Low alkaline phosphatase level is seen only in rare condition like hypophosphatasia.

SUGGESTED READINGS

1. Graham R William. Bone structure and metabolism. Medicine Group (Journals) Ltd. Medicine. 1997;60-98.
2. Pitt MJ. Rickets and osteomalacia. In: Resnick D (Ed). Diagnosis of Bone and Joint Disorders, 4th edition. Philadelphia: PA: Saunders; 2002. pp. 1901-935.
3. Specker BL, Tsang RC. Bone mineralization. Ann Nestle. 1987;45:18-25
4. Mehls O, Klans G. Childhood renal osteodystrophy. Ann Nestle. 1989;47:144-57.
5. Thangavelu S, Vijayakumar M. Approach to Rickets in children. In: Vijayakumar M, Nammalwar BR (Eds). Principle and Practice of Pediatric Nephrology, 2nd edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2013. pp. 795-803.

CHAPTER 97

Disorders of Sodium and Potassium

Sushmita Banerjee

INTRODUCTION

Sodium (Na^+) is the major extracellular cation in the body, whereas potassium (K^+) is the main intracellular cation. Their location across the cell membrane is maintained by the Na^+/K^+-adenosine triphosphatase pump, which by an active process extrudes Na^+ from the cell and pushes K^+ into the cell.

Sodium balance occurs in close conjunction with water balance, with the same homeostatic pathways causing parallel changes in Na^+ and water. The mechanisms of Na^+ and K^+ balance are also closely interlinked and both are dependent on renal function. Boxes 1 and 2 list the common causes of Na^+ and K^+ balance in children.

Box 1: Etiology of sodium imbalances

Causes of hyponatremia

- Associated with reduced or normal total body water:
  - Excess Na^+ loss compared to water loss, from:
    - GIT (diarrhea, vomiting, fistulae, ileostomies)
    - Skin (burns, cystic fibrosis)
    - Kidney (tubular diseases: Bartters syndrome, Fanconi's syndrome, hypoaldosteronism, cerebral salt wasting)
  - Administration of hyponatremic fluids in sick patients or hyponatremic feeds in infants
- Associated with increased total body water:
  - Increased levels of antidiuretic hormone (SIADH, iatrogenic)
  - Fluid overload (oliguric renal failure, excessive fluid administration, nephrotic syndrome, hepatic cirrhosis congenital heart failure)

Causes of hypernatremia

- Associated with normal or increased total body water:
  - Administration of hypernatremic fluids to sick patients or hypernatremic feeds to infants
  - Hyperaldosteronism
- Associated with decreased total body water:
  - Inadequate fluid administration to sick patients
  - Fluid losses (excess water loss compared to Na^+ loss): GI/renal (diabetes insipidus, osmotic diuresis in diabetes mellitus)/skin diseases

GIT, gastrointestinal tract; SIADH, syndrome of inappropriate antidiuretic hormone secretion; GI, gastrointestinal; Na^+, sodium.

Box 2: Etiology of potassium imbalances

Causes of hyperkalemia

- Increased total body potassium
  - Reduced excretion: renal failure, mineralcorticoid deficiency, type 4 renal tubular acidosis, and K^+ sparing diuretics
  - Increased intake: iatrogenic potassium administration
- Increased cell breakdown: hemolysis and tumor lysis (also increased total body potassium)
- Increased catabolism: sepsis and burns
- Redistribution from ICF to ECF: acidosis, insulin deficiency

Causes of hypokalemia

- Reduced total body potassium:
  - Inadequate intake, iatrogenic
  - Renal loss: renal artery stenosis, tubular diseases, mineralcorticoid excess, diuretics, and other drugs
  - GIT loss: diarrhea, vomiting, fistulae, stomas
- Redistribution from ECF to ICF:
  - Alkalosis
  - Beta-2 agonists
  - Insulin
  - Periodic paralysis

ICF, intracellular fluid; ECF, extracellular fluid.

CLINICAL FEATURES

Electrolyte abnormalities are commonly seen in children with vomiting, diarrhea, and dehydration. They also occur when patients are otherwise ill and dependent on extraneous fluid therapy to maintain balances. This is particularly seen in pediatric intensive care unit patients who may also have disorders of different organs and altered homeostatic mechanisms. More rarely, electrolyte abnormalities occur due to chronic diseases which may be genetically acquired.

The symptoms of Na^+ imbalance are often nonspecific and can include lethargy, irritability, drowsiness, confusion, convulsions, and coma. There are often associated abnormalities in water balance, with history of vomiting

or diarrhea and clinical features of dehydration, hypo- or hypervolemia.

Abnormalities in K^+ balance may present as an emergency and significant hyperkalemia can cause ventricular arrhythmias and death. Acute severe hypokalemia can cause acute profound weakness, cardiac arrhythmias, ileus, myopathy, and respiratory failure. Characteristic electrocardiogram changes are used in monitoring of severity and treatment. Hypokalemia is associated with appearance of U wave, flattening of T wave, and ST depression. In hyperkalemia, there is appearance of tall T waves, widening of QRS complex, and disappearance of P waves.

Chronic disorders, most commonly the renal tubular diseases, present with chronic weakness, recurrent dehydration and fever, failure to thrive, short stature, rickets, and polyuria. Hypertension may be associated with conditions like Liddle's syndrome and hyperaldosteronism. Ultimately, the diagnosis of the specific etiology is necessary for directing specific treatment, and for predicting long-term outcome.

DIAGNOSTIC TESTS

Patients who are at risk of having electrolyte abnormalities, as discussed above, should have biochemical tests including serum Na^+, K^+, chloride as well as urea and creatinine levels checked at presentation, and regularly thereafter until resolution. Further investigations are directed according to the specific etiology suspected. The definitions are given in table 1.

Useful Biochemical Indices in Investigation of Sodium and Potassium Abnormalities

- Renal sodium excretion can be measured as a spot urinary sodium or the fractional excretion of sodium.

$$\text{FeNa} = \frac{\text{Urinary sodium} \times \text{serum creatinine}}{\text{Urinary creatinine} \times \text{serum sodium}} \times 100$$

  The spot urinary sodium concentration may be unreliable and variable as it would depend on the volume and concentration of the urine sample. The FeNa measurement is more reliable, fairly easy to perform, and requires a random spot urine sample with a simultaneous blood sample. These indices are useful in:
  - The investigation of oliguric acute renal failure, to detect whether the etiology is prerenal or renal. In prerenal acute renal failure due to volume depletion and avid salt and water reabsorbtion, urinary Na^+ is low (<5–10 mg/dL in a spot sample or FeNa <1%). A urine Na^+ >40 mmol/L is strong evidence against extracellular fluid (ECF) volume contraction. In acute tubular necrosis, there is tubular damage with lack of tubular Na^+ reabsorbtion causing high urinary sodium excretion (>20 mg/dL in a spot sample or FeNa >2.5%)
  - In the investigation of hyponatremia, low urinary sodium (<5–10 mg/dL in a spot sample or FeNa <1%) indicates extrarenal sodium losses, whereas high urinary sodium (>20 mg/dL in a spot sample or FeNa >2.5%) indicates renal sodium loss or syndrome of inappropriate antidiuretic hormone.
- Plasma (P) and urine (U) osmolality: the normal threshold for AVP release ranges from 275 to 290 mOsm/kg H_2O. Patients who are in a antidiuretic mode due to volume depletion or increased plasma osmolality, will normally concentrate their urine and will have U:P osmolality ratio greater than 1. Conversely, in the diuretic mode, due to the presence of hypervolemia or hyponatremia, dilute urine will be produced and U:P osmolality will be less than 1. If the serum Na is below 130 mmol/L, or if the serum osmolality is less than 270 mosm/kg H_2O the urine should be maximally dilute. These parameters are useful in the investigation of:
  - Syndrome of inappropriate antidiuretic hormone, where there is inappropriate arginine vasopressin secretion causing intravascular free water excess and dilutional hyponatremia, with inappropriately concentrated urine. U:P osmolality is greater than 1
  - Diabetes insipidus, where the lack of action of arginine vasopressin causes dilute urine to persist even in the presence of hypernatremia and dehydration. U:P ratio is less than 1.
- Urinary potassium levels of >20 mg/dL in the presence of low serum K^+ is an indication of renal K^+ loss. Similarly, a high urine potassium/creatinine ratio >15 mEq/g indicates renal K^+ loss.
- Transtubular potassium gradient (TTKG): in the presence of normal renal function, this assesses the response of the distal tubule and collecting duct to aldosterone which is influenced by serum potassium.

$$\text{TTKG} = \frac{\text{Urinary potassium} \times \text{Serum osmolarity}}{\text{Serum potassium} \times \text{Urinary osmolarity}}$$

  Normal value being 8–9. A high TTKG in the presence of hypokalemia and indicates renal potassium loss. A low TTKG in the presence of hyperkalemia indicates inability of the kidneys to excrete K^+, due to mineralcorticoid deficiency or inacivity.
- Renin and aldosterone levels: raised levels of both renin and aldosterone levels occur in diseases with primary renal Na^+ and water loss, and contribute to the development of hypokalemia (e.g., Bartter's syndrome, RTAs, and pseudohypoaldosteronism). Both these levels are suppressed in Liddle's syndrome. Primary diseases of the adrenals associated with reduced or increased levels of aldosterone will be associated with conversely increased or decreased renin, respectively. The titers of these hormones are affected by body position and stress, therefore, standard

TABLE 1: Standard definitions

Hyponatremia	Na^+ <135 mEq/L
Hypernatremia	Na^+ >145 mEq/L
Hyperkalemia	K^+ >5.5 mEq/L
Hypokalemia	K^+ <3.5 mEq/L

levels are described according to body position in which sample is taken (e.g., on 2-hour supine samples).

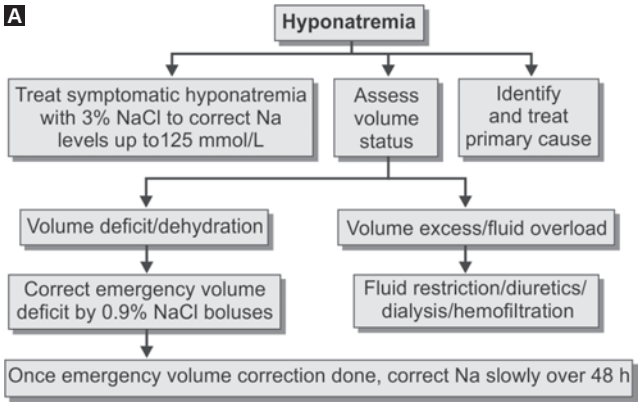
Note: Spurious hyponatremia (due to high serum lipids or proteins) is unusual nowadays due to technical improvements in sodium assay.

MANAGEMENT

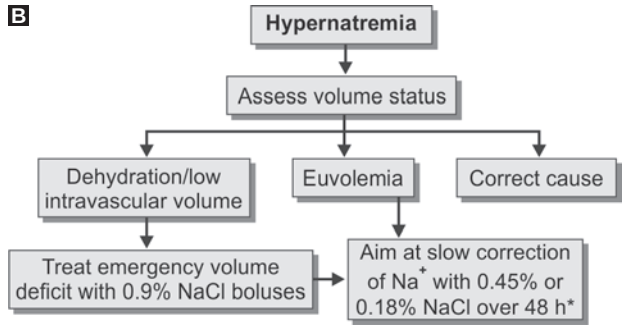
Hyponatremic symptoms are more marked, if the disorder develops acutely, and occur due to fluid shift from ECF to intracellular fluid (ICF) causing brain edema. The rate of correction should equal assessed rate of development. Acute symptomatic hyponatremia is corrected on an emergency basis with hypertonic saline. However, generally, abnormal sodium levels are corrected slowly over 48–72 hours, particularly in conditions of chronic hyponatremia, to prevent rapid reversal of fluid shifts from the brain cells to the ECF which can cause a central nervous system demyelinating disorder known as central pontine myelinosis (Algorithm 1).

ALGORITHM 1

Management of sodium imbalances.
A, Hyponatremia; B, Hypernatremia



The total sodium correction is calculated as: Deficit + assessed ongoing losses, where Deficit (mmol) = (desired Na – present Na) × 0.6 × wt (kg). The change in serum Na should not exceed 0.5 mmol/L/h.



*To calculate decrease in serum Na with 1 liter of infusate: Change in serum Na = (infusate Na^+ – serum Na^+)/total body water (0.6 × wt) + 1.

Note: The change in serum Na^+ should not exceed 0.5 mmol/L/h.

Correction should be limited to 8 mmol/L in the first 24 h and 18 mmol/L in the first 48 h.

Acute hypernatremia causes brain cell shrinkage due to fluid shifts from ICF to ECF compartments, and in severe cases, can cause intracerebral hemorrhage.

Hypernatremia may be associated with severe dehydration and volume depletion which needs emergency correction. However, again further Na^+ correction should be slow to prevent rapid fall in ECF osmolarity which may cause reverse fluid shift into brain cells and cerebral edema.

Sodium abnormalities in particular are often associated with abnormalities in water balance, and the correction of overt hypo- or hypervolemia takes precedence.

Clinical Pearls

- Sodium abnormalities are often associated with anomalies of water balance
- In such cases, restoration of intravascular volume to normal takes precedence.

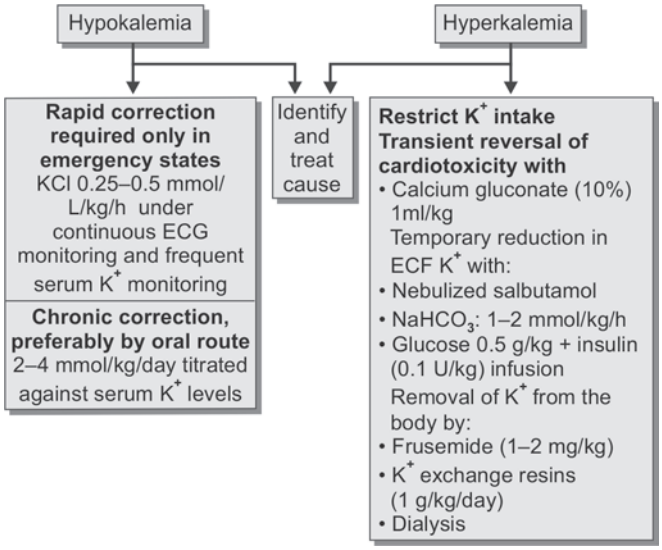
Abnormalities in K^+ balance may need to be treated on an emergency basis, since significant hyperkalemia can cause cardiac arrhythmias and death and severe hypokalemia can cause weakness, muscular paralysis, and respiratory failure. Once the acute stage is corrected, determination of etiology allows planning of a long-term corrective therapy. Details of treatment are given in algorithm 2.

Clinical Pearls

- In hyperkalemia, methods to shift K^+ to intracellular spaces are quick acting and should be instituted first for rapid effect
- Methods to remove K^+ from the body take time but are effective in the long term.

ALGORITHM 2

Management of potassium imbalances



CONCLUSION

Sodium and potassium abnormalities occur in a large number of acute and chronic conditions. The imbalances may be acute and severe and need emergency treatment. Occasionally, the etiology is chronic and requires prolonged specific and supportive treatment with long-term monitoring and follow-up. A systematic clinical and biochemical work-up will usually indicate the cause and guide directed therapy once the acute situation is controlled.

KEY POINTS

- ☞ Sodium and potassium imbalances are common in acutely ill children, and in some renal and endocrine diseases
- ☞ Abnormalities of intravascular volume often coexist with Na^+ imbalances and take precedence in management
- ☞ After emergency management, further correction of Na^+ levels should match the duration of evolution of the abnormality: acutely occurring Na^+ imbalances can be treated rapidly, while chronic imbalances of Na^+ require slow correction to prevent complications
- ☞ Potassium imbalances can present as major emergencies, and need rapid recognition and correction
- ☞ Once the emergency electrolyte imbalances are corrected, a diagnostic work up and specific management of the cause is instituted.

SUGGESTED READINGS

1. Alfonzo AV, Isles C, Geddes C, Deighan C. Potassium disorders—clinical spectrum and emergency management. Resuscitation. 2006;70(1):10-25.
2. Bagga A, Sinha A, Gulati A. Protocols in Pediatric Nephrology. New Delhi: CBS Publishers; 2012. pp. 41-54.
3. Khilnani P. Electrolyte abnormalities in critically ill children. Crit Care Med. 1992;20(2):241-50.
4. Moritz ML, Ayus JC. Disorders of water metabolism in children: hyponatremia and hypernatremia. Pediatr Rev. 2002;23(11):371-80.

CHAPTER 98

Acute Glomerulonephritis

Noopur Singhal, Abhijeet Saha

INTRODUCTION

The term acute glomerulonephritis (AGN) defines a pathological process that may manifest clinically as acute nephritic syndrome, nephrotic syndrome, or rapidly progressive glomerulonephritis (GN). Nephritic syndrome is a clinical syndrome defined by the association of hematuria, proteinuria, and often arterial hypertension and renal failure.

Acute postinfectious glomerulonephritis (APIGN) includes a large proportion of GN resulting from a variety of infectious agents, most common being streptococci. The common infectious agents implicated in the causation of APIGN have been enumerated in box 1. Acute poststreptococcal glomerulonephritis (APSGN) is the prototype of APIGN occurring due to immune complex deposition. Less common diseases include immunoglobulin A (IgA) nephropathy, systemic lupus erythematosus, shunt nephritis, endocarditis-associated GN, and Wegener's granulomatosis. Diagnostic approach has been mentioned in algorithm 1.

In the clinical scenario of a child with edema, hypertension, and oliguria, the initial evaluation must be targeted to differentiate acute nephritis from nephrosis. Table 1 lists important clinical and laboratory criteria to differentiate between these two entities.

ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Acute poststreptococcal glomerulonephritis is a non-suppurative, immunologically mediated complication of group A β-hemolytic streptococcal infection. It continues to remain

Box 1: Etiology of postinfectious glomerulonephritis

Bacteriae

- Gram-positive bacteria (*streptococci*, *staphylococci*, *pneumococci*, *enterococci*, *Listeria monocytogenes*)
- Gram-negative cocci (*meningococcus*, *Neisseria gonorrhoeae*)
- Gram-negative coccobacilli (*hemophilus*)
- Gram-negative bacilli (*Salmonella*, *Klebsiella*, *Serratia*, *Yersinia*, *Proteus*, *Pseudomonas*)
- Other infections (*Legionellosis*, *brucellosis*, *bartonellosis*)

Mycobacteria, Rickettsia, Mycoplasma, Chlamydia and Spirochetes

- Tuberculosis and nontuberculous *mycobacteria*
- Syphilis (*Treponema pallidum*)
- Leptospirosis (*Leptospira interrogans*)
- Rickettsial diseases (*Coxiella burnetii*)
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*

Viruses

DNA viruses

- Hepatitis B
- Varicella zoster
- Epstein-Barr
- Cytomegalovirus
- Parvovirus B19
- Adenovirus

RNA viruses

- HIV
- Coxsackie, Enteric cytopathic human orphan (ECHO) virus
- Hepatitis A, hepatitis C
- Dengue virus
- Mumps and measles
- Hantavirus and rotavirus

Fungi

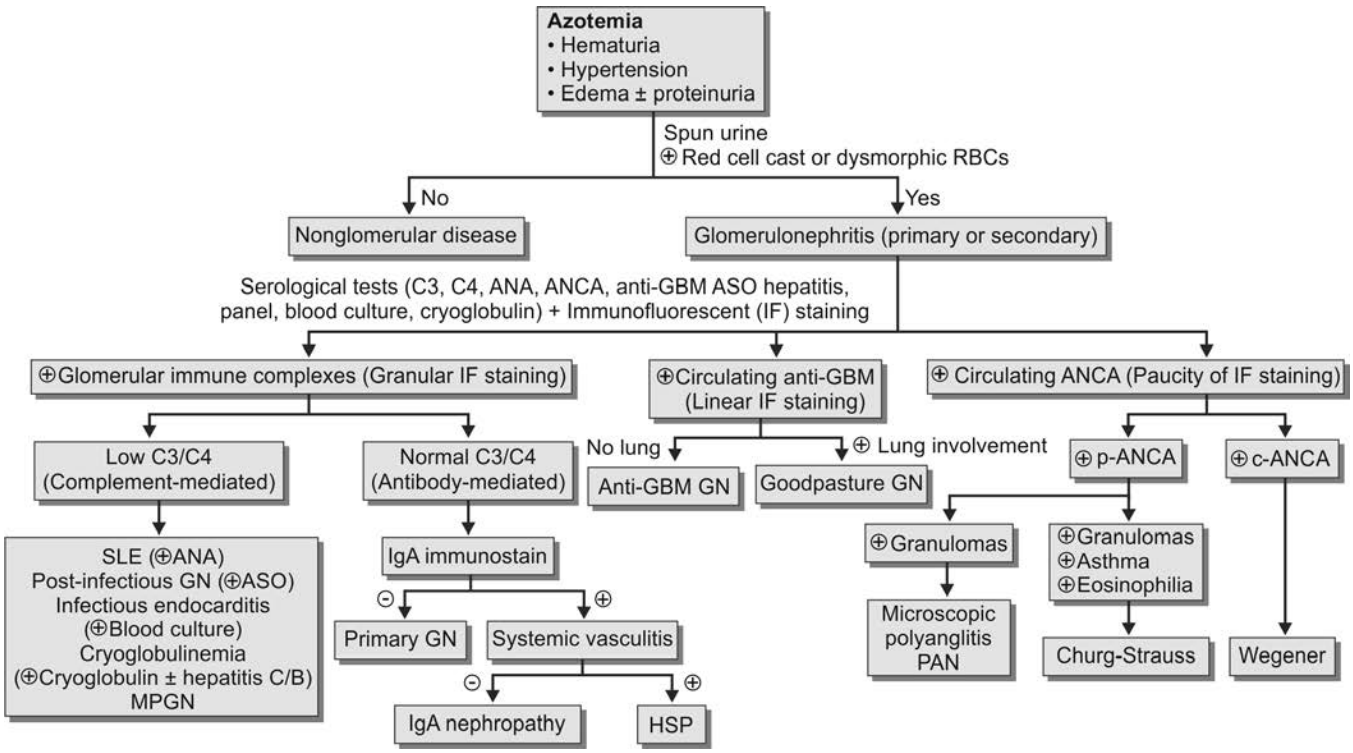
- *Candida albicans*
- *Histoplasma capsulatum*
- *Coccidioides immitis*

Parasitic infestations

- *Plasmodium falciparum, P. malariae*
- *Schistosoma haematobium, S. mansoni*
- *Toxoplasma gondii*
- Filariasis, trichinosis, hydatid disease
- Amebiasis (*Entamoeba histolytica*)

ALGORITHM 1

Algorithm of approach to the patient with acute glomerulonephritis



RBCs, red blood cells; ANA, antinuclear antibody; ANCA, anti neutrophil cytoplasmic antibody; ASO, antistreptolysin-O; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; GBM, glomerular basement memberane; HSP, Henoch-Schonlein purpura; MPGN, membranoproliferative glomerulonephritis; PAN, periarteritis nodosa; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SLE, systemic lupus erythematosus.

TABLE 1: Differences between nephrotic syndrome and nephritic syndrome

	Nephrotic syndrome	Nephritic syndrome
Edema	Gross	Mild to moderate
Hematuria	Absent/minimal	Marked/gross
Hypertension	Absent/minimal	Common
Urine output	Normal/decreased	Decreased
Serum cholesterol	Elevated	Mildly elevated/normal
Proteinuria	Gross	Moderate
Glomerular filtration rate	Normal	Decreased

an important cause of acute renal failure and hospitalization for children in developed and developing nations despite having an excellent spontaneous cure rate.

EPIDEMIOLOGY

Out of the estimated worldwide yearly burden of APSGN of 472,000 cases; approximately 404,000 occur in children (9.3 cases per 100,000 population). The male and female ratio is 2–3:1. The risk of nephritis in epidemics varies from 5% with throat infections to as high as 25% with pyoderma.

Group A streptococci are most commonly typed by their surface M proteins, which are virulence factors. They can also be divided into two groups based on the presence or absence of a lipoproteinase that causes serum to become opaque (serum opacity factor). Each of these two groups contains a characteristic group of M proteins. The opacity factor-positive group contains the "nephritogenic" strains. Nephritogenic strains are further subdivided into those primarily associated with pyoderma (M47, M49, M55, M56, M57, and M 60), and those that most often cause pharyngitis.(M1, M4, M25, and some M12 strains).

Acute poststreptococcal glomerulonephritis is one of the most common causes of acute kidney injury in children of developing countries. Poor hygiene and lack of access to medical care increases the risk in these countries.

PATHOGENESIS

The fundamental pathogenic mechanism of postinfectious GN is believed to be the deposition of immune complexes within the glomerular tufts. Other proposed mechanisms include elicitation of an autoimmune response between streptococcal components and renal components (molecular mimicry); and alteration of a normal renal antigen eliciting autoimmune reactivity.

Much of the early work on the pathogenesis of APSGN focused on the group A-specific streptococcal M proteins but it has now been discounted as the nephritogenic antigen because, in addition to the increasing number of M-serotype strains that are nephritogenic (M serotypes 1, 2, 4, 12, 18, 42, 49, 56, 57, and 60), some M-type strains are non-nephritogenic.

Nephritogenic Streptococcal Antigens

Two possible antigens being currently investigated as the potential cause of PSGN include the nephritis-associated plasmin receptor, identified as glyceraldehyde-3-phosphate dehydrogenase, and a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B that is generated by proteolysis of a zymogen precursor. Both of these fractions are capable of activating the alternate pathway of the complement system.

Glomerular binding and plasmin activation are considered key pathogenic properties of these proteins. When deposited in glomeruli, glyceraldehyde 3-phosphate dehydrogenase, streptococcal cationic proteinase exotoxin B (speB), or zymogen (whether bound by specific antibody or not), can interact with plasmin or plasminogen to cause glomerular damage by degrading the glomerular basement membrane (GBM) through the activation of latent metalloproteinases or collagenases (Fig. 1). The circulating or *in situ* immune complexes can then move across the altered GBM and accumulate as "humps" in the subepithelial space.

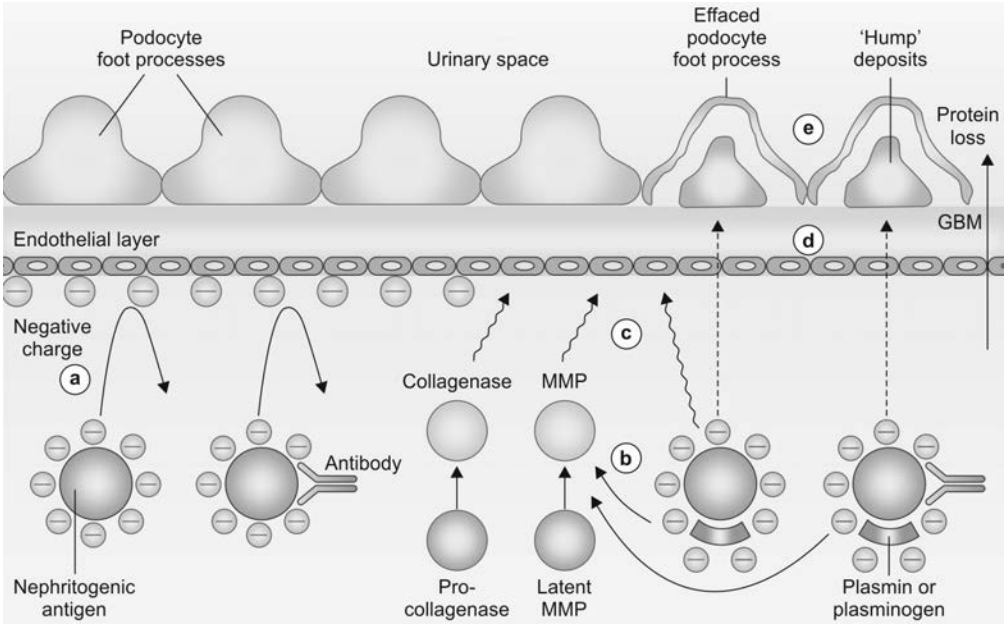
Immune Complex Deposition and Complement Activation

The critical role played by an *in situ* immune reaction resulting from the antibody meeting free antigen deposited in the glomeruli was suspected by Rodriguez-Iturbe. This possibility was emphasized by the difficulty of inducing GN and the near impossibility of inducing subepithelial immune deposits (humps), the prototype lesion in the APSGN, with preformed immune complexes. Large amounts of preformed complexes may produce GN, but this is leukocyte-mediated and the localization of the immune deposits is largely subendothelial.

Complement activation is a central feature in APSGN. The alternate pathway is preferably activated as substantiated by the serum complement profiles (low C3 and normal C4) and immunofluorescence pattern typically comprising of immunoglobulin G (IgG), C3, and C5. These deposits virtually never contain the classical pathway components C1q and C4.

Cellular Immune Mechanisms

Immunocompetent cells like macrophages and T helper cells infiltrate the glomeruli. There is increased circulatory levels of IL-6, IL-8, tumor necrosis factor-α, and monocytic chemotactic protein-1. The infiltrating immune cells play an important role in the development and severity of inflammation.



GBM, glomerular basement membrane; MMP, matrixmetalloproteinase; speB, streptococcal cationic proteinase exotoxin B.

Fig. 1: Possible pathogenic mechanism of post-streptococcal glomerulonephritis. (a) The putative nephritogenic antigens streptococcal cationic proteinase exotoxin B (speB) or zymogen and glyceraldehyde 3-phosphate dehydrogenase are normally repelled in both their free and antibody-bound forms by the negatively charged glomerular basement membrane (GBM); (b) However, these antigens can interact with plasmin or plasminogen to activate procollagenase and latent matrixmetalloproteinase; (c) The active enzymes (and the nephritogenic antigen itself, in the case of speB or zymogen) degrade the GBM, and abolish its negative charge; (d) The nephritogenic antigen and immune complexes can then pass through the damaged GBM and form the characteristic "hump"-like deposits under the podocyte processes; (e) Damage to the GBM also causes effacement of podocyte foot processes, which leads to loss of protein in the urine

Autoimmune Reactivity

Though a number of autoimmune findings have been reported in APSGN, they represent epiphenomena and do not define a specific clinical course of the disease. Anti-IgG antibodies are frequently seen in serum and in glomerular deposits. This autoimmune reactivity may modulate the course of APSGN.

PATHOPHYSIOLOGY

The primary physiological abnormality in children with APSGN is reduction in glomerular filtration rate (GFR) due to infiltration of the GBM by inflammatory cells and reduction in permeability of the basement membrane. The endothelial or mesangial factors released by glomerular injury, over expression of epithelial sodium channel and interstitial inflammatory cells also contribute to sodium and fluid retention by the distal tubule. Intravascular and subsequent interstitial fluid retention leads to hypertension and edema. Significant reductions in GFR cause azotemia, acidosis, hyperkalemia, and hyperphosphatemia. Anemia occurs as a consequence of volume expansion and is usually normocytic normochromic.

CLINICAL PRESENTATION

The classical presentation of APSGN is a triad of abrupt onset of gross hematuria, edema, and hypertension, and is usually, but not always preceded by an episode of group A β-hemolytic streptococcal pharyngitis or pyoderma. The latency between the streptococcal infection and the onset of the clinical syndrome is 7–14 days in sore throat, while it is 2–4 weeks in pyoderma. In some cases, mild pharyngitis may go unnoticed whereas preceding pyoderma can be detected by healed scars.

The median age at presentation is between 6–8 years. The rarity of APSGN in children younger than 2 years is attributed to the low rate of streptococcal pharyngitis in this group and an immature immune (antibody) response.

Three phases of the disease can be identified as the latent, acute, and the recovery phases (Fig. 2). The recovery phase occurs after resolution of fluid overload with diuresis, normalization of blood pressure and resolution of proteinuria and gross hematuria. Urine volume usually increases 4–7 days after hospital admission, and this increase is rapidly followed by resolution of edema and normalization of blood pressure. Microscopic hematuria takes several months to resolve and can persist for 1 year after the acute attack.

Acute poststreptococcal glomerulonephritis can have varying severity, mild cases may just present with microscopic hematuria with mild proteinuria, while those at the other end of the spectrum may have anuria and severe hypertension. Edema is turgid, unlike in nephrotic syndrome where it is flaccid and may increase to the entire body in unrestricted fluid intake. Proteinuria is usually mild and not in the nephrotic range. Massive proteinuria may be found in about 2–4% of cases and its persistence is a risk factor for progression to chronic renal disease.

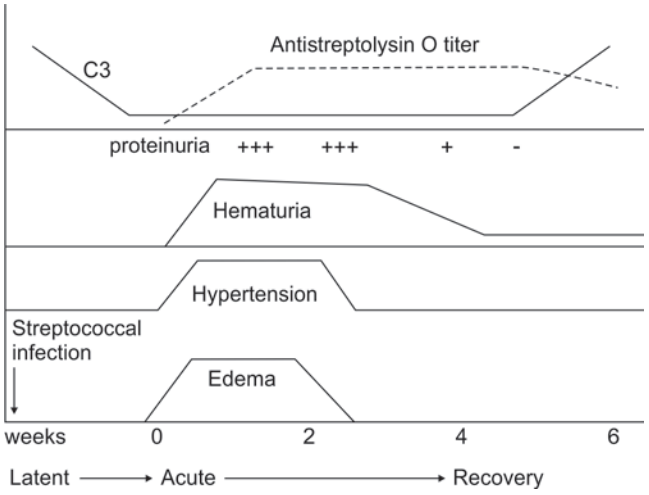


Fig. 2: Summary of the typical clinical course of post-streptococcal acute glomerulonephritis

Clinical Pearls

Indications for hospitalization

- Severe edema
- Hypertension
- Severe azotemia
- Respiratory distress

Clinical evaluation should include a detailed description of hematuria which is an almost universal finding in APSGN. Hematuria is typically described as "coke, "tea", or "smoky" colored in 25–60% of these children. Urine color is uniform throughout the stream and the gross hematuria of AGN is virtually always painless. It is also important to detect any symptoms suggestive of complications especially dyspnea due to fluid overload or headaches, visual disturbances, or alteration in mental status due to hypertension. Any history of rash, arthritis, hepatosplenomegaly, recent weight change, or recent medication exposure should lead to search for alternative causes.

Clinical Pearls

When to suspect rapidly progressive glomerulonephritis?

- Persistent oliguria
- Severe azotemia
- Nephrotic range proteinuria

Hypertension due to sodium and water retention and consequent expansion of extracellular space occurs in up to 80% of children with APSGN. Cerebral complications of hypertension including headache, drowsiness, seizure, mental status, and visual changes occur in 30–35% of the children. Patients may present with clinical and radiologic signs of pulmonary edema. Evidence for congestive heart failure may be found in almost half of these children. Initially,

blood pressure is high, buthypotension occurs in later stages when heart failure and shock supervenes. Other atypical presentations of poststreptococcal GN have been listed in the clinical pearl below.

Rapidly rising azotemia and persistent oliguria should raise a suspicion of rapidly progressive GN.

Clinical Pearls

Atypical presentations of acute poststreptococcal glomerulonephritis

- Subclinical disease
- Seizures
- Acute hypertensive crisis
- Acute pulmonary edema
- Acute kidney injury
- Reversible posterior leukoencephalopathy syndrome
- Autoimmune hemolytic anemia
- Rash similar to Henoch-Schönleinpurpura

INVESTIGATIONS

Urine examination shows acidic pH, dysmorphic red blood cells, red cell casts, granular casts, and neutrophils suggestive of glomerular inflammation. Mild to moderate (1-2+) proteinuria is commonly seen. Blood urea is increased in 60–65% of cases and estimated creatinine clearance is decreased to less than 90 mL/min/1.73 m^2 in 20%. The GFR is often decreased during the acute phase of the disease. A mild degree of normocytic normochromic anemia is also seen due to volume overload. Hypoalbuminemia may be present in those with nephrotic range proteinuria.

Serologic evidence of a recent streptococcal infection should be sought in suspected cases of APSGN because positive streptococcal serology is more sensitive (94.6%) for diagnosis than history of recent infection (75.7%) or positive cultures (24.3%). The most important serological marker is antistreptolysin O (ASO) titer. ASO titers are higher in pharyngitis-associated APSGN whereas cases following pyoderma are more likely to demonstrate elevated anti-deoxyribonuclease (DNase) B titer. Streptozyme test, which includes four antigens (DNase B, streptolysin O, hyaluronidase, and streptokinase) is reported to be positive in 80% cases. Acute reduction in serum C3 level in APSGN with a typical return to normal levels within 6 weeks of onset is of foremost diagnostic importance. A minimal decrease in C4 can occur transiently.

Renal Biopsy Findings

A renal biopsy is not indicated for diagnosis of APSGN but is usually performed when atypical clinical manifestations are present or the resolution is delayed. Conditions which require a renal biopsy in the course of poststreptococcal GN are listed in table 2.

TABLE 2: Indication for renal biopsy

Early stage	Recovery phase
• Short latent period • Severe anuria • Rapid progressive course • Hypertension >2 weeks • Depressed GFR >2 weeks • Normal complement levels • Nonsignificant titers of antistreptococcal antibodies • Extrarenal manifestation	• Depressed GFR >4weeks • Hypocomplementemia >12 weeks • Persistent proteinuria >6 months • Persistent microhematuria >18 months

GFR, glomerular filtration rate.

Light Microscopy

On light microscopy, there is diffuse hypercellularity of endothelial and mesangial cells and infiltration of the glomerular tuft with polymorphonuclear cells with obliteration of the capillary lumina. GBM is normal and there is little or no evidence of tubular or vascular injury (Fig. 3). Rarely, patients with APSGN may have crescent formation in over 50% of glomeruli, leading to the clinical picture of rapidly progressive GN.

Immunofluorescence

Immunofluorescence pattern typically seen during the acute phase of APSGN shows discrete granular deposits of IgG and C3 in the capillary loops and mesangium (Figs 4 and 5). Three patterns of the deposits are described in box 2. The garland pattern is associated with heavy proteinuria and worse long-term prognosis. Absence of immunofluorescence (IF) deposits should prompt search for c-ANCA and p-ANCA antibodies.

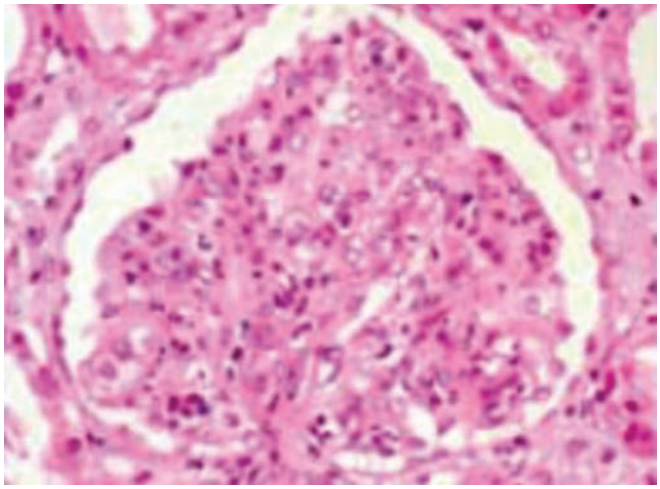


Fig. 3: Acute postinfectious glomerulonephritis. Glomerulus showing cellular proliferation obstructing capillaries and there are abundant polymorphs (hematoxylin and eosin)

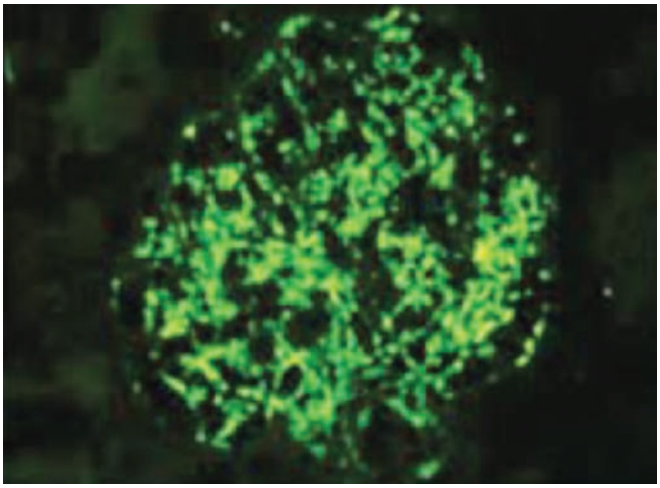


Fig. 4: Acute postinfectious glomerulonephritis. Immunofluorescence for immunoglobulin G showing smaller and spaced parietal granular deposits giving a "starry sky" appearance

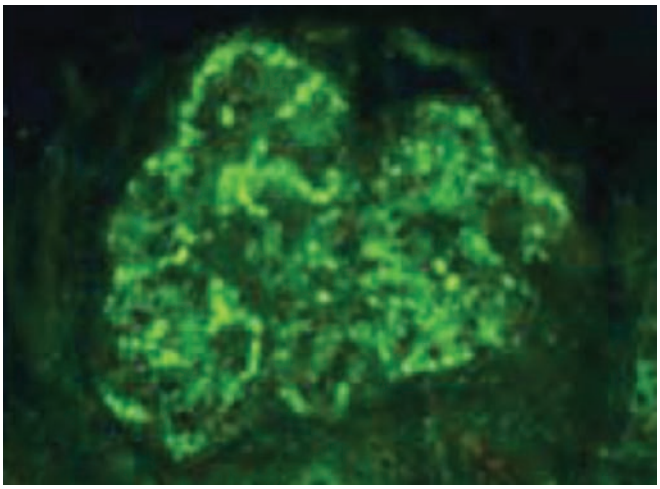


Fig. 5: Acute postinfectious glomerulonephritis. Immunofluorescence for C3 showing extensive granular deposits in the capillary walls giving it a garland appearance

Box 2: Immunofluorescence patterns in acute poststreptococcal glomerulonephritis

- Starry sky appearance (discrete mesangial and basement membrane deposits, usually of complement)
- Mesangial pattern (thick deposits in the mesangium)
- Garland pattern (heavy garland-like deposits in the basement membrane)

Electron Microscopy

The hallmark pathologic finding in electronmicroscopy is subepithelial "hump" that represents subepithelial immune complex deposition. Immunoelectronmicroscopy has facilitated the demonstration of IgG, C3, and SPEB within the subepithelial humps.

DIFFERENTIAL DIAGNOSIS

Acute poststreptococcal glomerulonephritis in majority of the cases is a straightforward diagnosis. The differential diagnosis includes several glomerulonephritides related to chronic infection, infectious glomerulonephritides without an immune-mediated etiology, and other primary and secondary glomerular diseases. It should be differentiated from IgA nephropathy (short latent period), membranoproliferative GN (persistent hypocomplementemia, unresolving nephritic syndrome), lupus nephritis (persistent hypocomplementemia, systemic manifestation), vasculitides (polyarteritis nodosa), Henoch-Schonlein purpura (normal C3), hemolytic uremic syndrome (hemolysis, thrombocytopenia), endocarditis-associated nephritis, and shunt nephritis.

MANAGEMENT

Treatment of APSGN is largely supportive and should be targeted toward the problem of hypertension and fluid overload. Restriction of fluid and sodium intake with adequate caloric intake is recommended. Hypertension is managed with fluid restriction and administration of loop diuretics (furosemide). Two or more antihypertensive drugs may be needed including calcium-channel blockers. Although captopril has been shown to reduce blood pressure and improve GFR in APSGN patients, angiotensin converting enzyme inhibitors should be used with caution due to possible renal failure and hyperkalemia. Severe hypertension may mandate the use of sodium nitroprusside infusion or vasodilators (hydralazine).

Pulmonary edema is uncommon and should be treated with oxygen and loop diuretics. Digitalis is not indicated, because it is ineffective and may result in intoxication. Rarely, overt heart failure and pulmonary edema may complicate the clinical course. Occasionally, acute kidney injury, severe fluid retention unresponsive to diuretics, pulmonary edema, and intractable hyperkalemia necessitate hemodialysis or continuous venovenous hemofiltration. Management of hypertensive emergencies, acute kidney injury, acute pulmonary edema, and severe hyperkalemia must be done as per standard guidelines.

Acute poststreptococcal glomerulonephritis is prevented by early antibiotic treatment, and the spread of nephritis associated streptococcal infection is contained by prophylactic antibiotic treatment to individuals at risk. Early administration of penicillin is reported to prevent or ameliorate the severity of AGN. Single dose of intramuscular benzathine penicillin G or alternatively oral penicillin V for 10 days is recommended. Erythromycin or azithromycin are used in patients allergic to penicillin.

Clinical Pearls

Antibiotic therapy in acute poststreptococcal glomerulonephritis

- Children <27 kg: benzathine penicillin G single dose 600,000 units intramuscularly
- Children >27 kg: benzathinepenicillin G single dose 1.2 million units intramuscularly
- Oral penicillin V 250 mg 2–3 times per day for 10 days

Allergic to penicillin

- Erythromycin 40 mg/kg/day for 10 days
- Azithromycin for 5 days.

PROGNOSIS

Acute poststreptococcal glomerulonephritis is typically characterized by rapid resolution and an excellent prognosis. Clinical improvement begins by 4–6 days with decrease in edema and hypertension and increase in urine output. Gross hematuria clears in first week, but microscopic hematuria may persist for up to 6–12 months. Intermittent mild proteinuria may persist, which is of no significance. Mortality is extremely rare but may result due to severe hyperkalemia or pulmonary edema.

Recurrence of disease is rare since immunity to streptococcal M protein is type-specific and long-lasting and nephritogenic serotypes are limited. Long-term antibiotic prophylaxis is thus not recommended. Certain histologic findings may predict a poor prognosis. Garland pattern on IF has been associated with heavy proteinuria and poor outcome. Extracapillary crescent formation is the most ominous histological finding in PSAGN. Patients with APSGN should be followed up for several years for proteinuria and blood pressure, and if there is persistent proteinuria or a decline in renal functions, a renal biopsy is indicated.

Endocarditis Associated Renal Disease

Microscopic hematuria and proteinuria are indicative of renal lesion in a child with infective endocarditis. Azotemia may develop, but is mild except in cases that develop crescentic GN. Serological findings include reduced C3 and C4. Antibiotic treatment needs to be given for 4–6 weeks.

Shunt Nephritis

Infected ventriculoatrial shunts and rarely ventriculoperitoneal shunts may be complicated by development of postinfectious GN. Common microorganisms causing shunt infections are *S. epidermidis* in about 75% of cases and less frequently *S. aureus*. Renal involvement is indicated by proteinuria (nephrotic range), hematuria, and hypertension. Laboratory findings include reduced C3 and C4 levels with isolation of the organism from blood or shunt fluid cultures. Renal biopsy mostly shows membranoproliferative GN. Treatment of shunt nephritis includes intravenous antibiotics and removal of infected shunt.

Henoch-schönlein Purpura and Immunoglobulin A Nephropathy

Although clinically different, these two entities are histologically identical. A typical case of Henoch-Schonlein purpura presents with gross hematuria, edema, purpura, arthritis, and abdominal pain. IgA nephropathy manifests with recurrent gross hematuria. Renal histology varies from mild mesangial proliferation to crescentic GN. Prominent IgA deposition in the mesangium is characteristically seen.

Hepatitis B and C Virus-related Glomerulonephritis

Renal involvement with hepatitis B is particularly common in East Asian countries and South Africa. The lesions seen commonly with this infection are membranous GN, membranoproliferative GN, and occasionally vasculitis. Hepatitis C virus infections are more commonly associated with proliferative GN.

KEY POINTS

- ☞ Acute poststreptococcal glomerulonephritis is a non-suppurative complication of group A β-hemolytic streptococci
- ☞ Clinical triad of abrupt onset of gross hematuria, edema, and hypertension
- ☞ Acute reduction in serum C3 levels with return to normal levels within 6 weeks is characteristic
- ☞ Treatment is largely supportive
- ☞ Prevention of glomerulonephritis is by early administration of penicillin after streptococcal infection.

SUGGESTED RAEDINGS

1. Ahn SY, Ingulli E. Acute poststreptococcal glomerulonephritis: an update. Curr Opin Pediatr. 2008;20(2):157-62.
2. American Academy of Pediatrics, Committee on infectious diseases. Group A streptococcal infections. In: Redbook, CBS Paediatric series, American Academy of Pediatrics; 2006. pp. 610-20.
3. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005;5(11):685-94.
4. Eison TM, Ault BH, Jones DP, Chesney RW, Wyatt RJ. Poststreptococcal acute glomerulonephritis in children: Clinical features and pathogenesis. PediatrNephrol. 2011;26(2):165-80.
5. Kanjanabuch T, Kittikowit W, Eiam-Oug S. An update on acute postinfectious glomerulonephritis worldwide. Nat Rev Nephrol. 2009;5(5):259-64.
6. Kasahara T, Hayakawa H, Okubo S, Okugawa T, Kabuki N, Tomizawa S, et al. Prognosis acute of poststreptococcal glomerulonephritis (APSGN) is excellent in children, when adequately diagnosed. Pediatr Int. 2001;43(4):364-67.
7. Rodrguez-Iturbe B, Batsford S. Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int. 2007;71(11):1094-104.
8. Rodriguez-Iturbe B, Musser JM. The current state of poststreptococcal glomerulonephritis. J Am Soc Nephrol. 2008;19(10):1855-864.
9. Srivastava RN. Acute glomerulonephritis. Indian J Pediatr. 1999;66:199-205.
10. Vijayakumar M. Acute and crescentic glomerulonephritis. Indian J Pediatr. 2002;69:1071-74.

CHAPTER 99

Approach to Hematuria in Children

Mukta Mantan, Anand S Vasudev

INTRODUCTION

Hematuria is an uncommon condition in childhood. Yet it is frightening to the parents and results in an almost immediate referral to a pediatrician. An approach to this entity will be discussed in this chapter. The incidence of gross hematuria in children is estimated to be around 0.13%. Asymptomatic microscopic hematuria is common in unselected populations of children, with a prevalence that ranges from 0.4 to 4.1%. However, on repeated evaluations, the prevalence of persistent microscopic hematuria is about 0.5% based on the surveys of school going children.

DEFINITION

Hematuria is defined as the presence of five or more red blood cells (RBCs) per high-power field in multiple centrifuged urine examinations (at least 3; 1 week apart). Children are referred for presence of gross hematuria, persistent isolated microscopic hematuria, and microscopic hematuria with clinical symptoms or with proteinuria.

GROSS HEMATURIA

Gross hematuria must be confirmed by microscopic demonstration of RBC. If no RBCs are seen on microscopy, a dipstick test is done to look for other causes of red colored urine. If the dipstick is positive, it is indicative of hemoglobinuria (usually caused by severe intravascular hemolysis) or myoglobinuria from rhabdomyolysis (due to muscle trauma or strenuous exercise). A negative dipstick test would point toward the discoloration due to porphyria, drugs such as rifampicin, pigments in foods, ingestion of beetroot and urates (Box 1).

Glomerular and Extraglomerular Hematuria

bright-red urine, visible clots or crystals with normal-looking eumorphic RBCs (Fig. 1) suggest bleeding from the urinary tract (extraglomerular). Cola-colored urine, presence of RBC casts, and deformed (dysmorphic) RBCs suggest glomerular bleeding. Phase contrast microscope or staining with special stains (Wright stain) is required for detection of dysmorphic RBCs (Fig. 2). Presence of more than 20% dysmorphic RBCs suggests glomerular hematuria (Table 1). The causes of hematuria are listed in table 2.

Box 1: Causes of red colored urine

- Food items
  - Ingestion of beetroot, blackberries, food coloring agents
- Drugs
  - Nitrofurantoin, phenophthalein, pyridium, rifampicin, phenothiazines, sulfasalazine
- Metabolites
  - Homogentisic acid, melanain, methemoglobin, porphyrins, urates, tyrosinosis

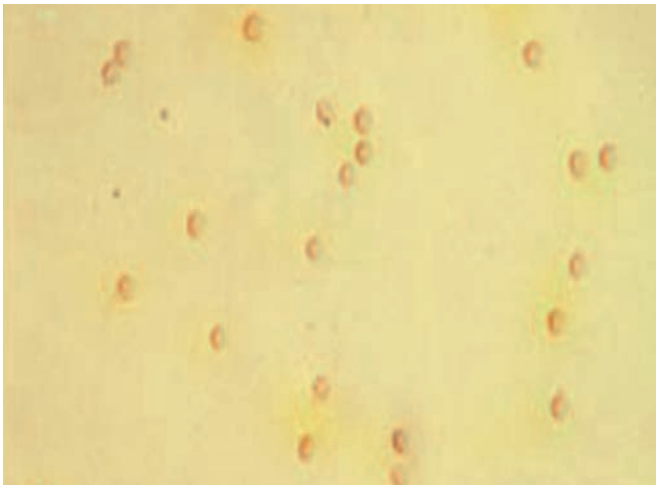


Fig. 1: Urine microscopy showing normal red blood cell

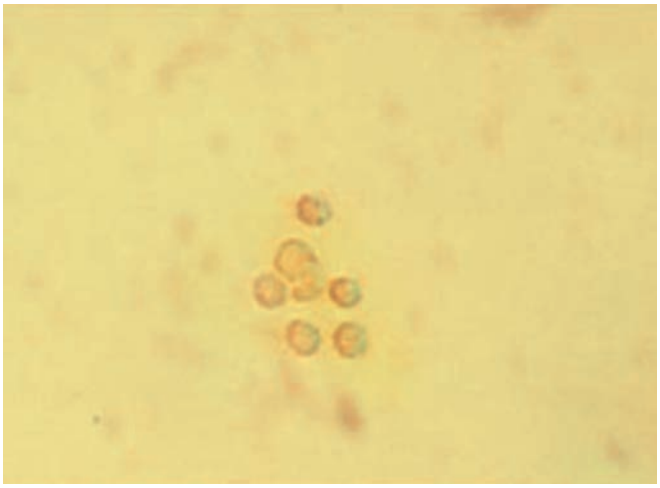


Fig. 2: Urine examination with phase contrast microscopy showing dysmorphic red blood cell

TABLE 1: Differentiation of glomerular and extraglomerular hematuria

Glomerular hematuria	Extraglomerular hematuria
Color red or brown	Bright red usually
Clots absent	Clots present
Proteinuria (2 + or more)	No proteinuria; 1+
Red cell casts	Absent cellular casts
Dysmorphic RBC >20%	Dysmorphic RBC <20%

RBC, red blood cells.

TABLE 2: Causes of hematuria

Glomerular	Extraglomerular
Acute onset • Acute glomerulonephritis (PSGN, others*) • Rapidly progressive glomerulonephritis • Hemolytic uremic syndrome **Chronic glomerulonephritis** • Membranous, membranoproliferative GN, IgA nephropathy • Thin basement membrane disease • Alport syndrome • Focal segmental glomerulosclerosis • Goodpasture's syndrome **Multisystem disease** • SLE, HSP, vasculitis	• Urinary tract infections • Urolithiasis; hypercalciuria • Cystic kidney disease • Vascular malformations (kidney or bladder) • Wilm's tumor • Renal vein thrombosis • Trauma • Bleeding and clotting disorders • Drugs (NSAIDS)

*Typhoid, Pneumococcal pneumonia, meningococcemia, shunt nephritis, bacterial endocarditis, varicella, mumps associated

PSGN, poststreptococcal glomerulonephritis; GN, glomerulonephritis; IgA, immunoglobulin A; SLE, systemic lupus erythematosis; HSP, Henoch–Schönlein purpura; NSAIDS, nonsteroidal anti-inflammatory drugs

TABLE 3: Clinical pointers in history to identify the causes of hematuria

Clinical signs/symptoms	Likely diagnosis
Edema, hypertension	Glomerulonephritis
Dysuria, loin pain, colic	Calculi, hypercalciuria
Joint pains, rash, edema	SLE, HSP, vasculitis
Positive family history, deafness	Alport syndrome, thin basement membrane disease
Renal lump	Polycystic kidney disease, Wilm's tumor, hydronephrosis
Bleeding tendency	Coagulation and bleeding disorders

SLE, systemic lupus erythematosus; HSP, Henoch-Schonlein purpura

History and Physical Examination

Some clinical pointers in history and examinations may indicate the cause for hematuria (Table 3).

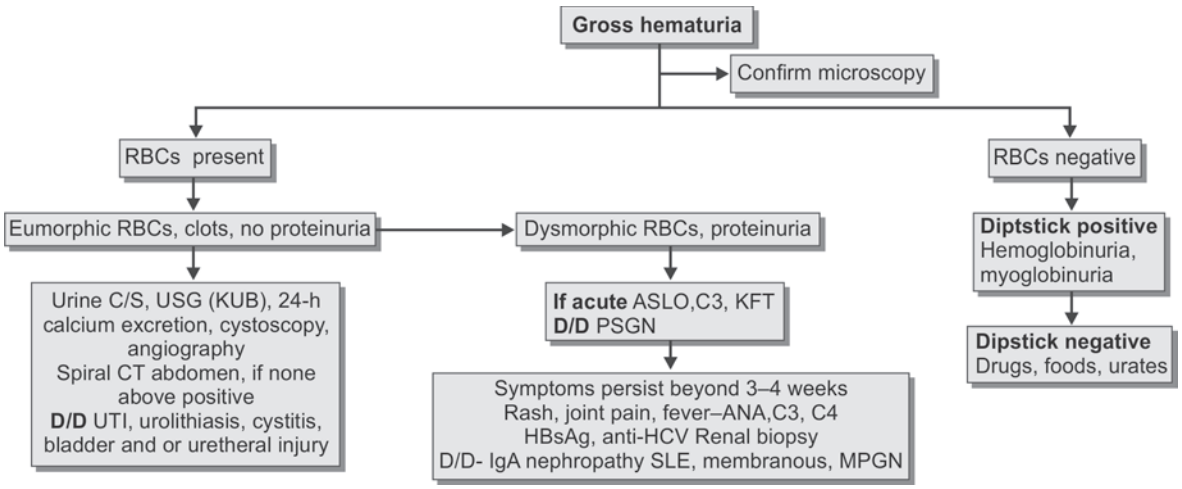
Investigations

An episode of gross hematuria needs evaluation. After confirming hematuria, algorithm 1 can be followed. If the onset is acute and proteinuria is present, the likelihood of an episode of postinfective glomerulonephritis (PIGN) is high. The relevant investigations like anti-streptolysin (ASLO) titers, complement C3 levels and kidney function tests (KFT) should be done. An elevated ASLO (>200 IU/L), low C3 levels with normal or deranged KFT are confirmative of poststreptococcal glomerulonephritis (PSGN). If the history is of prolonged (3–4 weeks) duration, other causes like immunoglobulin A (IgA) nephropathy, membranous or membranoproliferative disease are more likely. Patients with IgA nephropathy are likely to have recurrent episodes of gross hematuria, especially with episodes of upper respiratory tract infections. Presence of fever, joint pains, photosensitive rash points toward a diagnosis of systemic lupus erythematosus. Most of these conditions can be identified on a renal biopsy specimen which should include light microscopy, immunofluorescence, and electron microscopy (if available). Serological tests that help in identification of the underlying cause are hepatitis B surface antigen (HBsAg) and antihepatitis C virus (HCV) for related nephropathy [membranous and membranoproliferative glomerulonephritis (MPGN)]. Antinuclear antibodies (ANA) and anti-dsDNA for lupus nephritis; antineutrophilic cytoplasmic antibodies (P-ANCA and C-ANCA; both these are immunofluorescence based tests) for identification of vasculitis (microscopic polyangiitis, Wegener's and Churg Strauss disease). Identification of ANCA can also be done by enzyme-linked immunosorbent assay (ELISA) based tests (antimyeloperoxidase-anti-MPO corresponding to P-ANCA; antiproteinase-3-antiPR3 corresponding to C-ANCA) which are simpler and yield faster results.

Presence of extraglomerular hematuria points towards local causes, polycystic kidneys, hydronephrosis, urolithiasis, and hypercalciuria. Vascular abnormalities of urinary bladder can also cause hematuria rarely. An ultrasound kidney, ureter,

ALGORITHM 1

Approach to gross hematuria



ANA, antinuclear antibodies; ANCA, antineutrophilic cytoplasmic antibodies; ASLO, antistreptolysin; HBsAg, hepatitis B surface antigen; IgA, immunoglobulin A; KUB, kidney ureter bladder; KFT, kidney function tests; MPGN, membranoproliferative glomerulonephritis; PSGN, poststreptococcal glomerulonephritis; RBC, red blood cell; UTI, urinary tract infection; C/S, culture sensitivity; USG, ultrasonography; CT, computed tomography; D/D, differential diagnosis; HCV, Hepatitis-C virus; SLE, systemic lupus erythematosus.

bladder (KUB) would identify any structural abnormalities and/or, stones in kidney. Ureteric stones are usually not identified with ultrasound and require a radiograph of KUB region. If calculi are identified, a complete urinary biochemistry needs to be done (24-h urinary excretion of calcium, oxalates and urates). If there is a difficulty in collecting 24 hours sample spot, urine sample can be used for determining urinary calcium/creatinine ratio and oxalate/creatinine ratio. Hypercalciuria is defined as urine calcium to creatinine ratio greater than 0.2 (under 6 months of age: >0.8; 6–12 months: >0.6) or a 24-hour calcium excretion exceeding 4 mg/kg/day. Referral to a pediatric surgeon/urologist will be required when clinical evaluation and work up indicates a structural urogenital abnormality, an obstructing calculus or a tumor. The most common malignant renal tumor in childhood is Wilm's tumor and is associated with a palpable abdominal mass and hematuria in most patients. Other primary urinary tract tumors, e.g., hemangiomas, rhabdomyosarcomas, lymphomas resulting in hematuria are rare. Cystoscopy to identify the source of bleeding is best performed during active bleeding.

Clinical Pearl

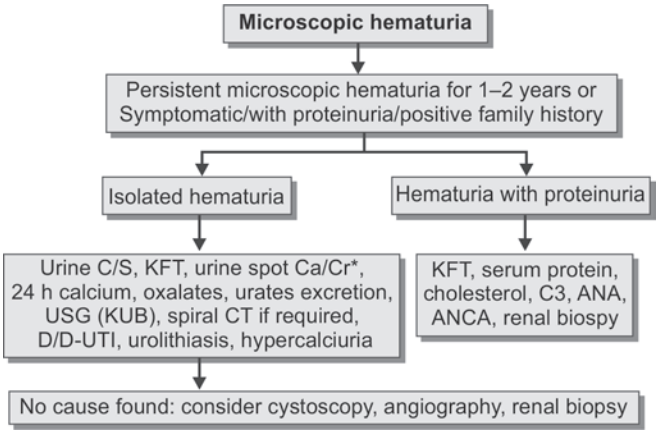
- Neither visual description nor the dipstick alone is sufficient to diagnose gross hematuria; urine microscopy is required.

MICROSCOPIC HEMATURIA

Isolated microscopic hematuria is benign on most occasions. However, it needs to be evaluated if it is symptomatic, i.e., associated with edema, hypertension, rash, fever, joint pains or deranged KFT. Also, persistent microscopic hematuria (more than 1–2 years duration) needs an evaluation. The approach for evaluation is given in algorithm 2. If the hematuria is associated with proteinuria, chronic glomerulonephritis is the chief suspect, hence investigations as suggested for gross hematuria should be performed (C3, ANA, ANCA, renal biopsy). Other causes of asymptomatic isolated microscopic hematuria are benign familial hematuria, IgA nephropathy, MPGN, Alport syndrome. If the hematuria is nonglomerular, investigations should be done to identify hypercalciuria and urolithiasis. Invasive investigations, like cystoscopy and angiography, would be required if no cause is found on other investigations.

ALGORITHM 2

Approach to microscopic hematuria



ANA, antinuclear antibodies; ANCA, antineutrophilic cytoplasmic antibodies; KFT, kidney function tests; KUB, kidney ureter bladder; UTI, urinary tract infection; USG, ultrasonography; CT, computed tomography; D/D, differential diagnosis; C/S, culture sensitivity.

*Urine spot calcium/creatinine ratio (>0.2 mg/mg abnormal)

Indications for Renal Biopsy

Glomerular hematuria persisting for more than 4 weeks and without features of PSGN merits a renal biopsy. Also, decreased complement levels beyond 3 months indicate a need for renal biopsy to rule out other causes like IgA nephropathy, membranous or MPGN nephropathy. Patients with deranged renal functions (urea and creatinine) and/or presence of proteinuria also need a renal biopsy to detect the presence of chronic glomerulonephritis. Patients with rapid worsening of renal functions presenting like RPGN should have an early biopsy to detect crescentic glomerulonephritis. Presence of ANA, HBsAg, anti-HCV or ANCA positivity is also an indication for renal biopsy.

MANAGEMENT

The definitive management of hematuria is based on the underlying etiology. Briefly the management of the two most common causes of hematuria, i.e., postinfective glomerulonephritis and idiopathic hypercalciuria are discussed below.

Postinfective Glomerulonephritis

The investigations useful in confirming the diagnosis are a urinalysis, complete blood count, antistreptolysin O (ASLO) titers, blood urea, serum creatinine, complement C3 levels. Most patients with PSGN would have elevated ASLO titers (>200 IU/L); low complement levels (<60 mg/dL) and mildly deranged KFT. Urinalysis always shows glomerular hematuria, presence of RBC casts, and leukocyturia. Proteinuria is usually less than 2+. If these tests are negative and there is resolution of symptoms, a presumptive diagnosis of postinfectious glomerulonephritis can be made. Most patients with an acute PIGN would resolve of their hematuria and edema within 10–14 days. The kidney functions also normalize by this time. Persistence of gross hematuria or proteinuria beyond 4 weeks is unusual and often becomes an indication for kidney biopsy in these patients. Hypertension and fluid overload can be managed by use of diuretics like furosemide in doses of 2–4 mg/kg/day in two or three divided doses. If hypertension persists, it can be controlled with calcium channel blockers or use of β-blockers. Amlodipine in doses of 0.2–0.5 mg/kg/day; atenolol in doses of 0.5–2 mg/kg/day are often sufficient in controlling elevated blood pressure. Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers postinfective glomerulonephritis is not recommended as most patients with acute glomerulonephritis have a transient reduction in their glomerular filtration rate. The duration for use of diuretics and antihypertensives is usually less than 2 weeks. Patients with severe fluid overload and acute renal failure may require renal replacement therapy in the form of peritoneal or hemodialysis. This occurs in less than 10% patients of acute glomerulonephritis.

Patients having persistence of gross hematuria or heavy proteinuria beyond 4 weeks duration need a renal biopsy to determine the underlying cause. Presence of rapidly progressive renal failure is an urgent indication for biopsy. Persistence of hypocomplementenemia (beyond 12 weeks) or absence of is another indication.

Immunoglobulin A Nephropathy

The condition is typically associated with gross hematuria but at times, may present with microscopic hematuria.

The diagnosis of IgA nephropathy is confirmed on renal biopsy that shows predominantly immunoglobulin IgA deposits in the mesangium on immunofluorescence. While ACE inhibitors are given to all patients with IgA nephropathy, immunosuppressants like steroids, azathioprine, or mycophenolate mofetil may be required in patients having nephrotic range proteinuria.

Alport Syndrome

Alport syndrome should be suspected in patients (especially males) with persistent glomerular microscopic hematuria once structural abnormalities of the kidney and urinary tract have been ruled out. A positive family history of hematuria or renal failure may be a pointer towards the diagnosis. Light microscopy may show variable thickening of the glomerular basement membrane. Initially the changes are thinning of the membrane that later change to basket weaving and lamellation of the glomerular basement membrane. These changes are most marked on electron microscopy and may not be well marked in pediatric patients as compared to adults. Early treatment with ACE inhibitors has been shown to slow down the progression to end stage renal disease in children.

Idiopathic Hypercalciuria

It is found to be a common cause of gross as well as microscopic hematuria. A family history of renal calculi may be present. A spot urinary calcium to creatinine ratio of more than 0.2 or a 24-hour urinary calcium excretion of over 4 mg/kg is abnormal. The condition is managed with a high fluid intake, low salt and protein intake, and use of hydrochlorthiazide. This will reduce urinary calcium excretion, stop hematuria, and prevent stone formation. Do not restrict dietary calcium intake.

Benign Familial Hematuria

It is characterized by persistent, isolated microscopic hematuria. Other family members may also have microscopic hematuria. Glomerular capillary basement membrane thinning is seen on electron microscopy. Though the condition is usually benign but these children need a long-term follow-up.

CONCLUSION

Hematuria is an uncommon condition in childhood. An episode of gross hematuria and symptomatic microscopic hematuria should always be evaluated. Asymptomatic microscopic hematuria needs evaluation only if it persists on repeated microscopic examination of urine (beyond 1 year). An effort should be made to identify the underlying cause of hematuria. Treatment of the cause results in resolution of hematuria on most occasions.

Clinical Pearls

Hematuria and proteinuria

- The presence of both hematuria and proteinuria is sinister
- Renal biopsy should be considered whenever glomerular or tubulointerstitial lesions are suspected.

What to tell the parents?

- For children with only microscopic hematuria, reassurance is sufficient. They should, however, be instructed to notify as and when gross hematuria occurs. These children should have an annual urine examination to detect any proteinuria, a much more sinister marker of glomerular disease.

SUGGESTED READINGS

1. Crompton CH, Ward PB, Hewitt IK. The use of urinary red cell morphology to detect the source of hematuria in children. Clinical Nephrology. 1993;39:44-47.
2. Diven SC, Travis LB. A practical primary care approach to hematuria in children. Pediatr Nephrol. 2000;14:65-72.
3. Feld LG, Waz WR, Perez LM, Joseph DB. Hematuria: An integrated medical and surgical approach. Pediatr Clin North Am. 1997;44:1191-1210.
4. Kashton CE. Familial hematuria. Pediatr Nephrol. 2009;24:1951-8.
5. Kashton CE. Familial hematuria: What we know and what we dont. Pediatr Nephrol. 2005;20:1027-35.
6. Stapleton FB. Hematuria associated with hypercalciuria and hyperuricosuria: a practical approach. Pediatr Nephrol. 1994;8:756-61.
7. Vehaskari VM. Asymptomatic hematuria-A cause for concern? Pediatr Nephrol. 1989;3:240-41.
8. Wood EG. Asymptomatic hematuria in childhood: A practical approach to evaluation. Indian J Pediatr. 1999;66:207-14.

CHAPTER 100

Approach to Urinary Tract Infection

Pankaj V Deshpande

INTRODUCTION

Urinary tract infections (UTIs) in children generate the strongest emotions across the pediatric field! It has evoked a lot of fear in parents as well as health carers to the extent that each episode is viewed as a disaster for the kidneys! There has been literature *ad nauseum* about UTIs in children and if you consider this to be another of those articles, (I wouldn't blame you!) I am hoping that you will be slightly wrong as I take you along to look at the practical aspect of approaching a child with UTI and look at it with the same care as with other illnesses rather than dread!

In the first year of life, both boys and girls have the same rate of developing a UTI (certainly in the first 6 months). Thereafter, the incidence in girls is higher than boys.

DEFINITION

Urinary tract infection in children is based on the presence of a positive urine culture in a symptomatic child. There are several parts to this statement. Firstly, the child has to be symptomatic, either in the form of urinary symptoms or have a fever without an identifiable source. Secondly, urine culture being positive would vary according to the method of collection of urine (clean catch, catheter, suprapubic, etc.).

As you will realize, the common test used for diagnosing UTI is not included in the pure definition of UTI. Pyuria (presence of leukocytes in the urine) is only an indicator of inflammation and not always the sign of UTI in children.

CLINICAL FEATURES: (WHEN TO SUSPECT)

The first major task is to be aware of UTIs in children but also that only appropriate tests done at the appropriate times will help you in diagnosing but not over or underdiagnosing UTIs! Unfortunately, both are common!

In infants and children up to 2 years of age, the symptoms may be subtle. Fever without a focus is an important feature to be aware of! Let us be clear that this means that on clinical examination, you cannot identify a source of the fever. All of us are pretty good clinicians and hence, let us use our clinical skills well! There is no point in sending tests in a child with fever and a severe cough or cold! You have identified a cause of fever and doing tests at this stage will only serve to confuse you!

Apart from this, if the infant is obviously crying persistently (not an occasional episode in 2 days) while voiding, has turbid/discolored urine or has a poor stream of urine (in a boy), UTI should be thought of. Persistent jaundice in a neonate beyond 2 weeks of age is an examination question more than a practical reality!

In older children, the symptoms are more likely to be related to the urinary tract as they will be able to communicate their ailment better. Presence of frequency of voiding, dysuria (pain while voiding), urgency with daytime wetting may be seen more commonly here. They may also have fever, loin pain, vomiting and in some cases, may actually have diarrhea as the presenting symptom. Fever without focus should also prompt a thought about UTI though it will be less common than in infants.

Clinical Pearl

Urine test for urinary tract infection should be done only in symptomatic children

- Fever without focus
- Urinary symptoms, especially in older child.

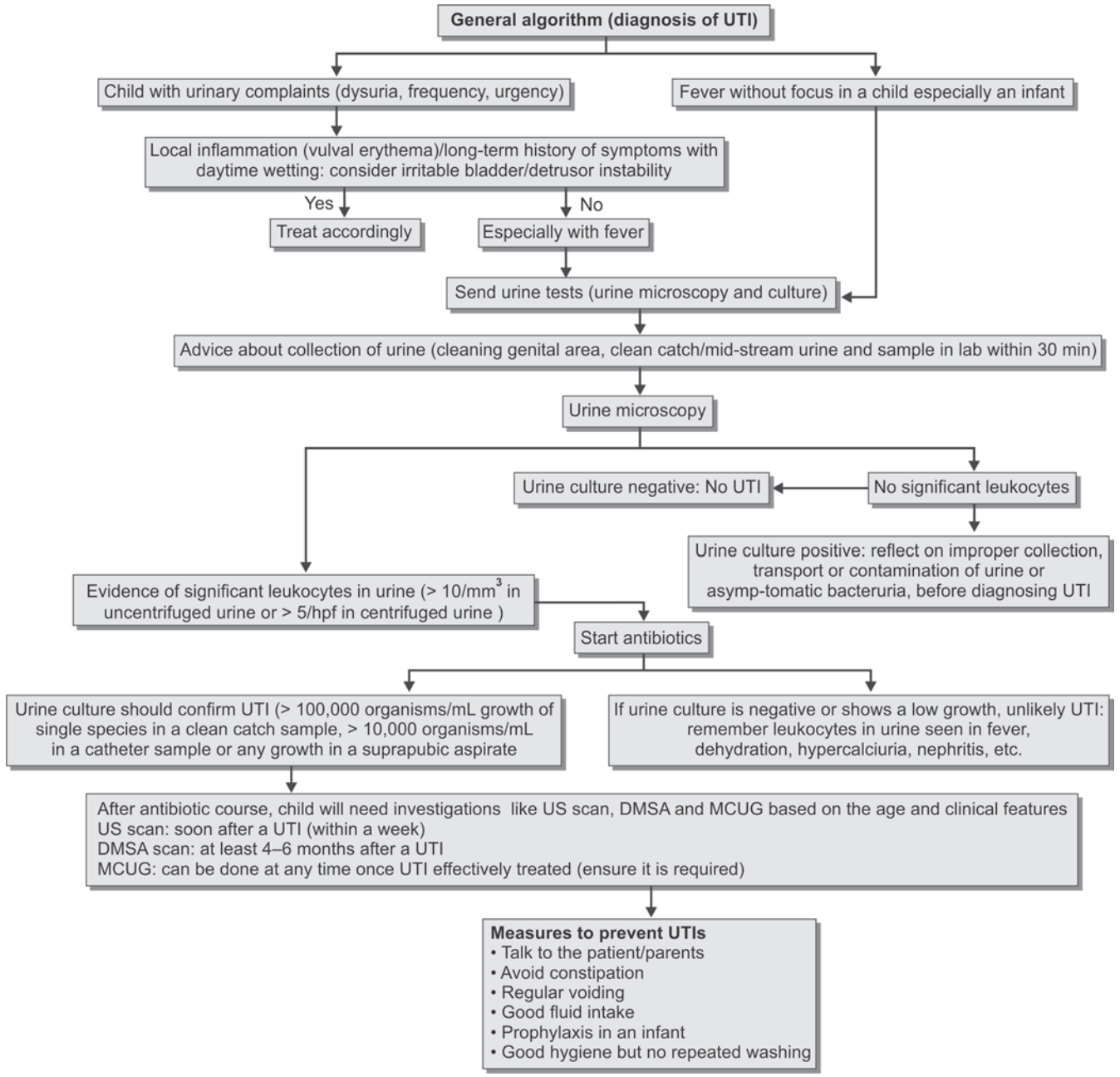
DIAGNOSIS

This aspect of UTIs always raises a hornet's nest and strong emotions! I am not going to quote all literature about this aspect but let us get our basic concepts right before embarking on other thought provoking aspects of diagnosis (Algorithm 1).

As explained above, once a UTI is suspected, urine tests will be required to diagnose or rule out a UTI. Those who have sat

ALGORITHM 1

Algorithm for diagnosis and management of UTI



UTI,urinary tract infection; US, ultrasound; DMSA, dimercaptosuccinic acid; MCUG, micturating cystourethrogram.

patiently beside their child (boy or girl) waiting for him/her to pee (void) will realize the eureka moment when the child pees (voids)! The two tests that are used commonly are a routine examination of urine with microscopy and a urine culture.

Unfortunately, there is no advice given to the parents in most places which causes a lot of heartburn amongst doctors regarding results as they cause a lot of confusion! Sample collection is crucial to the diagnosis of UTI.

For a clean catch/mid-stream urine sample, the genital area is cleaned with normal soap and water and dried. In an older child, a mid stream sample can be attempted but in an infant, a clean catch sample is good enough. This implies that the urine is collected straight into the container and not on a plastic sheet, *"dabba"* or cotton! Once collected it needs to be transported to the microbiology lab immediately and plated within 30–60 minutes. If a delay is anticipated, the sample

should be stored in the refrigerator at 4°C (to a maximum of 24 h). This implies that the urine sample will not be left on the table for 2 hours before being given in the lab. This is because it will allow the growth of contaminant organisms.

If the urine is collected appropriately as described above, a pure growth of more than 100,000 organisms/mL is considered as significant and positive. Recent literature would even suggest that a count of 50,000 may also be significant. However, lower counts are more likely to represent contamination and efforts should be made to collect the urine appropriately, unless the child is completely asymptomatic.

Clinical Pearl

- Advice regarding collection of urine (cleaning, clean catch, and appropriate transport).

If the urine is collected by using a urinary catheter, the cleaning should be adhered to and strict asepsis maintained or you may be the cause of the child's subsequent UTI! If this is done, a colony count of more than 10,000 organisms/mL will be considered significant and positive.

Suprapubic aspiration of urine (using a syringe and needle to aspirate urine directly from the bladder) is possible in young children as the bladder is an abdominal organ till 5 years of age. In this case, the trick lies in knowing when to do the aspiration. If one waits till about half to one hour after the last void, the chances of obtaining urine increase. In this case, any growth of organisms is considered significant and implies a UTI.

It is important to note that bag urine samples have a high contamination rate and are not recommended for urine collection in children. In any case, bag urine is often collected in an inappropriate manner (as the child needs to be upright before collection and the bag removed soon after voiding) and hence, should not be used in children.

Clinical Pearl

- Method of urine collection important to determine significant colony count. Bag urine not recommended.

Microscopy of the urine may reveal the presence of leukocytes. There is ample literature about what constitutes significant pyuria, but it is very important to note that leukocytes may be present in the urine for varied other reasons and do not always imply a UTI. They may be seen in any fever, dehydration, hypercalciuria, urolithiasis, inflammatory conditions like interstitial nephritis, glomerulonephritis and in fact, in any inflammatory condition in the body (even a severe respiratory infection). For the purpose of diagnosing UTI, presence of more than 5 leukocytes/hpf in fresh centrifuged sample or more than 10 leukocytes/mm^3 in an uncentrifuged sample is considered significant. Presence of a positive urine culture in the absence of leukocytes in the urine, especially in an older child, should be a cue for a thoughtful consideration about whether it is really a UTI. Though, leukocyturia is considered to have less than an ideal role in predicting UTI, we should realize that more than only a positive urine culture may not indicate a UTI. Here, the symptoms of a child play an important role. Positive cultures may be due to many reasons, the chief being improper collection and contamination and no test is 100% accurate!

Clinical Pearl

- Presence of significant number of leukocytes in urine can be due to many reasons, urinary tract infection (UTI) being one of them. Unless associated with symptoms and a positive urine culture, it does not represent a UTI.

Urine dipstick can be used as a better way to screen for UTI. Presence of leukocytes is detected by the presence of leukocyte esterase and the conversion of nitrate to nitrite is detected by the nitrite test. When both are positive, the predictive value for a UTI is very high (UTI very likely). It should be remembered that false positives for both leukocytes and nitrites can occur (especially in exposed sticks, medications, etc.).

Dipslide has been used to plate the urine immediately after it is collected with good results.

DIFFERENTIAL DIAGNOSIS

I think it is extremely important to realize that every "positive" urine test is not a UTI. As explained above, urine routine showing "significant" number of leukocytes when the child is asymptomatic, carries no meaning in the general population of children! Similarly, one of the biggest problems with a positive urine culture is contamination as the collection is not ideal in children and several authors have addressed this issue suggesting that a fair number of children/adults receive antibiotic therapy when they do not have a UTI. The most important message is that in the absence of symptoms suggesting UTIs, urine tests are not required and do not indicate a UTI!

Similarly, there are several conditions in children that mimic a UTI and unfortunately all these children keep on receiving antibiotics for suspected UTIs. I will mention a couple of them. One of the common causes of dysuria, frequency, and urgency in girls is vulval erythema. Remember, this is not a bacterial or fungal infection. They will present with exactly the same symptoms as a UTI and unless local examination is done properly, they will all have urine tests done. Often the urine tests are abnormal as they reflect local inflammation rather than a UTI and they get treated with antibiotics and have many unnecessary tests done! It is an extremely common condition in outpatient department (OPD) practice, more so in the tropical countries and the common causes of worsening this condition are repeated washing of the genital area and use of antifungal creams. These children do not have a UTI and do not need antibiotics. A similar condition would be vulvovaginitis secondary to an infective etiology.

Another condition that gets treated with multiple courses of antibiotics is detrusor instability in children that presents with

frequency, urgency, and dysuria. They also will have daytime wetting, the information usually not being volunteered. Again, stimulant drinks worsen this condition and no amount of antibiotic therapy will alleviate the symptoms.

Another "mimic" of a different category is a positive tests for urine routine and/or urine culture when the child is asymptomatic. Assuming the urine is collected in an ideal manner, this indicates asymptomatic bacteruria and needs no treatment!

When interpreting a urine test, all the above factors need to be borne in mind.

Clinical Pearl

- Remember urinary tract infection mimics like vulval redness, detrusor instability, and asymptomatic bacteruria.

COMMON ORGANISMS

Briefly, gram-negative organisms usually cause UTIs. They include *E. coli, Klebsiella*, *Proteus* and in some cases, *Pseudomonas*. *Enterococci* may be seen in infants and some older children. UTIs due to gram-positive cocci, like *Staphylococcus*, should raise suspicion of obstructive pathology in the urinary tract. Atypical infections with fungi-like *Candida* are also seen especially in children exposed to many antibiotics.

TREATMENT

Once a suspicion of UTI has been confirmed on the urine tests, an antibiotic course has to be started. Remember, urine culture reports become available after 24–48 hours and hence, antibiotics have to be started based on local practice. The table below suggests the antibiotics that can be used (Algorithm 1).

A single antibiotic is adequate to clear a UTI. Table 1 provides the options available . Following are the indications for parenteral antibiotics, options of which are described in table 2:

- Inability to tolerate oral antibiotics
- Persistent vomiting
- Sick looking/"toxic" child
- Very young infants (less than 3 months of age) with high grade fever.

In case of an "office" UTI (OPD treatment), antibiotic course of 7–10 days is sufficient. In children needing parenteral antibiotics, a total duration of 14 days would be required. However, once the fever and symptoms settle in 48–72 hours, the antibiotic can be changed to an appropriate oral antibiotic.

There is no need to repeat the urine culture after the treatment is complete. Urine culture may need to be done again only if there is no symptomatic improvement suggesting that UTI persists.

One of the common queries that crop up is regarding the antibiotic sensitivity pattern. It usually becomes available after about 48–72 hours of starting therapy. Unless the child has not responded in terms of symptoms, there is usually no need to change antibiotics. *In vitro* and *in vivo* sensitivities are quite different and an antibiotic that is perceived as resistant often works well in eliminating a UTI.

TABLE 1: Oral antibiotics

Drugs	Dose
Cefixime	10 mg/kg/day in 2 doses
Co-amoxiclav	35 mg of amoxicillin, in 2 doses
Ciprofloxacin	10–20 mg/kg/day in 2 doses
Ofloxacin	15–20 mg/kg/day in 2 doses
Cephalexin	50 mg/kg/day in 3 doses

TABLE 2: Intravenous antibiotics

Drugs	Dose
Ceftriaxone	75–100 mg/kg/day in 1–2 doses
Amikacin	10–15 mg/kg single dose
Gentamicin	5–6 mg/kg/day single dose
Co-amoxiclav	35 mg/kg/day of amoxicillin in 2 doses

Other/Nonpharmacologic Therapy

Often the most forgotten part! One needs to make an effort to try and decipher the reason for developing the UTI. This not mean jumping to radiological investigations, but talking to the child and parents! Local factors, especially bladder bowel dysfunction is a major risk factor for UTI. Addressing constipation, voiding regularly, ensuring an adequate fluid intake, and keeping the postvoid residue to a minimum are some factors that go a long way in preventing UTIs. Using a cotton underwear and clean hygienic practice should also be advised.

Clinical Pearl

- Do not forget to talk to the child/parent regarding constipation, regular voiding, and adequate fluid intake.

FOLLOW UP AND SUBSEQUENT CARE

Once the antibiotic course is completed, one of the dilemmas is about prophylaxis, especially in view of recent literature. The recommendation here is that prophylaxis is advocated for all infants who have a UTI till all radiological investigations are complete or till 1 year of age. For older children, the role of prophylaxis looks less clear and if used, should be till all investigations are complete or factors that are believed to be a risk factor for recurrent UTIs are addressed (e.g., constipation). There certainly seems no role for long-term prophylaxis for years together. The commonly used prophylactic agents are:

- Co-trimoxazole (to give trimethoprim in the dose of 1–2 mg/kg) once a day
- Nitrofurantoin 1 mg/kg once a day
- Cephalexin 15 mg/kg once a day.

The ideal prophylactic agent should not change the normal periurethral flora. Hence, co-trimoxazole and nitrofurantoin are better agents than cephalexin. There is no need to rotate prophylactic agents. If the urine culture shows resistance to the preventive agent, there is usually no need to change the agent after the treatment of the UTI.

There is no role for checking urine regularly (once a week/fortnight/month) for reasons made very clear above. If the child has symptoms, he/she should have urine tests done.

Clinical Pearl

- Regular urine test to detect urinary tract infections has no role. Do urine test only in symptomatic children as explained.

Radiological Investigations

There are recommended guidelines about the investigations required after a child develops a UTI. They are listed in Table 3.

These are the minimum investigations suggested for the particular age group. Additional investigations are recommended in the presence of recurrent UTIs, pyelonephritis or abnormal investigations like an ultrasound scan.

Unfortunately, the recommended tests get done at the wrong time and are liable to wrong interpretation.

An ultrasound scan of the kidneys and bladder should be done as soon as possible in a child with UTI. For an inpatient, it should be when the child is admitted and for an outpatient, it should be soon and certainly within a week. Please be careful about interpreting the evidence of cystitis on the ultrasound scan as a mildly thickened bladder wall. Unless the bladder is full, thickness cannot be interpreted with accuracy and will look "thickened"! One needs to look at the scan and not the report.

The dimercaptosuccinic acid (DMSA) scan is useful in showing up nonfunctioning areas of the kidneys. Acute changes secondary to a UTI can last for as long as 4–6 months. The DMSA scan is used to determine changes that may need to long-term monitoring. Hence, it is pointless to do a DMSA scan soon after a UTI. Please remember that a DMSA scan should be done at least 4–6 months after an episode of UTI (the later, the better).

One should also realize that all changes seen on a DMSA scan do not indicate scarring secondary to a UTI (though the report may say so!). One presumes that the DMSA scan would have shown normal kidneys before the episode of UTI to be able to confidently report scarring. That is a very big presumption. There are many children who are born with abnormal kidneys/imperfect embryogenesis/dysplasia and changes seen on a DMSA scan are similar to those reported as scarring. Note that the ultrasound scan may actually show normal kidneys in these children. Hence, abnormalities on a DMSA scan have to be interpreted with caution. Clinical interpretation is more important rather than what is printed on the report (e.g., a single UTI is unlikely to cause a small kidney with very poor function).

Clinical Pearls

- Dimercaptosuccinic acid scan for detecting long-term changes should be done at least 4–6 months after a urinary tract infection (UTI)
- Ultrasound scan soon after a UTI
- Micturating cystourethrogram, if required, after the UTI is adequately treated.

TABLE 3: Recommended guideline for investigating urinary tract infections in children

Age	Investigations recommended
Less than 1 year	US scan, DMSA, and MCUG
1–6 years	US scan, DMSA
More than 6 years	US scan

US, ultrasound; DMSA, dimercaptosuccinic acid; MCUG, micturating cystourethrogram.

Finally, an micturating cystourethrogram (MCUG) is not indicated in all children with UTIs. Far too many MCUGs are done for weak indications. In children less than 1 year of age with a UTI or when bladder outlet obstruction is suspected, it is definitely indicated. Symptoms suggesting bladder outlet obstruction are as follows:

- Poor urine stream
- Dribbling of urine
- Abdominal swelling (bladder)
- Voiding by pressing the abdomen
- Bilateral hydronephrosis and hydroureter on ultrasound scan
- Large thick walled trabeculated bladder on ultrasound
- Antenatal scans with bilateral hydronephrosis/hydroureter or large bladder.

Please remember to give antibiotics to the child when the MCUG is being done. A 7-day course of antibiotics (2 days before and 5 days after MCUG) is a fair practice. One could also use intravenous antibiotics before MCUG or follow any other local practice guideline for the purpose. I have seen several children who have developed a UTI after an MCUG when antibiotics have not been used and that is not acceptable.

It would be impossible to start commenting on actions required for various abnormalities seen on various scans as that would take up too much space. It should be remembered that an intravenous pyelogram is an extremely poor test for renal scarring and is not recommended.

CONCLUSION

Last but not the least, do not forget to check the renal function of the child. As explained above, the only way to detect children with abnormal DMSA scans (abnormality existing before the UTI) is looking at the renal parameters. Ensure a serum creatinine is done at least 2 weeks after the episode of UTI and interpret appropriately to calculate the estimated glomerular filtration rate. Also ensure a urine protein/creatinine ratio is done to look for proteinuria at the same time.

Urinary tract infection is a fairly common condition in children and instead of alarming everyone including ourselves, let us analyze the situation correctly and take appropriate steps so that management of a child with UTI is kept simple. Let us also realize that recent literature is suggesting that long-term outcome for the kidneys is good in the face of an occasional UTI also! So it's not all doom and gloom!

KEY POINTS

- ☞ Urine test for urinary tract infection (UTI) should be done only in symptomatic children. This includes children having fever without focus and or exhibiting urinary symptoms
- ☞ Appropriate advice regarding cleaning, collection of urine as a clean catch, and transport absolutely vital in making a diagnosis of UTI
- ☞ Presence of significant number of leukocytes in the urine does not always indicate UTI. In the absence of symptoms and/or a positive urine culture, be careful of misdiagnosing UTI
- ☞ Do not forget to consider UTI mimics like vulval redness and detrusor instability in the differential diagnosis of UTI
- ☞ In most cases, oral antibiotics suffice as treatment. In special circumstances, intravenous antibiotics are needed to treat UTI
- ☞ Apart from pharmacologic treatment, please ensure that appropriate advice regarding prevention of further UTIs like treating constipation, fluid intake, etc. are also provided
- ☞ Appropriate radiologic investigations need to be done after UTI, but ensure they are done at the appropriate times.

SUGGESTED READINGS

1. Indian Society of Pediatric Nephrology, Vijayakumar M, Kanitkar M, Nammalwar BR, Bagga A. Revised Statement on management of Urinary tract Infection. Indian Pediatrics. 2011 (48):709-17
2. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011; 128(3):595-610.
3. Tosif S, Baker A, Oakley E, Donath S, Babl FE. Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: observational cohort study. 2012;48(8):659-64.
4. Bachur R, Harper MB. Reliability of urinalysis for predicting UTI in young febrile children. Arch Pediatr Adolesc med. 2001;155(1):60-5.
5. Luco M, Lizama M, Reichhard C, Hirsch T. Urine microscopy as a screen for urinary tract infection in a pediatric emergency unit in Chile. Pediatr Emerg Care. 2006;22(10):705-9.
6. Silver SA, Baillie L, Simor AE. Positive urine cultures: A major cause of inappropriate antimicrobial use in hospitals? Can J Inf Dis Med Microbiol. 2009;20(4):107-11.
7. Fischer GD. Vulval disease in prepubertal girls. Australian J Dermat. 2001; 42:225-36.
8. Fischer G, Rogers M. Vulval diseases in children: a clinical audit of 130 cases. Pediatr Dermatol. 2000;17:1-6.
9. Hannula A, Perhomaa M, Venhola M, Pokka T, Renko M, Uhari M. Long-term follow-up of patients after childhood UTI. Arch Pediatr Adolesc Med. 2012;166(12): 1117-22.

CHAPTER 101

Antenatal Renal Anomalies: Outcome and Postnatal Management

Mehul A Shah

INTRODUCTION

Antenatal ultrasonographic-detected renal anomalies were first reported by Garrett et al. in 1970. Since then, with routine screening during pregnancy and availability of sophisticated equipment, the incidence of antenatal renal anomalies has increased. Initial reports showed 1% incidence of major structural fetal anomaly with approximately 50% of those 1% affecting central nervous system (CNS), 30% genitourinary, 15% gastrointestinal (GI), and 5% cardiopulmonary systems. Data from the past decade and half indicate a higher incidence of renal anomalies, especially fetal hydronephrosis (HN) in up to 4.5% of pregnant women.

It is well recognized that delay in the maturation of renal system can lead to transient dilatation of the urinary tract. Also, the fetal upper urinary tract dilatation can be a dynamic process related to the effect of bladder (full bladder can cause back-pressure changes on upper tract). The early diagnosis of renal anomalies allows the obstetrician to plan delivery, especially in those women with associated oligohydramnios, early neonatal management, and prevention of long-term complications such as recurrent urinary tract infections (UTIs), hypertension, and renal failure. On the other side, the disadvantages of early detection of renal anomalies include over work up and also excessive parental anxiety since approximately 70% of these anomalies are benign and known to resolve spontaneously.

Two risks should be avoided when managing antenatal detected renal anomalies: (1) delayed therapy and (2) excessive treatment. Hence, knowledge about the correlation of fetal renal ultrasonography (USG) abnormalities and the final outcome is important for proper counseling. The challenge, within the babies with antenatal detected renal anomalies, is to identify the small (<25%) number of babies who have significant renal disease requiring later surgery or long-term follow up of renal function without subjecting the majority (~75% of those detected antenatally) to unnecessary investigations and antibiotics. Certainly, baby boys with posterior urethral valves (PUVs), and other babies with pelviureteric junction obstruction (PUJO), vesicoureteral reflux (VUR), vesicoureteric junction obstruction (VUJO), and multicystic dysplastic kidneys needs further evaluation in the neonatal period.

Clinical Pearl

- Most antenatal renal anomalies are BENIGN and only ~25% have significant nephrouropathy that require further evaluation.

NORMAL FETAL URINARY TRACT

The fetal kidneys can be identified *in utero* by the 15th gestational week, but visualization of internal renal architectures is usually not possible until after the 20th week. The pelvicalyceal system and capsule are highly echogenic while the medulla is almost anechoic. The urine-filled pelvis may appear prominent without obstruction. The fetal bladder can also be identified in the early second trimester. Hourly fetal urine production increases from 12 mL/h at 32 weeks to 26 mL/h at term. The ureters are not imaged sonographically unless they are dilated.

The amniotic fluid volume reflects renal function and patency of the genitourinary tract. The total volume of amniotic fluid, which ranges from 500 to 2,000 mL, is also an important factor in a fetus with HN. In early gestation, the source of amniotic fluid is a transudate of maternal plasma. By 20 weeks, most amniotic fluid is fetal urine. The volume increases until the end of the second trimester at a relative constant rate, then it remains steady, and then decreases shortly before term. The normal amniotic fluid index (AFI) is between 8 and 20 cm. Decreased amniotic fluid volume, called oligohydramnios (<8 cm), often indicates decreased fetal kidney function (dysplasia). The other cause of oligohydramnios is placental insufficiency. On the contrary, polyhydramnios (AFI >20 cm) is often associated with renal tubulopathy (such as Bartter's syndrome) indicating fetal polyuria, GI tract obstruction, CNS malformation, and maternal diabetes mellitus.

TABLE 1: Hydronephrosis grading systems

	Society for Fetal Urology Grading System (qualitative)	Blachar's Grading System (quantitative)
Grade 0: Normal	No hydronephrosis, intact central renal complex	Pelvis APD <4 mm
Grade 1: Mild	Dilated renal pelvis	Pelvis APD 5–9 mm
Grade 2: Moderate	Dilated renal pelvis (more than grade 1)	Pelvis APD 10–15 mm
Grade 3: Severe	Dilated renal pelvis + dilated calyces	Pelvis APD >15 mm + cortical thinning
Grade 4: Severe	Dilated renal pelvis + dilated calyces + cortical thinning	–

APD, anteroposterior diameter

Renal malformations detected antenatally, now referred to as congenital anomalies of the kidney and urinary tract can be broadly classified into three groups:

1. Upper tract dilatation, without bladder abnormalities (most common), and includes ureteric dilatation [antenatal hydronephrosis (AH)]
2. Cystic kidney diseases (including multicystic dysplastic kidneys, polycystic kidney disease, and cystic dysplasia)
3. Bladder outlet obstruction (posterior urethral valves).

Grading System for Hydronephrosis

There are different grading systems in the literature to assess severity of HN (Table 1). Some are based on qualitative change in the pelvicalyceal system that are subjective and not reproducible (such as Society for Fetal Urology system) and some are based on quantitative changes (such as Blachar's grading system for HN). Blachar's grading system is based on anteroposterior renal pelvis diameter (APRPD), and is a quantitative system, thus more likely to be reproducible.

Clinical Pearl

- Anteroposterior diameter of renal pelvis is the preferred method for assessing severity of hydronephrosis and should be insisted in the report.

ANTENATAL HYDRONEPHROSIS

As with the grading system for postnatal HN, there is no uniformly accepted definition of AH. In general, most authors would define AH when the APRPD is greater than 5 mm at 20 weeks of gestation and greater than 7 mm at 34 weeks. The APRPD greater than or equal to gestational age in months is considered significant (for e.g., at 6 months, 6 mm or greater dilatation of pelvis is significant). Of importance to note is that presence of calyceal dilatation or hydroureter at any stage is significant. Prenatal USG examination is important not only in mid pregnancy (~20–22 weeks) but also in the third trimester to detect upper tract anomalies that can be missed in early scans. In the study by Bernanrdica Valent-Moric et al., almost 47% of AH was detected between 30 and 38 weeks of gestation. Hence, a third trimester USG between 30 and 38 weeks' gestation is necessary in addition to targeted imaging for fetal anomalies scan at 20 weeks to detect renal anomalies.

Clinical Pearl

- Third trimester scan is necessary to detect at least 40% of renal anomalies.

Antenatal Hydronephrosis: Postnatal Outcome

Based on several published reports, the following observations can be made:

- ~70% with AH are transient or isolated or benign (resolve spontaneously)
- 10–15% have VUR
- 8–10% have PUJO
- 5–10% have other urinary tract anomalies (PUV, VUJO, duplex, etc.)

Antenatal Renal Anomalies: When to Worry?

(only ~ 5–10% of all antenatal renal anomalies)

- Oligohydramnios (indicates renal dysplasia/decreased renal function)
- Bilateral hydroureteronephrosis (boys/girls)–PUV, high grade VUR
- Bilateral severe HN (boys–PUVs, although not always)
- Bilateral enlarged and echogenic kidneys (ARPKD)
- Other organ anomalies (CNS, syndromic).

Clinical Pearl

- Only ~5–10% of all antenatal renal anomalies cause major problems.

Postnatal Evaluation

The goal of evaluation is to identify all infants with significant nephrouropathy (~25% of all antenatal renal anomalies) without subjecting the majority (~75%) to unnecessary radiological investigations and thereby, minimizing parental anxiety, costs, and radiation exposure.

The possibility of significant nephrouropathy increases with the severity of HN, persistence of HN into the third trimester, and bilateral involvement. Certainly, presence of oligohydramnios (AF <8 cm) and bilateral severe HN indicates high possibility of PUV in a male baby.

According to the study by Bernardica Valent-Moric, the incidence of significant nephrouropathy was 95% (19 of 20) in infants with severe HN, 53% (23 of 43) in infants with moderate HN, and 29% (23 of 82) in infants with mild HN.

The management of infants with AH is based upon two factors: severity of HN and presence of unilateral or bilateral HN. With severe or bilateral HN, the first postnatal USG is done within 2 days of birth, and in others, the first USG is postponed until 7–10 days of life when diuresis is established.

Table 2 shows the timing of various radiological imaging in relation to severity of HN. There is practically no role of

TABLE 2: Postnatal evaluation of antenatal hydronephrosis— timing of imaging studies

	USG	MCUG	DTPA/EC/MAG3 renal scan
Unilateral or bilateral mild hydronephrosis	1st: 7–14 days 2nd: 1–2 months†	3–6 months age* (Algorithm 1)	2–3 months age (Algorithm 1) may not be required in most cases
Bilateral moderate-to-severe‡ hydronephrosis or unilateral/bilateral hydroureteronephrosis	1st: 1–3 days 2nd: 1–2 months	Boys: 2–4 days (before discharge) to r/o PUV Girls: 2–3 months	2–3 months age
Severe hydronephrosis in a solitary kidney	1st: 1–3 days 2nd: 1–2 months	Boys: 2–4 days Girls: 2–4 days	2–3 months or may be earlier if serum creatinine is increasing, or urosepsis

*Perform MCUG in first week of life if there is any suspicion of PUV (in boys)

†Always perform second USG at 1–2 months even if first USG was normal

‡Hydronephrosis: mild, pelvis APD 5–9 mm; moderate, pelvis APD 10–15 mm; severe, pelvis APD >15 mm.

USG, ultrasonography; DTPA, diethylene triamine pentaacitic acid; MCUG, micturating cystourethrogram; EC, ethylcysteine; MAG3, mercaptoacetyltriglycine; APD, anteroposterior diameter.

intravenous pyelogram (IVP) in neonates or infants. Rarely, IVP or magnetic resonance urogram may be required to evaluate ectopic/single/malrotated kidney with either HN or hydroureteronephrosis (where there is a doubt regarding presence of only PUJO, only VUJO or both).

Clinical Pearl

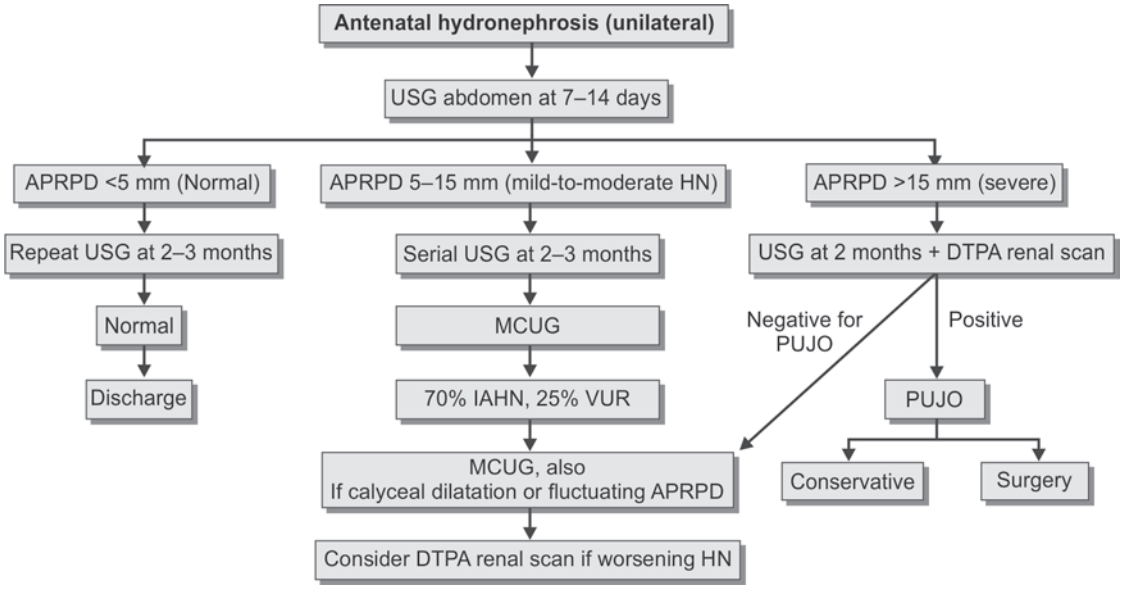
- Possibility of significant nephrouropathy in infants with severe hydronephrosis (anteroposterior renal pelvis diameter >15 mm) is 95%.

UNILATERAL OR BILATERAL MILD-TO-MODERATE HYDRONEPHROSIS (ANTEROPOSTERIOR RENAL PELVIS DIAMETER 5–14 MM)

Ultrasonography at 7–10 days and 1–2 months (second USG is always done even if first USG is normal—since first USG may be normal due to the effect of physiological oliguria in first few weeks of life where HN may not be apparent) (Algorithm 1).

ALGORITHM 1

Approach to a newborn with antenatal hydronephrosis



IAHN, isolated antenatal hydronephrosis; VUR, vesicoureteral reflux; PUJO, pelviureteric junction obstruction; APRPD, anteroposterior renal pelvis diameter; USG, ultrasonography; DTPA, diethylene triamine pentaacitic acid; MCUG, micturating cystourethrogram.

If HN is persisting on the second USG, then a micturating cystourethrogram (MCUG) is performed to rule out VUR. Infants with normal MCUG and increasing HN will require diethylene triamine pentaacitic acid (DTPA) or ethylcysteine (EC) renal scan at 3–6 months to rule out PUJO. If the HN is stable or improving, a DTPA renal scan may not be necessary.

If the suspicion of PUV is high (poor urinary stream, palpable bladder, oligohydramnios), USG and MCUG should be performed before baby is discharged from nursery.

The majority of cases with mild or moderate HN appear to resolve by 18 months of age, In one study of 282 infants with mild-to-moderate HN, majority resolved by 18 months age (i.e., APRPD less than 5 mm on two consecutive USG) and only 6% had significant nephrouropathy (14 had PUJO and 4 had VUR).

UNILATERAL SEVERE HYDRONEPHROSIS

Here, USG is performed in first week of life followed by another at 1–2 months age. Since the possibility of PUJO is higher, DTPA or EC renal scan is next performed at 2–3 months of age. If the DTPA scan is negative for obstruction, then a MCUG is done to rule out VUR.

SEVERE HYDRONEPHROSIS (BILATERAL OR SOLITARY KIDNEY)

Infants with severe bilateral AH and/or bladder distension should have serial renal function tests done in first few days of life. USG and MCUG [under intravenous (IV) cefotaxime cover] are performed in first 2 days of life to exclude PUV in boys and VUR in boys and girls. If there is no evidence of bladder outlet obstruction (PUV or neurogenic bladder), then a DTPA or EC renal scan is performed between 2 and 3 months of age to rule out PUJO or VUJO.

Obtaining DTPA renal scan in first month of life does not provide accurate results due to renal function immaturity [i.e., low glomerular filtration rate (GFR) physiologically and DTPA molecule is excreted mainly by glomerular filtration]. Hence, a dynamic scan is delayed until 2–3 months age when the GFR is roughly 50–60 mL/min/1.73 m^2 [except mercaptoacetyltriglycine (MAG3) renal scan that can be performed in first month since MAG3 is excreted mainly by tubular secretion and this function matures faster than the GFR in newborns].

ROLE OF PROPHYLACTIC ANTIBIOTICS

Based on the low risk of UTI in most babies with PUJO and isolated HN as well as the current evidence suggesting an early diagnosis followed by prompt treatment of febrile UTI in children with VUR, most babies do not need chemoprophylaxis. This is also suggested from our observation of only 4 out of 115 babies with antenatal renal anomalies developing febrile UTI (2 had PUV, 1 VUJO, and 1 had isolated HN).

In babies with documented VUR or PUV or those with severe HN pending further imaging (MCUG and DTPA renal scan), cephalexin should be used for UTI prophylaxis at 5 mg/kg/dose two times a day.

Clinical Pearl

- If renal ultrasonography (USG) is performed on day 1–3 of life, repeat renal USG is mandatory between 2 and 4 weeks of age (since in first few days, because of physiological oliguria, hydronephrosis may not be evident)

ISOLATED ANTENATAL HYDRONEPHROSIS

It is defined as isolated renal pelvic dilatation without associated urinary tract abnormalities (i.e., absence of calyceal dilatation, cortical thinning, hydroureter, VUR, PUJO, and bladder anomalies) i.e., these infants have a normal MCUG and a normal DTPA renal scan.

In a paper published by Sidhu et al. from the Hospital for Sick Children, Canada, following observations were made:

- APRPD <12 mm, Society of Fetal Ultrasound grade 1–2: benign condition, most improve (95%)
- Presence of cortical thinning: marker of deterioration
- Severe grades: variable rates of stabilization (60%).

The authors concluded that there is sufficient evidence to suggest that mild HN (APRPD <12 mm) is a self-limited condition and that clarification is required for moderate-to-severe HN.

Rarely, HN may worsen after initial improvement (<2%). As a result, if there is persistent dilation at 3 months of age (in absence of VUR or PUJO), we suggest to monitor the degree of HN with an ultrasound performed at 1 and 2 years of age, and if needed, between 3 and 5 years of age. Most often the resolution of mild-to-moderate HN occurs by 18 months of age in majority of patients.

VESICOURETERAL REFLUX

After isolated (benign) HN, VUR is the next common urinary tract abnormality detected though antenatal screening in approximately 10–15% babies.

Vesicoureteral reflux is associated with long-term complications related to recurrent UTIs as well as dysplasia associated with high-grade reflux. These complications include hypertension, proteinuria, chronic kidney disease, and pregnancy-related complications in women.

Through antenatal screening, VUR is suggested by

- APRPD <15 mm (15% incidence)
- APRPD >15 mm and PUJO is ruled out on DTPA scan
- Fluctuating renal pelvis anteroposterior diameter on serial USGs
- Hydroureteronephrosis.

Diagnosis

The diagnosis is made using MCUG done under antibiotic cover (1 day before and 2 days after MCUG). Treatment of VUR depends upon several factors especially severity of reflux and includes chemoprophylaxis, surgical therapy in elect cases, circumcision in boys, and only observation in infants with grades 1–2 VUR.

PELVIURETERIC JUNCTION OBSTRUCTION

Pelviureteric junction obstruction is often due to lack of or decreased ganglion cells with resultant decreased peristalsis. It is suggested by APRPD greater than 15 mm and diagnosis is confirmed by DTPA (or EC) renal scan at 2–3 months of age. This renal scan is delayed until 2 months of age since there is a natural maturation of renal function and GFR usually triples that of newborn period at 2 months (~60 mL/min/1.73 m^2) that permits better visualization of the kidneys. Occasionally, EC or MAG3 renal scan may be performed in the first few weeks of life especially if there is bilateral severe HN or HN in a solitary kidney. IVP essentially does not have a role in diagnosis of PUJO.

Since the natural history of PUJO is that of spontaneous resolution in a significant number of cases, majority of children with PUJO can be managed conservatively. Conservative management includes 3–4 monthly USG and DTPA renal scan until 1 year of age and then 6 monthly for another 1 year. Early detection and prompt treatment of UTI is very important. Since the risk of UTI is low, chemoprophylaxis is usually not indicated.

Surgery for PUJO is indicated in following conditions:

- Palpable renal mass
- Presence of cortical thinning
- APRPD >25 mm
- Split renal function <40% on DTPA renal scan
- Recurrent UTI's.

MULTICYSTIC DYSPLASTIC KIDNEY

Multicystic dysplastic kidney (MCDK) is the most common cystic renal anomaly and occurs in approximately1 in 2,000 births. The MCDK is a nonfunctioning kidney characterized by multiple noncommunicating cysts and absence of identifiable renal parenchyma. It results from disturbance in ureteric bud development during early pregnancy. The differential diagnosis of MCDK includes severe PUJO (dilated pelvi-calyceal system appears as "cysts"), autosomal dominant polycystic kidney disease, and simple cysts (usually single). There is a 25–30% incidence of renal anomalies on the contra lateral side (i.e., the normal kidney). Of these, VUR (reflux) is the most common followed by PUJO, VUJO, and duplex system.

The natural history of MCDK includes spontaneous involution/regression in 75% cases and decrease in size to smaller than 5th percentile after 6 years of age in majority. The outcome of children with MCDK is benign. The incidence of hypertension and malignancy/Wilm's tumors is essentially zero percent.

Evaluation of a neonate with antenatal suspicion of MCDK includes

- Renal USG between 7 and 21 days of life
- DTPA/dimercaptosuccinic acid renal scan at 3 months of age
- MCUG at 3–6 months of age to rule out VUR on the normal side.

Management of MCDK is conservative. Until mid-1980s, infants were subjected to surgery (nephrectomy) that is now reserved for infants with huge renal mass. Most children are followed conservatively with:

- Renal USG once in a year for 5 years and then every 2–3 years
- Asessment of growth and blood pressure (BP) once a year (routine)
- Moderate salt and nonvegetarian (meat) protein reduction in family's diet to decrease the risk of hypertension and proteinuria in later life
- Avoidance of contact sports to prevent trauma to contra-lateral hypertrophied kidney.

POSTERIOR URETHRAL VALVES

Posterior urethral valves are the most serious and fortunately less common of the antenatal renal anomalies. During the antenatal period, PUV can be suggested by bilateral hydroureteronephrosis/bilateral HN, echogenic renal cortex, distended bladder, and decreased amniotic fluid. Adequate AFI is one of the most important predictors of long-term renal outcome in PUVs. Oligohydramnios is associated with more than 75% incidence of renal failure and pulmonary hypoplasia.

Postnatal evaluation includes observation of urinary stream, presence of renal and bladder mass, and respiratory status (distress, oxygen requirement, lung expansion on X-ray). Renal USG is to be performed on day 1–2 followed by MCUG under antibiotic cover. Serial monitoring of renal parameters and serum electrolytes including bicarbonate is very important. In most cases, cystoscopy and primary fulguration of valves can be performed in the neonatal period. Postfulguration, infants need to be maintained on cephalexin prophylaxis (until at least 6 months or longer duration in presence of VUR). Long-term follow-up for growth, blood pressure, metabolic acidosis (Type IV renal tubular acidosis), and renal and bladder function is mandatory.

Approximately 25–30% of children with PUVs can progress to end-stage renal disease (chronic renal failure). Poor prognostic markers include oligohydramnios, bilateral high grade VUR, and echogenic kidneys. Appropriate and timely intervention can decrease the morbidity associated with PUVs.

PRENATAL COUNSELING

Obviously, presence of fetal kidney dilatation causes parental anxiety and raises a number of doubts regarding the immediate and long-term outcome of the baby specifically regarding the kidney function. Since most studies report lower incidence of significant uropathies (PUV, PUJO, and VUR), first thing to do is to reassure the family regarding the common nature and usually benign course of most conditions. Most unilateral HN or cystic kidneys have a good long-term outcome as long as the other kidney is normal. When dealing with unilateral HN, the family can be counseled regarding the step-wise work up of the baby between birth and 3 months of age. Unilateral

fetal HN of any severity does not need any intervention or early delivery.

With bilateral severe HN, possibilities of PUV, VUR, PUJO and other uropathies is discussed. Of all the uropathies, PUV is the only one that is associated with chronic kidney disease chronic renal failure in approximately 30% children. Adequacy of amniotic fluid in the second and third trimester is an important prognostic marker for future/long-term renal function. If amniotic fluid is decreased (especially if AFI is <5 cm] in presence of bilateral HN, the risk of postnatal kidney failure requiring dialysis and kidney transplantation is very high (~90%). In case of VUR or PUJO, even if surgery is required, the timing of surgery is usually between 2 and 24 months of age and not immediately after birth.

The indication for early delivery is usually based on obstetric factors. The only fetal factor that may necessitate early delivery is when there is worsening oligohydramnios (usually seen in boys with PUV or neurogenic bladder associated renal dysplasia) After inducing lung maturation with steroids, early delivery can then be planned.

CONCLUSION

Antenatal renal anomalies are being identified more frequently. Postnatally, balance between overinvestigation and underevaluation is required. The goal is to identify significant nephrouropathy (such as PUV, VUR, PUJO, VUJO, and MCDK) before long-term complications set in and prevent complications such as recurrent UTI's, renal stones, hypertension, proteinuria, and kidney failure. Transient (isolated or benign) HN is the most common cause of AH. Unilateral HN can be completely evaluated by 3 months of age starting with a renal USG between 7 and 14 days of life followed by second USG at 2 months of age and then MCUG (if APRPD is between 5 and 15 mm) or DTPA renal scan (if APRPD > 15 mm). If renal USG is done in the first week of life, a repeat renal USG should be performed between 2 and 4 weeks of age, once the urine output is established. Two normal renal USGs (APRPD <5 mm) in first 2 –3 months of life can rule out approximately 95% of urinary tract abnormalities. Calyceal dilatation and cortical thinning always indicate a serious pathology. Bilateral hydroureteronephrosis or severe bilateral hydronephrosis should be evaluated with serial creatinine, USG, and MCUG in first week of life (mainly to detect PUV). The only major anomaly that should not be missed before discharge of a new born baby boy is posterior urethral valves.

KEY POINTS

- ☞ Approximately 75% of antenatal renal anomalies are benign and ~25% have significant nephrouropathies. Balance between overinvestigation and underinvestigation is important
- ☞ First postnatal ultrasonography (USG) should be obtained between 7 and 14 days in babies with unilateral hydronephrosis (HN) or bilateral mild HN.
- ☞ Based on second USG at ~ 1–2 months, further investigations [micturating cystourethrogram (MCUG) or diethylene triamine pentaacitic acid renal scan] can be planned
- ☞ We do not want to miss posterior urethral valves in baby boys before discharge. Obtain serial renal function test, USG, and MCUG in first few days of life if there is bilateral moderate-to-severe HN, hydroureteronephrosis, or distended bladder in baby boy.

SUGGESTED READINGS

1. Alconcher LF, Tombesi MM. Natural history of bilateral mild isolated antenatal hydronephrosis conservatively managed. Pediatr Nephrol. 2012;27:1119-23.
2. Blachar A, Blachar Y, Livne PM, Zurkowski L, Pelet D, Mogilner B. Clinical outcome and follow-up of prenatal hydronephrosis. Pediatr Nephrol. 1994;8:30-5.
3. Brunisholz Y, Vial Y, Maillard-Brignon C, Meyrat BJ, Frey P, Hohlfeld P. Prenatal diagnosis of urinary malformations: results in a series of 93 consecutive cases. Swiss Med Weekly. 2001;131:95-8.
4. Duncan KA. Antenatal renal pelvis dilatation: the long-term outlook. Clin Radiol. 2007;62:134-9.
5. Gupta DK, Bajpai M, Chandrasekharam VVSS, et al. Antenatally detected pelviureteric junction obstruction: safety of conservative management by our protocol. Indian Journal of Urology 2000;17:24-7.
6. Hadlock FP, Deter RL, Carpenter R, Gonzalez ET, Park SK. Sonography of fetal urinary tract anomalies. Am J Radiology. 1981;137:261-7.
7. Ismaili K, Avni FE, Alexando M. Routine VCUG is of no value in neonates with unilateral MCDK. J Pediatr. 2005;146:759-63.
8. Khalid I, Avni FE, Wissing M, Hall M. Long-term clinical outcome of infants with mild and moderate fetal pyelectasis: validation of neonatal ultrasound as a screening tool to detect significant nephro-uropathies. J Pediatr. 2004;144:759-65.
9. Kitagawa H, Pringle KC, Stone P, Flower J, Murakami N, Robinson R. Postnatal follow-up of hydronephrosis detected by prenatal ultrasound: the natural history. Fetal Diagn Ther. 1998;13:19-25.
10. Narchi H. Risk of hypertension with multicystic kidney disease: a systematic review. Arch Dis Child. 2005;90:921-4.
11. Sidhu G, Beyene J, Rosenblum ND. Outcome of isolated antenatal hydronephrosis: a systematic review and meta-analysis. Pediatr Nephrol. 2006;21:218-24.
12. Valent-Morić B, Zigman T, Cuk M, Zaja-Franulović O, Malenica M. Postnatal evaluation and Outcome of infants with antenatal hydronephrosis. Acta Clin Croat. 2011;50:451-55.
13. Zaccara A, Giorlandino C, Mobili L, Brizzi C, Bilancioni E, Capolupo I, et al. Amniotic fluid index and fetal bladder outlet obstruction. Do we really need more? J Urol. 2005;174:1657-60.

CHAPTER 102

Acute Kidney Injury

VK Sairam

INTRODUCTION

Acute kidney injury (AKI) is a sudden loss of renal function that occurs due to multiple causes leading to a decline in glomerular filtration rate (GFR) and accumulation of urea and nitrogenous waste products. It also results in fluid imbalance and electrolyte dysregulation. The presence of AKI results in increase in mortality and morbidity of children. Hence, it is very essential that pediatricians are aware of this entity and be competent to prevent and treat it.

The new terminology AKI has replaced acute renal failure. It is now widely used by Nephrologists to indicate acute loss of renal function. AKI presents with wide range of clinical manifestation from a slight rise of serum creatinine to an anuric renal failure. The rise in serum creatinine is considered to be the marker of an acute event of the kidney. It has to be remembered that serum creatinine rise is often delayed and imprecise. It is a value that reflects GFR in a steady state and does not reflect GFR in a patient with changing renal function. Despite these limitations, serum creatinine continues to be the most widely used laboratory parameter to indicate AKI.

The recognition for a definition for AKI, the pediatric Risk, Injury, Failure, loss of kidney function, and End-stage kidney disease (RIFLE) classification was proposed. This will enable us to recognize children with AKI early and intervene appropriately. It has graded levels of injury (risk, injury, failure, loss of kidney function and ESRD) based on the elevation of serum creatinine or urine output.

The etiology of AKI in developed countries in the last two decades has been changing from primary glomerular diseases to hospital-acquired renal diseases. The causes that lead to hospital-acquired AKI are sepsis, nephrotoxic drugs, and renal ischemia. In developing countries, the etiology is due to dehydration, sepsis, and primary renal diseases such as postinfective glomerulonephritis (PIGN) and hemolytic uremic syndrome (HUS). The incidence of AKI is increasing in developed countries due to increased number of complicated patients taken care in the neonatal and pediatric intensive care units.

CLASSIFICATION

The classification of AKI is based on the anatomic location of initial injury. It is classified as prerenal, renal, and postrenal locations for AKI.

Prerenal AKI in children is due to hypovolemia [bleeding or gastrointestinal (GI) loss, or urinary loss or cutaneous, loss], or reduction of effective circulatory volume (nephrotic syndrome, cirrhosis, or septic shock)

Renal AKI is due to structural damage to the kidney due to glomerular disease or prolonged hypoperfusion, sepsis, or nephrotoxins.

Postrenal AKI is due to congenital or rarely acquired causes of obstruction of lower urinary tract.

Clinical Pearl

- The clinician should evaluate and understand the site of renal injury.

CLINICAL FEATURES

The signs and symptoms are directly related to the alteration of renal function. These include edema, reduced urine output or anuria, hematuria (microscopic or gross), hypertension, and in some children, breathing difficulties. There may be features of shock or heart failure or features of acute PIGN. There may be in few children features of joint pain, rash, and associated renal injury due to disorders such as systemic lupus erythematosus (SLE) or Henoch-Schonlein purpura (HSP). Rarely, patients with interstitial nephritis can present with rash, malaise, vomiting, and rise in serum creatinine.

On physical examination, edema, rise in blood pressure, respiratory distress, weight gain, and signs of underlying disease (PIGN, SLE, or HSP) can be detected. Also signs of volume depletion (dry mucous membrane, decreased turgor, orthostatic fall of blood pressure, or decreased blood pressure) are all indicative of a prerenal AKI.

DIAGNOSIS

Elevated blood urea nitrogen or urea and serum creatinine is a hallmark of AKI. Abnormal urine analysis is feature of nephritis. Other features such as hyperkalemia, hypo- or hypernatremia, high anion gap acidosis, hypocalcemia, or hyperphosphatemia are noted in AKI.

Urinalysis

Urine analysis is very helpful to detect the cause of AKI. The presence of red blood cell casts, dysmorphic red blood cells, and proteinuria are all indicative of nephritic urinary sediment. Muddy-brown granular casts is suggestive of acute tubular necrosis. Pyuria with white cell casts is indicative of urinary tract infections. White cell casts can also be seen in acute glomerulonephritis. The positive response to heme on dipstick with absence of RBC in the sediment is seen in patients with hemolysis or rhabdomyolysis. Patients with prerenal AKI have a normal urine analysis.

Urine specific gravity is less than 1.010 in acute tubular necrosis (ATN). Patients with prerenal disease have a specific gravity greater than 1.020.

Urine osmolality is more accurate measure of the concentrating ability. Patients with ATN have an osmolality of less than 350 mosmol/kg and patients with prerenal disease have osmolality greater than 500 mosmol/kg.

Fractional excretion of sodium (FENa) is used to differentiate prerenal AKI and intrinsic AKI.

$$\text{FENa} = \frac{\text{Urine sodium} \times \text{Serum creatinine}}{\text{Serum sodium} \times \text{Urine creatinine}} \times 100$$

Less than 1% prerenal, greater than 2% intrinsic renal AKI

FENa in neonates is higher. Less than 2% prerenal, greater than 2.5% intrinsic renal AKI.

Other Investigations

Blood urea nitrogen/creatinine greater than 20 suggestive of prerenal AKI and 10–20 suggestive of ATN.

Complete blood count with a peripheral smear is suggestive of thrombocytopenia and hemolytic anemia in patients with HUS. The presence of blasts cells are seen in patients with leukemia with tumor lysis-associated AKI. The presence of eosinophils in the urine is suggestive of interstitial nephritis.

Complement levels C3 is low in PIGN, membrano-proliferative glomerulonephritis (MPGN), and SLE. Serological testing for streptococcal infection is required in patients with PIGN. In patients with drug-induced nephrotoxicity, the drug levels are measured such as levels of aminoglycosides or acetaminophen. The rise in the levels of uric acid is seen in patients with leukemia, and lymphoma associated with tumor lysis syndrome. Lactate dehydrogenase is increased in patients with HUS, hemolytic disorders, or malignancies.

Biomarkers

Novel biomarkers such as neutrophil gelatinase-associated lipocalin, kidney injury molecule, or interleukin-18 have prognostic utility in setting of AKI and may allow clinicians to diagnose early and intervene.

Renal Imaging

Renal ultrasound is useful in patients whose etiology of AKI is not clear. The presence of a normal architecture of the kidneys is reassuring to the nephrologist. The presence of small-sized kidney means the etiology is of long-standing chronic disease. An acute injury to the kidney results in increased size of the kidney. The echogenicity is increased in patients with AKI or in patients with a chronic kidney disease. Renal ultrasound is diagnostic in patients with obstructive etiology such as posterior urethral valves, neurogenic bladder, or high grade reflux.

Renal biopsy is rarely required in patients with AKI. It is done in patients with rapidly progressive glomerulonephritis (RPGN) to enable guide therapy. Similarly, in patients with lupus nephritis associated AKI, renal biopsy is indicated.

Once diagnosis of AKI is made, then further evaluation is focussed on determining the cause. The evaluation consists of history, physical examination, and laboratory evaluation. Renal imaging is performed in most patients. Renal biopsy is very rarely required.

Clinical Pearl

- Urinalysis is an essential initial investigation in evaluation of a child with acute kidney injury and often forgotten.

TREATMENT

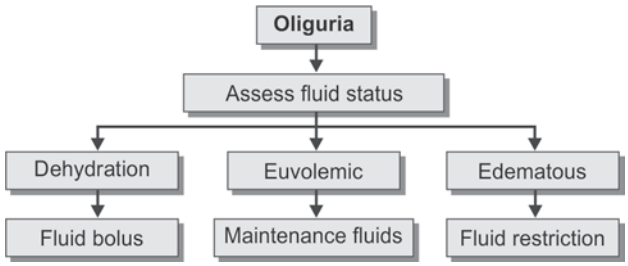
The management of a child with AKI should be initiated immediately under the guidance of a pediatric nephrologist. It is very essential to first assess the fluid status of the child and identify the etiology of AKI. The treating physician has to deal with the volume issues of the child and decide to treat accordingly (Algorithm 1). Any treatable underlying causes of AKI should be considered, such as RPGN and septic AKI, should be treated accordingly.

The principles of treatment of a child with AKI are: (Algorithm 2)

- Hypovolemic children require normal saline bolus of 10–20 mL/kg over 30 minutes repeated twice as needed. This is given to restore the renal function to prevent the progression of prerenal AKI to intrinsic renal AKI.
- In euvolemic children, fluid should be administered to a total of urine output in addition to insensible water loss (400–500 mL/m^2/day).
- Hypervolemic children with fluid overload require fluid removal and restriction of fluid intake. Furosemide is attempted to convert oliguric to nonoliguric AKI, thereby making it easy for the treating physician to give fluids and nutrition without altering the overall course of the disease. If the bolus of lasix (2–5 mg/kg/dose) provide a response immediately and the AKI is less than 24-hour duration, then a continuous lasix infusion (0.1–0.3 mg/kg/h) can be provided.
- In critically sick children, percent fluid overload correlates with overall survival rate. Fluid overload more than 10%

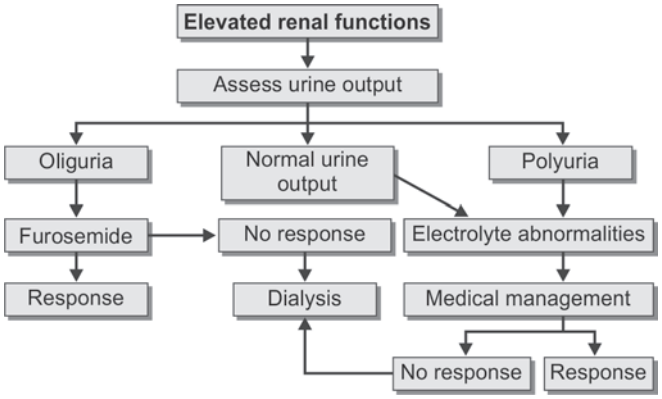
ALGORITHM 1

Assessment of initial fluid status and management



ALGORITHM 2

Management of acute kidney injury



correlates with higher morbidity and consideration of renal replacement therapy. It is highly recommended to initiate renal replacement therapy if the fluid overload is greater than 15%.

Percent fluid overload

$$= \frac{\text{Total fluid in litres} - \text{Total fluid out in litres}}{\text{Admission weight}} \times 100$$

Electrolyte dysregulation, such as hyperkalemia, hyperphosphatemia, hypocalcemia, and elevated anion gap metabolic acidosis is common in AKI and needs treatment accordingly. Children with AKI develop hypertension due to fluid overload or renin mediated and requires monitoring and treatment accordingly.

Acute kidney injury is associated with increased catabolic rate and therefore, good nutritional support is needed to enable good recovery. It is also very essential to avoid nephrotoxic drugs and all renally excreted drugs should be adjusted to a GFR of less than 10 mL/min irrespective of the present serum creatinine.

The renal replacement therapies are hemodialysis, peritoneal dialysis, and continuous renal replacement therapy. The choice of therapy depends on clinical situation and the expertise of the treating physician. The indications of renal replacement therapy are fluid overload, hyperkalemia, uremia, and life-threatening pulmonary edema or hypertension.

Clinical Pearl

- Assessment of fluid status of the child is the most important step in the management of acute kidney injury.

KEY POINTS

- There is a new terminology of acute kidney injury (AKI) for acute renal failure with a classification system of pediatric Risk, Injury, Failure, loss of kidney function, and End-stage kidney disease to enable treating physicians to recognize the condition early and intervene appropriately
- The incidence of AKI in developed countries is increasing due to increased number of complicated patients that are now taken care in intensive care units
- It is important to pinpoint the location of the renal injury (prerenal, renal, or postrenal). This is an essential step in understanding of AKI
- The detailed history of the presenting illness is an essential requirement and there may be clues on the physical examination and etiology of AKI
- The signs and symptoms are directly related to the alteration of renal functions
- Urine analysis is a very important initial investigation
- The most essential step in the management of AKI is for the clinician to learn to assess the fluid status of the child and treat accordingly
- Electrolyte dysregulation is common in AKI and needs treatment accordingly
- Underlying causes of AKI, if detected, should be treated
- Assessment of fluid overload and early initiation of appropriate renal replacement therapy
- It is also very essential to avoid nephrotoxic drugs and all renally excreted drugs should be adjusted to a GFR of less than 10 mL/min irrespective of the present serum creatinine. Other investigations to be done are based on the clinical presentation and initial course.

SUGGESTED READINGS

1. Goldstein SL. Advances in Pediatric renal replacement therapy for acute kidney injury. Semin Dial 2011;24:187-91.
2. Goldstein SL, Currier H, Graf Cd, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. Pediatrics. 2001:107;1309-12.
3. Hui-Stickle S, Brewer ED, Goldstein SL. Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. Am J Kidney disease. 2005;45;96-101.
4. Modem V, Thompson M, Gollhofer D, Dhar AV, Quigley R. Timing of continuous renal replacement therapy and mortality in critically ill children. Crit care med. 2014;42(4):943-53.
5. Krishnamurthy S, Narayanan P, Prabha S, Mondal N, Mahadevan S, Biswal N, et al. Clinical profile of acute kidney injury in a Pediatric intensive care unit form southern India. A prospective observational study. Indian J Crit care med. 2013;17:207-13.
6. Imani PD, Odiit A, Hingorani SR, Weiss NS, Eddy AA. Acute kidney injury and its association with in-hospital mortality among children with acute infections. Pediat Neph. 2013;11;2199-206.

CHAPTER 103

Enuresis

Jyoti Sharma

INTRODUCTION

Enuresis refers to intermittent incontinence in discrete episodes while asleep; sometimes called nocturnal enuresis (NE) to add extra clarity. It is essential to subgroup these children as having monosymptomatic (MNE) and nonmonosymptomatic enuresis (NMNE). The latter refers to children who have concomitant symptoms of lower urinary tract (LUT) malfunction, i.e., increased (>eight times) or decreased (<three times) voiding frequency, daytime incontinence, urgency, hesitancy, straining, a weak stream, intermittency, holding maneuvers, a feeling of incomplete emptying, postmicturition dribble, and genital or LUT pain.

Clinical Pearl

- Nonmonosymptomatic enuresis is more common; when a detailed history is obtained, the majority of children have at least subtle daytime symptoms
- Children and adult perceptions of daytime voiding symptoms differ. Hence, careful questioning of the child is recommended.

Genetic influences on primary NE are heterogenous and complex. When one or both parents have a history of enuresis, the incidence in children is 44 and 77% respectively, compared with a 15% incidence in children whose parents do not have a history of enuresis.

The term secondary enuresis is used to describe children who have had a previous dry period of at least 6 months; otherwise the term primary enuresis should be used. A cause for secondary enuresis can usually be identified and management is directed toward this (Table 1).

Dysfunctional voiding, which may also be associated with enuresis is characterized by an intermittent and/or fluctuating uroflow rate due to urethral sphincter overactivity during voiding in children with normal neurological function. This leads to very high filling and voiding pressures, prolonged voiding, incontinence, urinary retention, renal scarring, and hypertension. It is important to identify this disorder based on history and abnormal uroflowmetry since it requires specific management.

TABLE 1: Conditions that may precipitate secondary enuresis

Condition	Possible mechanism
Cystitis	Reduced bladder capacity
Constipation	Reduced bladder capacity
Sleep-disordered breathing	Impaired arousal
Diabetes mellitus	Nocturnal polyuria
Diabetes insipidus	Nocturnal polyuria
Chronic kidney disease	Nocturnal polyuria
Urethral obstruction	Reduced bladder capacity
Neurogenic bladder	Reduced bladder capacity
Psychological stress	—

The focus of this chapter is MNE and NMNE with symptoms of an overactive bladder and does not address conditions requiring special investigations and management, including dysfunctional voiding.

PATHOGENESIS

The three factors presumed to play a role in the pathogenesis and hence, also targeted for management are:

1. A disorder of sleep arousal: children do not wake up to the sensation of a full or contracting bladder
2. Nocturnal polyuria
3. A reduced nocturnal bladder capacity.

Nocturnal polyuria may be due to a combination of factors that include a low fluid intake during the school hours and large intakes in the evening, a high solute intake (dinner) close to the bedtime, and a low nocturnal secretion of antidiuretic hormone.

Reduced functional nocturnal bladder capacity increases with age, so younger children have a small normal functional bladder capacity. Presence of constipation further reduces bladder capacity and enhances the prevalence of bedwetting. The bladder is located in the narrowest dependant portion of the funnel formed by the pelvic bones and it cannot escape the impact of stool in the small pelvis of a child. Also, nocturnal colonic movement may stimulate detrusor contractions.

Other comorbid conditions associated with NE that need to be addressed for successful therapy are neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) and sleep disordered breathing due to adenotonsillar hypertrophy.

EVALUATION (SEE ALGORITHM 1)

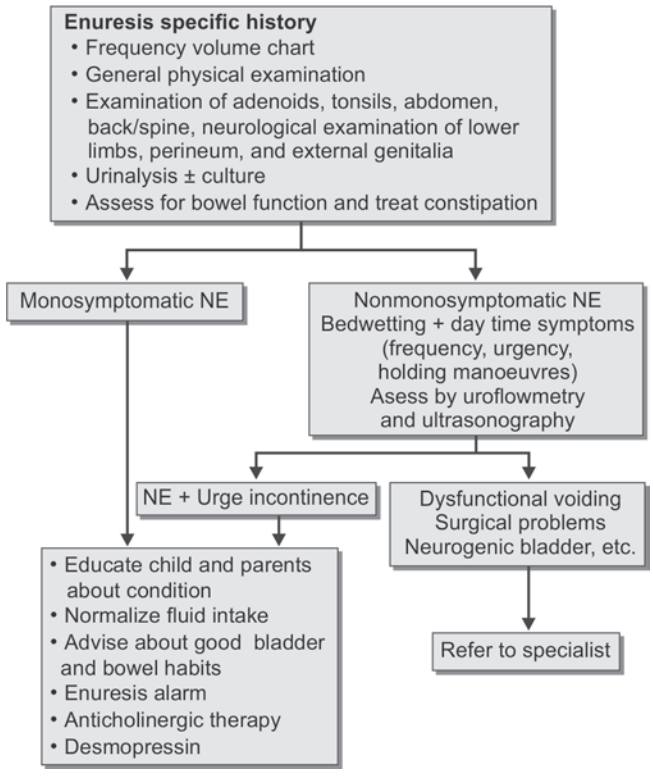
History

The most important aspect of the investigation is a meticulous history, which can establish the diagnosis, lead to more precise treatment recommendations, and minimize the need for invasive and expensive investigations.

Parents are requested to maintain a record over 2–3 days in a frequency-volume chart and record of bowel movements during a week. Points to be noted are details of fluid intake, daytime voiding pattern, and number and time of episodes of bedwetting. Some children void with a normal frequency or even a reduced frequency and yet have a low functional bladder capacity; these children often do not drink appreciably during the day, and urinary frequency is evident only after a fluid load. Other details required are a sleep history that should include the times the child goes to bed, falls asleep, and awakens in the morning, and the presence of snoring. Presence of an overactive bladder or dysfunctional voiding e.g., Vincent's curtsy, that usually present with frequency, urgency, maneuvers to suppress the urge to void (squatting behavior), and daytime and nighttime wetting should be noted. Constipation and cystitis are common associated problems in patients with overactive bladder or dysfunctional voiding. Differential diagnoses, such as neurogenic bladder and ectopic ureter, can be excluded on history. Neuropsychiatric abnormalities, if any, need to be identified.

ALGORITHM 1

Evaluation and management of a child with primary nocturnal enuresis



NE, nocturnal enuresis

Clinical Pearls

Usefulness of a voiding diary

- Provides objective data that may support the history
- Helps detect children with nonmonosymptomatic enuresis
- Detects children who require extra evaluation
- Detects families with low adherence to instructions

Physical Examination

The examination should be carried out to exclude pathological causes of incontinence, i.e., measurement of blood pressure, inspection of external genitalia and of the lumbosacral spine, palpation in the renal and suprapubic areas to look for enlarged kidneys or bladder, and a thorough neurologic examination of the lower extremities. Abnormal physical findings are absent in children when enuresis is the sole symptom.

Laboratory Testing and Imaging Studies

A urinalysis is warranted in all children to rule out urinary tract infection and glycosuria. A high specific gravity in a urine specimen obtained in the afternoon suggests low fluid intake during the day. Ultrasonography (USG) of the pelvis is helpful in children with day time symptoms. USG performed when the child feels the bladder is "full," can be used to estimate functional bladder capacity, which can be compared with norms for bladder capacity according to age (Box 1). USG should also be performed after voiding to assess the patient for bladder wall thickness and residual urinary volume; abnormal parameters suggest NMNE.

Box 1: Expected bladder capacity

- >2 years of age: {Age (years) + 2} × 30 mL
- Maximum bladder capacity is too small if <65% or too large if >130% of expected bladder capacity.

Clinical Pearls

Red flags on ultrasonography

- Thick bladder wall (>5 mm after voiding)
- Elevated residual urinary volume (>20 mL)

MANAGEMENT

Enuresis that occurs as infrequently as once a month is associated with reduced self-esteem, and treatment has been reported to improve self-esteem, regardless of the type or the success of therapy. Management should be instituted as soon as the child is motivated to be dry and the parents are supportive. An explanation of the probable cause of the enuresis is important. Motivation of the child needs to be sustained by providing emotional support and an attempt to remove any feelings of guilt. Efforts of the child to remain dry need to be rewarded with praise.

Behavioral Therapy

Behavioral modification directed at good bladder and bowel health offers the potential to cure NE without the need for medication (Box 2). It also increases the success rate of the alarm or pharmacological therapy. Clinical experience suggests that the ability to establish a rapport with the child and to induce and sustain motivation is important for successful behavioral therapy.

Box 2: Behavioral therapy: good bladder and bowel habits

- Advice regarding timed voiding, i.e., every 3–4 hours, frequent enough to avoid urgency/incontinence, including during school hours; and before going to bed
- Voiding should be unhurried and complete
- Instructions to drink liberal amounts during the day (50 mL/kg/day), not to drink excess with the evening meal, and to minimize fluid intake afterward
- Encouragement toward good bowel health, characterized by a soft bowel movement, with a diameter less than 2 or 3 cm, passed without discomfort every morning before the child leaves for school
- Strategies to improve bowel emptying include the intake of foods that soften stool, use of a stool softener, and patient and parent education about optimal posture to relax the pelvic floor muscles. Children should be counseled not to rush or push

Clinical Pearl

- Training programs that involve either "holding on" and waiting before voiding or stopping the flow of urine have not been shown to be effective, hence have no role.

If the above preliminary management program does not result in dryness in 3 months, then the use of an alarm should be considered.

Alarm Therapy

Alarm therapy is presumed to cure NE by the conditioning effects on arousal and by increasing nocturnal bladder capacity. The device consists of a sensor, attached to the child's underwear or to a mat placed below the child, which is activated when the child begins to wet the bed. It works on the principle that sustained use causes conditioned wakening to a full bladder. Success with alarm therapy is related to the motivation of the child and that of the parent who must participate in the therapy. It requires a minimum 3-month trial. Its use results in dryness in about two-thirds of children and the relapse can be minimized with behavioral therapy prior to alarm therapy, by close follow-up during therapy, and by 'overlearning,' which involves slowly increasing the evening fluid intake in successfully treated patients while continuing to wear the alarm.

Pharmacological Treatment

Pharmacological options are resorted when behavioral therapy and alarm fail (Table 2).

Desmopressin acetate (DDAVP) reduces nocturnal polyuria but relapse rates are high and offers only a control rather than a cure of the NE. It is recommended when fast-acting, short-term improvement is the priority, if alarm treatment is not successful, or the parents or child no longer want to use an alarm. It is most effective in children 8 years and older who have MNE with nocturnal polyuria, normal bladder capacity, and infrequent bed wetting. The immediate onset of action of DDAVP allows the flexibility of intermittent administration

TABLE 2: Drugs used in the management of enuresis

Drug	Dosage	Adverse Effects

• Anticholinergics
  ○ Oxybutynin
  ○ Tolteridine (has selectivity for urinary bladder over salivary glands)
	• Nighttime wetting: 0.1 mg/kg HS; nighttime wetting with daytime symptoms: 0.1 mg/kg/dose PO up to tid; not to exceed 5 mg/dose
	• 0.5–1 mg PO QD/BID
		• Include dry mouth, blurred vision, headache, nausea, dizziness, gastrointestinal upset, and tachycardia

• Desmopressin (DDAVP)	• 0.2 mg, may be titrated upward to a maximum of 0.6 mg • Melt tablet 120 μg OD, maximum dose is 360 μg • Should be administered 1 h before bedtime	• The adverse event of water intoxication and hyponatremic seizures can be avoided by withholding oral fluids 2 h prior to bedtime
• Imipramine	• 25 HS, may be titrated upward • 6–12 years: maximum dose 50 mg/dose • >12 years: maximum dose 75 mg/dose	• Drowsiness, lethargy, agitation, depression, sleep disturbance, and gastrointestinal upset may occur • Rare adverse effects include seizures, cardiac arrhythmias, and death from accidental overdose. Pretreatment electrocardiography to identify underlying rhythm disorders is recommended

for special occasions or long-term use to maintain dryness. For long-term use, DDAVP may be used for 3 months then 3-month quantities; a slow stepwise dose reduction over 6–7 months decrease relapse rates after discontinuation of therapy.

The International Children's Continence Society recommends that imipramine should be used only when all other therapies have failed, only after assessment by a healthcare professional who specializes in the management of bedwetting that has not responded to treatment. It should not to be used in combination with an anticholinergic.

Imipramine facilitates urine storage by decreasing bladder contractility and increasing outlet resistance. It inhibits reuptake of norepinephrine or serotonin (5-hydroxytryptamine) at presynaptic neuron. Parents should be warned about the potentially serious, dose-related adverse effects of cardiac arrhythmias. Reboxetine, a noradrenaline reuptake inhibitor, is pharmacologically related to imipramine but is without apparent cardiovascular toxicity. Further study is needed to define the role of this agent in clinical practice.

Anticholinergics are indicated when bladder capacity is found to be small or when there are symptoms of detrusor instability (urge syndrome).

Nocturnal enuresis is more common in children with ADHD, behavioral problems and adenotonsillar hypertrophy. Treatment of these conditions is important for success of management. Complete success of therapy is said to have occurred when there is no relapse even after 2 years of discontinuing therapy.

CONCLUSION

Nocturnal enuresis is very common and has the potential for an appreciable negative emotional impact on affected children. It is important to differentiate MNE from NMNE and pathological conditions associated with enuresis. Behavioral modification promoting good bladder and bowel habits and alarm therapy is the mainstay of management of NE. Pharmacological therapy is indicated when there are additional symptoms and when behavioral and alarm therapy fail. Treatment for comorbid conditions, like constipation and ADHD, must be offered simultaneously.

KEY POINTS

- ☞ A detailed history including a voiding diary are essential for the diagnosis of primary nocturnal enuresis
- ☞ Urinalysis and ultrasonography with a full bladder help rule out pathological conditions with which enuresis may be associated
- ☞ The mainstay of management of primary monosymptomatic nocturnal enuresis is behavioral modification directed at good bowel and bladder habits. Success depends on the motivation of the child and parents
- ☞ An alarm may be used when good bladder and bowel habits alone is not enough
- ☞ Medications are resorted when behavioral therapy and alarm fail.

SUGGESTED READINGS

1. Humphreys MR, Reinberg YE. Contemporary and emerging drug Treatments for urinary incontinence in children. Pediatr Drugs. 2005;7(3):151-62.
2. Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgül S, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the international children's continence society. J Urol. 2010;183:441-7.
3. Nunes DV, O'Flynn N, Evans J, Evans, Sawyer L, Guideline Development Group. Guidelines: Management of bedwetting in children and young people: summary of NICE guidance. BMJ. 2010;341:c5399.
4. Ramakrishnan K. Evaluation and treatment of enuresis. Am Fam Physician. 2008;78(4):489-96.
5. Robson WL. Evaluation and Management of Enuresis. N Engl J Med. 2009;360: 1429-36.

CHAPTER 104

Approach to Renal Tubular Disorders in Children

Manoj G Matnani

INTRODUCTION

Renal tubules are the real brains of the kidney. They reabsorb most of the glomerular ultrafiltrate and fine tune the remainder of urine by the processes of concentration, dilution, acidification, and secretion in order to maintain an intact homeostatic milieu on a continuous basis.

Hence, it is obvious that disorders of the renal tubules will lead to serious fluid-electrolyte and acid base disturbances, affecting the growth and development of the child and sometimes even pose a serious threat to survival.

PATHOPHYSIOLOGY (TABLE 1)

Functionally, various diseases affecting a particular segment of the kidney lead to the following pathophysiological features:

- Disorders affecting the proximal tubule, which is the main site of reabsorption of multiple solutes, e.g., Fanconi's syndrome
- Disorders affecting the loop of Henle and the early parts of the distal tubule, which fine tune the sodium chloride reabsorption and potassium secretion, e.g., Bartter's syndrome and its variants
- Disorders affecting the α-intercalated cells of the cortical collecting ducts, which is the main site for hydrogen ion secretion (aldosterone sensitive segment), e.g., distal renal tubular acidosis (RTA), type 4 RTA, and pseudo-hypoaldosteronism
- Disorders affecting the medullary collecting ducts, which is the anti diuretic hormone (ADH) sensitive segment (responsible for water reabsorption through aquaporin channels), e.g., nephrogenic diabetes insipidus (DI).
- Disorders affecting primarily the phosphate (PO_4^{3-}) reabsorption by the proximal tubule, e.g., X-linked hereditary hypophosphatemic rickets (XLHHR)

TABLE 1: Clinico-physiologic correlation of renal tubular disorders

Segment	Function	Disorder
Proximal tubule	Phosphate transport	Hypophosphatemic rickets
	Glucose transport	Renal glucosuria
	Amino-acid transport	Isolated, generalized amino aciduria
	Bicarbonate transport	Proximal renal tubular acidosis
Ascending limb of loop of Henle	Sodium-potassium chloride transport (NKCC-2 and others)	Bartter's syndrome and variants
Distal tubule	Proton secretion	Distal RTA
	Sodium chloride transport (sodium chloride cotransporter)	Gitelman's syndrome
Collecting duct	Sodium-potassium transport	Pseudohypoaldosteronism
	Sodium transport (epithelial sodium channel)	Liddle's syndrome
	Water transport	Nephrogenic diabetes insipidus

CLINICAL FEATURES (FIG. 1)

Clinical

- Recurrent episodes of dehydration, vomiting, fever causing growth retardation, and failure to thrive
- Polyuria, polydipsia causing constipation and preference for savory foods, and salt craving

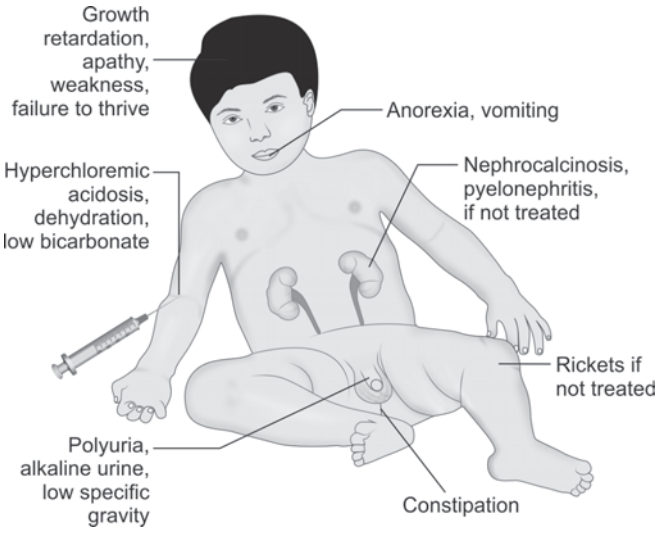


Fig. 1: Features suggestive of renal tubular disorders

- Refractory rickets, bone pains, and muscle weakness causing delayed gross motor milestones
- Renal calculi, and nephrocalcinosis if untreated for prolonged periods
- Hypertension seen in monogenic disorders, e.g., Liddle's syndrome/pseudohypoaldosteronism.

Laboratory

- Hyperchloremic metabolic acidosis
- Metabolic alkalosis with or without hypokalemia
- Hyponatremia with hyperkalemia
- Hypercalciuria with normal serum calcium.

The clinical phenotypes can be classified into following four groups:

1. Hyperchloremic normal anion gap metabolic acidosis: renal tubular acidosis, Fanconi's syndrome
2. Hypokalemic metabolic alkalosis: Bartter's syndrome and its variants
3. Polyuria with/without hypernatremic dehydration with normal acid-base status–nephrogenic DI
4. Rickets with phosphate wasting: Fanconi's syndrome, XLHHR.

Clinical Pearls

Suspect renal tubular disorder in a child with gastroenteritis if:

- The amount of dehydration is out of proportion to the number of loose stools
- Fairly preserved urine output despite severe dehydration.

EVALUATION OF RENAL TUBULAR DISORDERS (ALGORITHMS 1 AND 2)

- Estimate acid-base status—metabolic acidosis or metabolic alkalosis
  - If metabolic acidosis, determine

$$\text{Plasma anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

Normal plasma anion gap is 8–12 mEq/L. Normal anion gap is seen in RTA (renal loss of HCO_3^-) and diarrhea (gastrointestinal loss of HCO_3^-)

- Estimate urine anion gap (UAG)– The UAG (urine net charge) is useful for estimating NH_4^+ excretion in patients with hyperchloremic metabolic acidosis.

$$Na^+ + K^+ + \text{Unmeasured cations} = Cl^- + \text{Unmeasured anions}$$

- Since the sum of charges on cations and anions is equal, the difference between unmeasured anions (sulfates, phosphates, organic anions) and cations (calcium, magnesium) is relatively constant (about 80 mEq/L), hence,

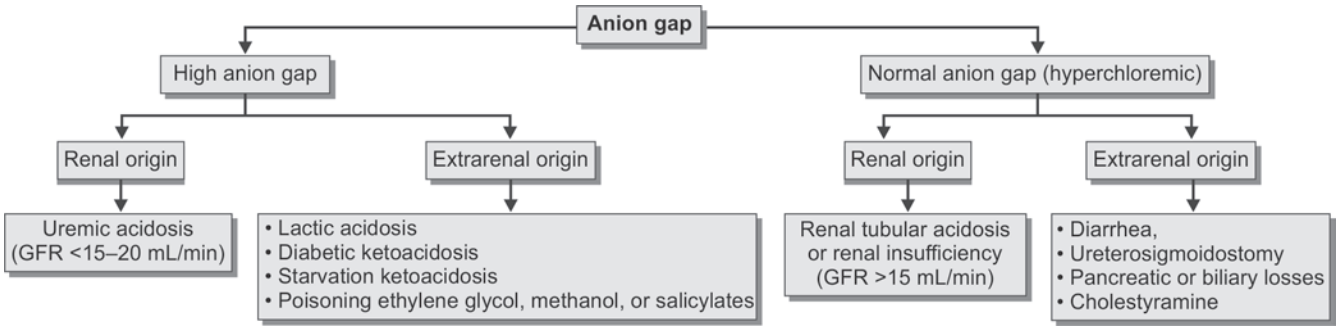
$$Na^+ + K^+ + NH_4^+ = Cl^- + 80$$

The UAG is the difference between the sum of urinary Na^+, K^+ and Cl^-, hence UAG gives an approximate estimate of urinary NH_4^+ excretion

$$UAG = 80 - NH_4^+$$

ALGORITHM 1

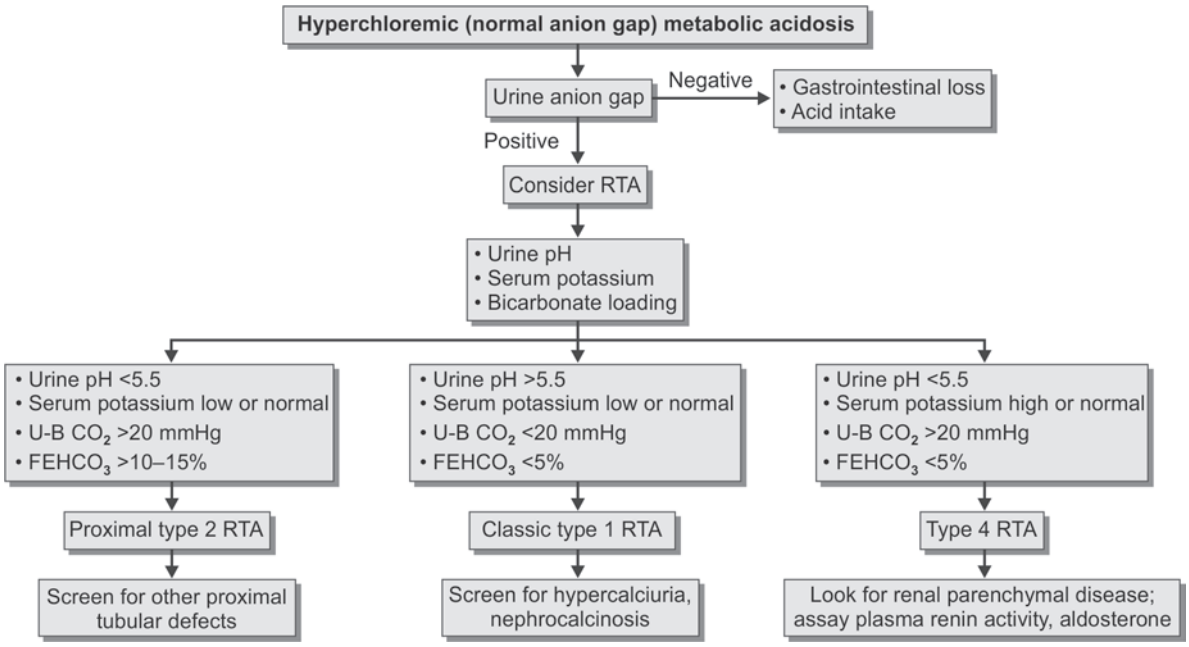
Approach to metabolic acidosis



GFR, glomerular filtration rate.

ALGORITHM 2

Evaluation of a patient with renal tubular acidosis



RTA, renal tubular acidosis; U-B Co_2, urine to blood CO_2 gradiam; FEHCO3, fractional excretion of bicarbonate.

A positive UAG indicates inappropriately low renal NH_4^+ excretion, as seen in RTA.

- Determine the urine pH: It is useful for assessing the integrity of distal urinary acidification.

  Presence of urine pH greater than 5.5 during metabolic acidosis suggests defective distal secretion of H+ (distal RTA); urine pH smaller than 5.5 is seen in proximal RTA or in patients with selective aldosterone deficiency (type 4 RTA)
- If systemic acidosis is absent, an oral ammonium chloride (0.1 mg/kg) load (acid load test) is given to induce acidosis and the capacity of the distal tubule to secrete H^+ is assessed by serial monitoring of the blood and urine pH (done at higher centers as an inpatient procedure)
- To characterize the type of RTA, bicarbonate loading test is done
  - Measurement of fractional excretion of bicarbonate ($FEHCO_3$) and urine to blood CO_2 gradient (U-B CO_2) allows characterization of RTA
  - The urine PCO_2 is above 70 mmHg and the U-B CO_2 gradient is above 20 mmHg in normal individuals
  - Urine PCO_2 below 50 mmHg and U-B CO_2 gradient below 10 mmHg suggests distal RTA
- $FEHCO_3$ (%) =

$$\frac{\text{Urine bicarbonate} \times \text{plasma creatinine}}{\text{Plasma bicarbonate} \times \text{urine creatinine}} \times 100$$

  - A value greater than 15% indicates bicarbonaturia, suggestive of proximal RTA
  - Levels in the normal range (<5%) indicate distal RTA
  - In hyperkalemic (type 4 RTA), levels vary from 5 to 10%
- Fludrocortisone furosemide test: This is a sensitive test to assess distal urinary acidification, used in patients with type 4 RTA.

Additional Tests for Renal Tubular Acidosis (Table 2)

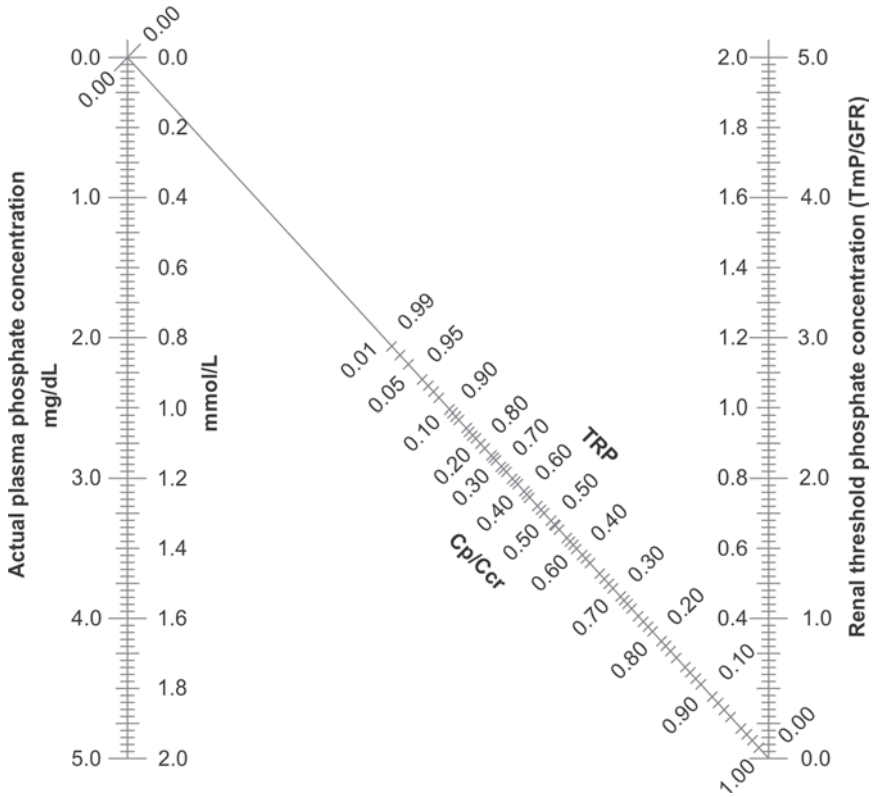
Proximal RTA (type 2) needs evaluation of other proximal tubular functions.

- Evaluation of aminoaciduria, glucosuria, and low molecular weight proteinuria (if available)
- Assessment of phosphate excretion to assess phosphaturia

TABLE 2: Investigations to differentiate types of RTA

	Proximal RTA	Distal RTA	Type 4 RTA
Plasma K^+	Normal/low	Normal/low	High
Urine pH	<5.5	>5.5	<5.5
Urine anion gap	Positive	Positive	Positive
Urine NH_4^+	Low	Low	Low
Fractional HCO_3^-	>10–15%	<5%	>5–10%
U-B PCO_2 mmHg	>20	<20	>20
Urine calcium	Normal	High	Normal/low
Other tubular defects	Often present	Absent	Absent
Nephrocalcinosis	Absent	Present	Absent
Bone diseases	Common	Often present	Absent

U-B PCO_2, urine to blood PCO_2 gradient.



TRP, tubular reabsorption of phosphate; GFR, glomerular filtration rate; TmP/GFR, tubular maximum for phosphate, corrected GFR.

Fig. 2: Bijvoet's nomogram for estimation of renal threshold phosphate concentration(TmP/GFR)

Fractional excretion of phosphate ($FEPO_4$) =

$$\frac{\text{Urine phosphate} \times \text{plasma creatinine}}{\text{Plasma phosphate} \times \text{urine creatinine}} \times 100$$

Tubular reabsorption of PO_4^{3-} (TRP) = 100 – $FEPO_4$.

Normally 5–15% of the filtered PO_4^{3-} is excreted and the tubular reabsorption is 85–95%

Limitation: TRP depends on plasma PO_4^{3-} levels and glomerular filtration rate (GFR) and is therefore, is not an optimal index of tubular PO_4^{3-} handling, especially in patients with hypophosphatemia.

Tubular maximum for PO_4^{3-}, corrected for GFR (TmP/GFR) is independent of plasma PO_4^{3-} and renal function. TmP/GFR (Bijvoet index) (Fig. 2) represents the concentration above which most PO_4 is excreted and below which most is reabsorbed. The normal value is 2.8–4.4 mg/dL with lower values for older children and can be calculated from the following nomogram.

Distal RTA (type 1): All patients should undergo:

- Hearing evaluation to diagnose proton adenosine triphosphatase channel defects causing distal RTA
- Renal ultrasound for medullary nephrocalcinosis (Fig. 3) and renal calculi
- Measurement of urinary calcium and citrate excretion to assess hypercalciuria and hypocitraturia

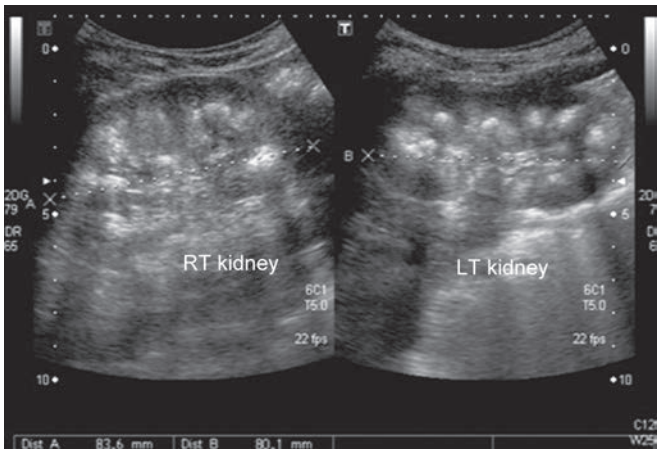
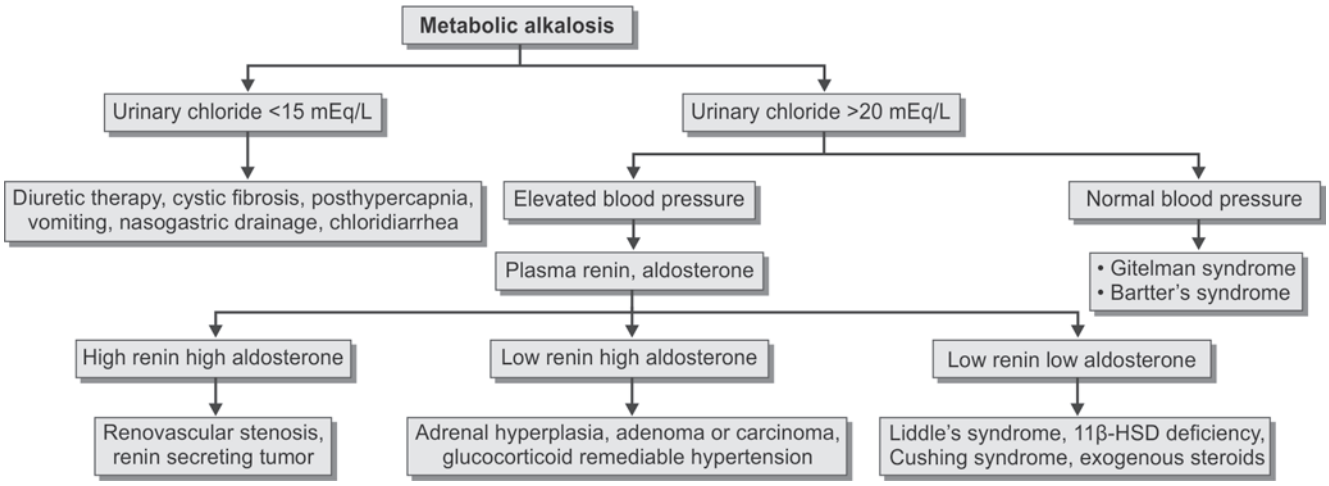


Fig. 3: Medullary nephrocalcinosis in a child with distal RTA

- Hypercalciuria (see appendix 1 for normal values) and hypophosphaturia occur due to:
  - The release of calcium phosphate from bone in order to buffer excess H^+ during acidosis
  - The direct effects of acidosis on tubular reabsorption of these ions
- Hypocitraturia results from:
  - Citrate utilization in proximal tubular cells
  - Due to high luminal pH favoring conversion of $citrate^{3-}$ to the readily absorbable $citrate^{2-}$

ALGORITHM 3

Evaluation of a patient with metabolic alkalosis and hypokalemia



11 β-HSD, 11b-hydroxysteroid dehydrogenase deficiency.

Hyperkalemic RTA (type 4): In children, aldosterone unresponsiveness is more common than aldosterone deficiency, and is commonly associated with obstructive uropathy.

Transtubular potassium gradient (TTKG): This provides an accurate estimate of aldosterone effect on late distal and cortical collecting tubules.

$$TTKG = \text{Urine } K^+ \times \text{Plasma osmolality}$$

It is an index of K^+ gradient in the distal tubular lumen (Plasma K^+ × Urine osmolality) and interstitial blood capillaries. Normal range is 6–12.

- Hypokalemia from extrarenal causes results in renal K^+ conservation and TTKG smaller than 2
- Higher TTKG suggests renal losses, as seen in hyperaldosteronism
- During hyperkalemia, the expected TTKG should be greater than 10, an inappropriately low level suggests hypoaldosteronism or tubular resistance to aldosterone.

EVALUATION OF METABOLIC ALKALOSIS (ALGORITHM 3)

- Rule out common causes first, viz. vomiting, nasogastric suction, diuretic usage, or drugs like bicarbonate and steroids
- Examine for presence of dehydration/hypovolemia and hypertension
- Clinical features like failure to thrive and triangular facies suggest Bartter's syndrome
- Laboratory investigations needed serum electrolytes (Na^+, K^+, Cl^-), urine electrolytes (Na^+, K^+, Cl^-), and plasma renin activity and aldosterone levels in patients with hypertension
- Rare monogenic disorders (Liddles, syndrome, 11β-hydroxysteroid dehydrogenase deficiency) present with hypertension, mild metabolic alkalosis, and hypokalemia and can be evaluated through the algorithmic approach mentioned in algorithm 3.

TREATMENT GUIDELINES

- Alkali supplements: bicarbonate solutions (Table 3) and tablets to correct acidosis. The requirement in distal RTA is around 2–5 mEq/kg/day, and higher, around 5–20 mEq/kg/day in proximal RTA/Fanconi's syndrome

TABLE 3: Commonly available alkali and phosphate supplements

Preparation	Composition (per 1000 mL)	Remarks
Bicitra	• 100 g sodium citrate • 60 g citric acid	1 mL = 1 mEq base
Polycitra	• 110 g potassium citrate • 100 g sodium citrate • 66.8 g citric acid	1 mL = 2 mEq base = 1 mEq Na^+ = 1 mEq K^+
Polycitra K	• 220 g potassium citrate • 66.8 g citrric acid	1 mL = 2 mEq base
Shohl solution	• 140 g citric acid • 90 g sodium citrate	1 mL = 1 mEq base
Joulie solution	• 136 g dibasic sodium phosphate • 58.8 g phosphoric acid	1 mL = 30 mg inorganic phosphorous
Neutral phosphate	• 18.2 g sodium dihydrogen phosphate • 145 g dibasic sodium phosphate	60 mL = 1000 mg inorganic phosphate
Sodium bicarbonate	• Solution (7.5%) • 325, 650 mg tab	1 mL = 0.9 mEq base 325 mg = 4 mEq base
Calcium carbonate	• 250, 500 mg tab	1000 mg = 22.3 mEq base

- Phosphate supplements with vitamin D are needed in Fanconi's syndrome and hypophosphatemic rickets
- Electrolyte solutions to correct hypokalemia and hyponatremia are needed in salt losing tubulopathies like Fanconi's syndrome, Bartter's syndrome, etc.
- Thiazides and sometimes prostaglandin inhibitors like indomethacin are used to decrease polyuria (to augment growth) in Bartter's syndrome and nephrogenic DI.

APPENDIX 1

Hypercalciuria is defined as

- Twenty four-hour urine calcium greater than 4 mg/kg/day
- Spot urine calcium: creatinine ratio greater than 0.8 (0–6 months)
  - Greater than 0.6 (6 months–2 years)
  - Greater than 0.2 (>2 years).

KEY POINTS

- ☞ Early diagnosis of renal tubular disorders is of paramount importance as most of them present with recurrent life-threatening episodes of vomiting and dehydration
- ☞ Early treatment is essential as it prevents growth failure, stunting, and wasting along with metabolic bone complications like recurrent pathological fractures, osteopenia etc.
- ☞ Early treatment of distal renal tubular acidosis (RTA) prevents grave consequences like medullary nephrocalcinosis and end-stage renal disease (ESRD), hence it is a preventable cause of ESRD
- ☞ Early treatment of distal RTA leads to good catch up growth in children
- ☞ It is important to rule out renal tubular disorder in patients presenting with recurrent dehydration as the blood gas and electrolyte abnormalities frequently overlap in both the conditions (e.g., metabolic acidosis and hypokalemia in gastroenteritis and RTA, metabolic alkalosis and hypokalemia in vomiting and Bartter's syndrome)
- ☞ Children with obstructive uropathy should undergo a detailed renal tubular evaluation to categorize the tubulopathy.

SUGGESTED READINGS

1. Ali U. Renal tubular disorders, Indian Academy of Pediatrics: Specialty series on Pediatric Nephrology. 212-23.
2. Bagga A, Bajpai A, Menon S. Approach to renal tubular disorders. Indian J Pediatric 2005;72:771-6.
3. Bagga A, Sinha A, Gulati A. Metabolic alkalosis, Textbook on Protocols in Pediatric Nephrology. 2012.pp. 66-72.
4. Bagga A, Sinha A, Gulati A. Renal Tubular Acidosis, Textbook on Protocols in Pediatric Nephrology. 2012. pp. 55-65.
5. Sobh M. Renal Tubular Disorders, Textbook on Essentials of Clinical Nephrology. 2000. pp. 197-211.

CHAPTER 105

Nephrotic Syndrome in Children

Mukta Mantan, Anand S Vasudev

INTRODUCTION

Nephrotic syndrome is a common chronic disorder in children, characterized by heavy proteinuria (>40 mg/m^2/h in timed urine sample), hypoalbuminemia, and edema. The proteinuria in nephrotic syndrome is relatively selective and constitutes primarily of albumin. The peak incidence of the disease is in between 2 and 6 years of age. Ninety percent of the children with minimal change disease respond to treatment with steroids. Majority of these relapse and about 50–60% become steroid-dependent or frequent relapsers. Frequency of relapses is higher in first 10 years after the diagnosis. By puberty the relapse rate decreases and most children show sustained remission.

Some common definitions to define the course of nephrotic syndrome are tabulated in table 1.

The most common etiology of childhood nephrotic syndrome is minimal change disease. The other glomerular etiologies causing nephrotic syndrome are focal segmental glomerular sclerosis, mesangioproliferative glomerulonephritis, membranoproliferative glomerulonephritis, and membranous nephropathy.

TABLE 1: Definitions

Terms	Definitions
Nephrotic syndrome	Presence of edema, serum albumin <2.5 g/dL and proteinuria >40 mg/m^2/h in timed urine sample or urine spot (mg/mg) Up/Uc >2
Relapse	Urinary protein excretion >40 mg/m^2/h or >+3 by dipstick on spot sample for 3 consecutive days
Remission	Urinary protein excretion <4 mg/m^2/h in timed sample, nil or trace by dipstick on spot sample for 3 consecutive days
Frequent relapses	Two or more relapses in 6 months of initial response or four or more in any 12-month period
Steroid dependence	Occurrence of 2 consecutive relapses during steroid therapy or within 2 weeks of its cessation in absence of infections
Steroid resistance	Failure to achieve remission after 4 weeks of daily therapy of steroids (prednisolone oral) 2 mg/kg/day
Initial resistance	Nonresponse to initial steroid therapy (2 mg/kg/day daily for 4 weeks)
Late resistance	Failure to respond in subsequent relapses after initial response to steroids

EVALUATION

The primary evaluation of a child with suspected nephrotic syndrome includes estimation of serum total proteins, albumin, globulin, cholesterol, urea, and creatinine concentrations. Urinary proteins can be estimated with dipsticks. Values of more than +3 proteins are indicative of nephrotic range proteinuria. Urinary spot samples can be used for determining the urinary protein or creatinine ratio. Values beyond 2 are suggestive of nephrotic range proteinuria**.** Hepatitis B status status should be determined if the child is unimmunized. Serum complement (C3) levels are recommended if persistent hematuria or hypertension occurs.

INDICATIONS FOR RENAL BIOPSY

Renal biopsy is indicated for children with steroid-resistant nephrotic syndrome, age at onset below 1 year or more than 12 years, gross or persistent microscopic hematuria, or persistent hypertension. Children with features suggestive of systemic lupuserythematosus, other secondary causes of nephrotic syndrome, or before starting calcineurin inhibitors should also be biopsied.

MANAGEMENT OF NEPHROTIC SYNDROME INCLUDES SPECIFIC AND SUPPORTIVE MANAGEMENT

Specific Management

Treatment of the Initial Episode

Indian Society of Pediatric Nephrology currently recommends that initial episode of nephrotic syndrome be treated with

prednisolone at 2 mg/kg (max 60 mg) or 60 mg/m^2 in single or divided dose for 6 weeks followed by 1.5 mg/kg (max 40 mg) or 40 mg/m^2 single morning dose on alternate days for next 6 weeks.

Management of Relapse

Identify and treat any infections present. Prednisolone is administered at a dose of 2 mg/kg/day until protein is nil or trace for 3 consecutive days followed by 1.5 mg/kg/day on alternate days for 4 weeks and then discontinued abruptly.

Frequent Relapser and Steroid-dependent

Long-term alternate day oral prednisolone is the initial strategy. Slow tapering of prednisolone is done to reach to a maintenance dose of 0.25–0.5 mg/kg on alternate days. These doses are given for prolonged periods of 9–18 months. Requirement of steroids at doses more than 0.5 mg/kg/day is an indication for use of alternative agents. The commonly used steroid sparing drugs are levamisole, mycophenolate mofetil, and alkylating agents (cyclophosphamide and chlorambucil). Calcineurin inhibitors like cyclosporine and tacrolimus are used sparingly for steroid-sensitive disease (Algorithm 1). Specific drug usage is given in table 2.

Steroid-resistant Disease

All patients with minimal change disease, focal segmental glomerulosclerosis, or mesangioproliferative changes on renal biopsy are treated with calcineurin inhibitors like cyclosporine and tacrolimus. The duration of treatment is at least 2–3 years for steroid-resistant disease. The response rate to these agents is about 70–80%. Intravenous steroids like methylprednisolone and dexamethasone have been used for prolonged periods in the past, but due to their poor response rates and high toxicity, their use is discouraged. Intravenous cyclophosphamide monthly pulses in doses of 500 mg/m^2 for 6 doses along with low dose alternate day steroids have a response rate of about 50%. This drug can be used if the cost of calcineurin inhibitors is a constraint.

Supportive Management

Diet

A balanced diet adequate in protein (1.5–2 g/kg) and calories is recommended. Fats should provide less than 30% calories and saturated fats should be avoided. Salt restriction is advised only for patients with persistent edema or hypertension.

ALGORITHM 1

Management protocol of childhood nephrotic syndrome

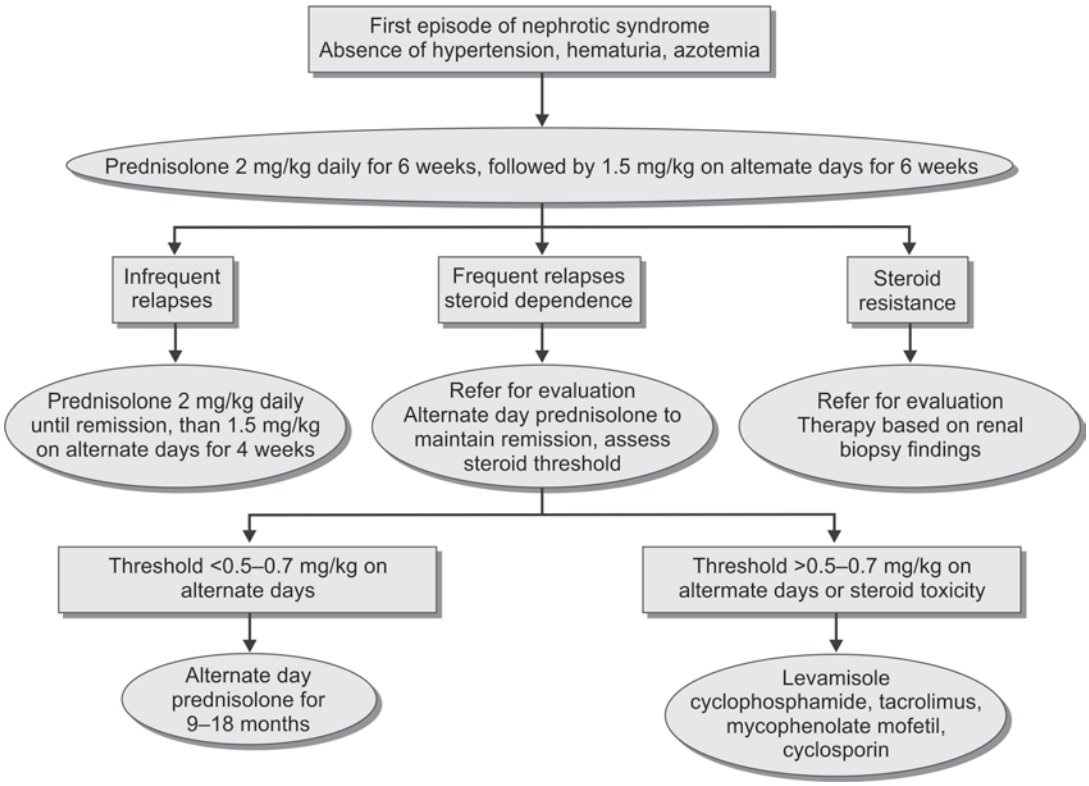


TABLE 2: Drugs used for treatment of steroid-sensitive nephrotic syndrome

Drugs	Dosage and side effects
Levamisole	Immunomodulatory drug. Doses of 2–2.5 mg/kg/day on alternate days for 12–24 months. Low dose alternate day prednisolone is coadministered. Side effects include neutropenia, rashes, cutaneous vasculitis, and gastrointestinal symptoms. Monitoring of total leukocyte counts recommended every 3–4 months. Available 50 mg/150 mg tablets
Cylcophosphamide	It is administered at a dose of 2–2.5 mg/kg/day for 12 weeks. Prednisolone is coadministered at a dose of 1.5 mg/kg on alternate days for 4 weeks, followed by 1 mg/kg the following 8 weeks; steroid therapy tapered and stopped in 2–3 months. The drug should be started preferably in remission. Side effects include bone marrow suppression with leukopenia, hemorrhagic cystitis, alopecia, vomiting, and gonadal toxicity. Monitoring of total leukocyte counts recommended every 2 weeks. Available as a 50 mg tablet
Mycophenolate mofetil	Is a purine antagonist; is a prodrug that is rapidly hydrolyzed to its active metabolite mycophenolic acid in the liver. It is given in doses of 25–35 mg/kg/day in 2 doses (12 hourly) for prolonged periods (1–2 years). Side effects include gastrointestinal intolerance. The drug can also cause lymphopenia. Monitoring of counts and LFT. Available as 250 mg/500 mg tablets.
Cyclosporine	Inhibits interleukin-2-driven T-cell activation. In SSNS used in doses of 3–5 mg/kg (100–150 mg/m^2) in 2 divided doses for 1–2 years. For SRNS duration of therapy 2–3 years. Co-administration of low dose corticosteroids is often required. Side effects includes nephrotoxicity, hypertension, and hypertrichosis. Monitor LFTs every 2–3 months. Kidney biopsy is recommended after 2–3 years of use to identify nephrotoxicity. While drug levels are recommended to monitor toxicity, finances often becomes a limitation. It is available as as syrup (100 mg/mL) and capsules (25, 50, and 100 mg)
Tacrolimus	Doses of 0.15–0.20 mg/kg/day. Available as 0.5 mg/1.0 mg/ 2.0 mg tablets. Side effects are nephrotoxicity, and hyperglycemia, neurotoxicity. Cosmetic side effects are less with tacrolimus compared to cyclosporine. Available as 0.5, 1.0 mg capsules/tablets
Rituximab	Is a chimeric monoclonal antibody that inhibits CD20 mediated B lymphocyte proliferation and differentiation. Used in severe steroid dependency. It is given at doses of 375 mg/m^2 as weekly infusion for 2–4 doses. It is an expensive drug and should be used as a salvage drug after using all the above drugs. Available in 100 mg/500 mg vials

SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; LFT, liver function test.

TABLE 3: Management of edema in nephrotic syndrome

Step 1	Assess volume status*
Step 2a	If hypovolemia give 5 or 20% albumin infusion**
Step 2b	If normovolemia or hypervolemia, furosemide 2–8 mg/kg/day. Add spironolactone 2–3 mg/kg/day at high doses of furosemide. Restrict sodium intake. If inadequate response, add metalozone (0.1–0.3 mg/kg/day) or hydrochlorothiazide 2–3 mg/kg/day.
Ill sustained response to above measures	
Step 3	Administer intravenous furosemide 2–3 mg/kg/day every 12 h
Step 4	Consider intravenous furosemide infusion 0.1–1.0 mg/kg/h if the intravenous bolus effect not sustained
Step 5	If significant edema persists, give 20% albumin infusion with intravenous furosemide over 4 h

*Assess volume status clinically-monitor pulse, blood pressure. In patients with hypovolemia, blood urea may be elevated, fractional excretion of sodium <0.2%

**20% albumin may be diluted in normal saline or 5% dextrose to prepare 5% albumin if preparation unavailable.

Source: Vasudevan A, Mantan M, Bagga A. Management of edema in nephrotic syndrome. Indian Pediatr. 2004;41:787-95.

Edema

Judicious use of diuretics helps in controling edema. A protocol of edema management is given in table 3. Rapid diuresis can occur with synergistic therapy, resulting in hypovolemia and hypokalemia. Monitoring of electrolytes is recommended during diuretic therapy.

The complications of nephrotic syndrome and their management is given in table 4.

TABLE 4: Complications of nephrotic syndrome and their management

Complication	Management
Infections	Most common being peritonitis, cellulitis, and pneumonias. Penicillin most effective. Injectable third-generation cephalosporins and aminoglycosides used in serious cases. Duration of therapy 10–14 days
Thrombo-embolism	Ultrasound Doppler for diagnosis of deep vein thrombosis is useful. Ventilation perfusion scan helps in identification of pulmonary embolism. Low molecular weight heparin+ oral warfarin for 3 months duration or till relapse persists. Aim INR between 2.5–3.0 when on warfarin therapy
Hyperlipidemia	Dietary management with fat restriction. No clear guidelines for use of statins in children. Simvastatin and atorvastatin can be used in children with persistent hypercholesterolemia in steroid-resistant disease
Hypertension	ACE inhibitors and ARB's preferred drugs. Beta-blockers and calcium channel blockers can be used additionally if not controlled. Use diuretics if edema present
Steroid toxicity	Short stature, cataract, glaucoma, and hypertension features of toxicity. Use alkylating and steroid sparing agents like cyclophosphamide, levamisole, cyclosporine, and mycophenolate mofetil

INR, international normalized ratio; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

KEY POINTS

- ☞ Treatment with daily steroids for 4 weeks distinguishes steroid-sensitive from steroid-resistant nephrotic syndrome
- ☞ Edema needs to be treated only if there is significant ascites, respiratory distress due to ascites or effusions, excoriation, and extrusion of fluid from the skin
- ☞ Intravenous albumin is indicated for treatment of hypovolemia in nephrotic syndrome
- ☞ Alternative agents like cyclophosphamide, levamisole, and mycophenolate mofetil are used in patients having a frequently relapsing or dependent course
- ☞ Calcineurin inhibitors along with low dose alternate day steroids are the first-line drugs for treatment of steroid resistant disease.

SUGGESTED READINGS

1. Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, Senguttuvan P, et al. Management of steroid sensitive nephrotic syndrome: Revised guideline. Indian pediatric nephrology group. Indian Pediatric. 2008;45:203-14.
2. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res. 2005;122:13-28.
3. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet. 2003;362: 629-39.
4. Gulati A, Bagga A, Gulati S, Mehta KP, Vijayakumar M, Indian Society of Pediatric Nephrology. Management of steroid resistant nephrotic syndrome. Indian Pediatr. 2009;46:35-47.
5. Lombel RM, Gipson DS, Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO Kidney Disease: Improving Global Outcomes. Pediatr Nephrol. 2013:28:415-26.
6. Vasudevan A, Mantan M, Bagga A. Management of edema in nephrotic syndrome. Indian Pediatr. 2004;41:787-95.

CHAPTER 106

Approach to Short Stature

Vaman V Khadilkar, Supriya Phanse Gupte

INTRODUCTION

Short stature although common can be a challenging problem to deal with. Growth monitoring of children from birth till adulthood provides invaluable information toward diagnosis and management of a whole range of pediatric disorders. Growth monitoring can prevent loss in the adult height, which may occur if diagnosis is delayed. Therefore, it is very important to monitor growth of the child on a regular basis. Parents often bring their child with complaint of short stature because they compare the height of the child with his/her peers at school. This can be misleading and needs to be confirmed by use of appropriate growth charts.

When a short child is referred, following important points need to be considered:

- Define whether the child is actually short or not using appropriate growth charts
- Differentiate a short normal child from a child with an organic cause
- Decide whether a child can be monitored or needs immediate referral.

DEFINITION

A child is short if the height is less than 2 standard deviations (SDs) below the mean for age and gender for country specific updated population standards. However, a child falling much below his midparental (target) range percentile and a child having a poor growth velocity (<25th percentile) also needs to be investigated.

ETIOLOGY

Most of the children presenting with short stature have physiological causes, namely familial short stature and constitutional delay in growth and puberty (CDGP). Chronic illness and malnutrition also form major contributors in a developing country like India. A small number have an endocrinopathy, a syndrome, or a skeletal dysplasia.

A wide variety of conditions both physiological and pathological can lead to short stature in children. In many cases, short stature may be the only presentation of the disease and therefore, investigating the cause of short stature is important.

Familial Short Stature

These are usually normal short children born to short parents. Their height falls below the 3rd percentile of population standards but is within the midparental height range. However, they need monitoring of growth velocity to ensure normal growth. Rarely, short stature in both the parents is caused by a heterozygous condition manifesting in a mild form and the child may be a homozygote with severe short stature such as in familial cases of growth hormone deficiency. In dominantly inherited conditions such as hypochondroplasia, the affected parent is short and transmits the mutated gene to the offspring resulting in short stature in the child. Treatment of these children is warranted.

Constitutional Delay in Growth and Puberty

This is usually seen in boys. These children grow well in infancy and early childhood. Thereafter, their height begins to falter on growth charts and usually lies just below the 3rd percentile below mid-parental height (MPH). It cruises parallel to the 3rd percentile from thereon. They also have delayed puberty further worsening the growth pattern at puberty. Family history of short stature in childhood and adolescence, late pubertal spurt, and achievement of final height as per genetic potential usually exists, mostly in the father. These children usually follow the same trend and will achieve their final height as per their genetic potential. If the puberty is delayed beyond the age of 15 years, it may require treatment in the form of small dose of sex steroids.

Box 1: Causes of short stature

- Physiological short stature:
  - Idiopathic short stature
    - Familial
    - Nonfamilial
  - Constitutional delay in growth and puberty
- Pathological short stature:
  - Malnutrition
  - Chronic illness:
    - Chronic anemia
    - Chronic renal disease, renal tubular acidosis
    - Chronic liver disease
    - Chronic pulmonary disease including asthma
    - Celiac disease, giardiasis
    - Hematological disorders, e.g., thalassemia
  - Endocrinopathies:
    - Growth hormone deficiency
    - Hypothyroidism
    - Cushing syndrome
    - Pseudohypoparathyroidism
  - Syndromes:
    - Turner syndrome
    - Down syndrome
    - Noonan syndrome
    - Other syndromes, e.g., Edward syndrome, Patau syndrome
  - Small for gestational age:
    - Nonsyndromic
    - Syndromic with primordial short stature: Russell-Silver, Seckel syndrome
  - Nutritional rickets, hypophosphatemic rickets
  - Skeletal dysplasia, osteogenesis imperfecta
  - Intracranial tumors, trauma, surgery, and irradiation
  - Psychosocial short stature
  - Medications: prolonged steroid intake, methylphenidate

Malnutrition and Chronic Illness

Chronic malnutrition leads to stunting of growth due to lack of nutrient supply, associated illnesses leading to a state of catabolism, anemia, and micronutrient deficiency. Chronic illnesses, such as chronic anemia, chronic kidney disease, liver disease, heart and respiratory disease including asthma, are catabolic states. In addition, poor appetite, electrolyte imbalance and congestive heart failure further worsen the condition. Malabsorption syndromes including celiac disease also cause stunting.

Growth Hormone Deficiency

These children usually have normal weight and height at birth. They grow normally in the first year of life as growth in this phase is influenced by nutrition and is mediated by insulin and related growth factors. Growth falters in early childhood leading to severe stunting. They have immature facies, childlike voice, and small hands and feet. Body proportions are preserved. Obesity is uncommon in Indian children unlike their counterparts in Western countries. They have low stimulated growth hormone levels, insulin-like growth factor 1 and insulin-like growth factor binding protein 3. They respond well to growth hormone therapy. Rare exceptions are conditions with growth hormone antibodies and growth hormone insensitivity syndromes.

Hypothyroidism

Short stature can be the presenting complaint of children with acquired hypothyroidism. They are short and puffy with coarse facies. Occasionally, a child with less severe congenital hypothyroidism (e.g., dyshormonogenesis) may present in childhood for the first time.

Cushing Syndrome

In childhood, it is usually the result of exogenous steroid administration or adrenal tumors. Rarely, in older children, a pituitary lesion or a carcinoid tumor may be the cause. These children are short and obese. Other stigmata, such as purplish striae, muscular weakness, and buffalo hump, are not commonly seen in children. Hypertension is an important indicator of this disorder in children.

Turner Syndrome

Short stature is a consistent feature of Turner syndrome especially as the child grows older. The other stigmata include webbing of neck, low posterior hair line, antimongoloid slant, widely spaced nipples, wide carrying angle, Madelung deformity, and short $4^{th}/5^{th}$ metacarpals or metatarsals. They develop ovarian failure early in life and so have no/delayed puberty and infertility. They are predisposed to autoimmune disorders such as autoimmune thyroid disease and celiac disease. Higher incidence of coarctation of aorta, left sided heart disease, renal disorders, and pigmented nevi have been noted in these children. All features may not be present in most children and short stature may be the only indicator of the disorder. Growth hormone is a licensed indication for treatment of short stature in Turner syndrome.

Psychosocial Short Stature

Emotionally deprived children do not grow well. They do not respond to nutritional supplementation or any other form of treatment. However, it is a reversible condition and these children grow well once placed in a loving environment as their pituitary hypothalamic function reverts to normal when they live in a stress free environment.

Small for Gestational Age Sequelae

Most small for gestational age (SGA) children catch up by 2–4 years of age. However, up to 30% do not catch up. Those who fail to catch up and remain below -2.5 SD score for the population are candidates for growth hormone therapy.

Skeletal dysplasias, hypophosphatemic rickets, and pseudohypoparathyroidism form rare causes of short stature and should be looked for.

MANAGEMENT

Measurement of Height/Length

It is important to accurately measure height with a stadiometer, to avoid errors in measurement. For children less than 2 years of age, the length is measured with the child in supine position with the help of an infantometer.

Calculate the Midparental Height (Target Height) and the Target Range

Midparental height (MPH) = (father's height + mother's height + 13)/2 for boys and
= (father's height + mother's height - 13)/2 for girls.

Target range = MPH ± 6 cm

Plot the child's height, and target height (with target range) on country specific contemporary growth charts: for children under the age of 5 years, use of WHO 2006 growth standards is recommended.

If previous height records are available, plot previous height readings to observe the pattern of the growth.

Calculate the annual growth velocity as change in height divided by change in time. For example, if a child grows 3 cm in 6 months, the annualized growth velocity is 3 divided by half year which is 6 cm.

Normal Growth Velocity

- In 1st year: 25 cm/year
- In 2nd year: 12 cm/year
- In 3rd year: 6 cm/year
- From 4th year till pubertal spurt: 5 cm/year
- During puberty: 6–8 cm/year in girls and 10–12 cm/year in boys.

Growth velocity can be plotted on growth velocity curves. Growth velocity less than 25th percentile is abnormal and needs investigations.

If previous height records are not available: assess the height of the child in relation to the midparental height.

If the height of the child is more than 3rd percentile and within target range, it is a normal child. No investigations are needed. Serial height measurements need to be plotted on growth charts at 6 monthly-yearly intervals. Monitor growth velocity annually.

If height of the child is less than 3rd percentile but within target range, it is a short normal child with familial short stature. Continue annual plotting on growth chart and monitor growth velocity. A high index of suspicion is needed to suspect and diagnose a subtle growth disorder in parents, such as hypochondroplasia, which may be inherited by the child.

Indications for Further Workup

- Height less than -2.5 SD of population standard for age and gender
- Height less than -1.5 SD below the MPH
- Growth velocity has deteriorated and dropped below 25th percentile.

Clinical Pearl

- A child with height plot above the 3rd percentile may still be abnormal if he falls below the target range or has a growth velocity less than 25th percentile.

Preliminary Workup

History

A detailed history of duration of apparent short stature, history of pubertal delay in adolescent boys and girls should be noted. Evidence of chronic illnesses, such as renal, liver, malabsorption, respiratory illness including asthma, and tuberculosis, should be looked for.

History of severe headache, vomiting suggestive of intracranial space occupying lesions, intracranial surgeries, craniospinal irradiation, head trauma, history of other malignancies, bone disorders, and prolonged steroid intake would add valuable information.

Birth history including birth weight (SGA), birth length, history of breech delivery, birth trauma, neonatal hypoglycemia, and neonatal jaundice should be asked for. Family history of consanguinity, short stature, delayed puberty, sterile uncle/aunts, and tuberculosis should be reviewed.

Developmental history suggestive of delayed milestones, and visual disturbances (r/o anatomical causes like corpus callosum agenesis, septo-optic dystrophy associated with multiple pituitary hormone deficiency) could be pointers toward an anatomical brain abnormality and congenital hypothyroidism.

A proper assessment of dietary intake helps to ensure adequate calorie intake and assess for malnutrition. Social history to assess for signs of child abuse and neglect should be looked for.

Anthropometry

Interpreting the severity of height and weight deficit can be very useful to reach the diagnosis. This can be assessed by calculating child's height age and weight age.

Height age is assessed by drawing a horizontal line from the present height plot to the 50th percentile and drawing a perpendicular on the X-axis (age in years) on the growth chart. The point on the X-axis where the perpendicular meets, gives the height age. Weight age is calculated in a similar way. If the weight age is more retarded than the height age, it is a case of malnutrition, chronic disease, or syndrome. The height age is more retarded than the weight age in endocrinopathies as weight is usually preserved.

In addition to height and weight, the upper segment/lower segment ratio (US/LS ratio) provides useful information and helps in establishing a definite etiology. The lower segment is measured from the superior border of pubic rami till the feet with the child standing upright. The upper segment (vertex-pubic symphysis) is calculated by subtracting the lower segment from the total height. Another method of assessing US/LS ratio is by measuring the sitting height and subtracting it from the standing height to get the subischial limb length.

TABLE 1: Pointers toward diagnosis from history

Small for gestational age (SGA)	SGA sequelae, Russell-Silver syndrome, Seckel syndrome
Breech delivery	Growth hormone deficiency (GHD), multiple pituitary hormone deficiency (MPHD)
Neonatal hypoglycemia, jaundice	GHD, MPHD
Family history of consanguinity	Genetic causes
Family history of delayed puberty with short stature with normal final height	Constitutional delay in growth and puberty
Family history of short stature	Familial short stature, parents with heterozygote state for conditions such as achondroplasia, hypochondroplasia
Short stature in infancy	Syndromic short stature, skeletal dysplasia
Short stature in childhood	GHD, hypothyroidism, MPHD, chronic illness, Turner syndrome
Intracranial tumors, irradiation, trauma, surgery	MPHD
Headache, vomiting, visual disturbances	Intracranial tumor
Persistent diarrhea, abdominal distension	Celiac disease
History of asthma, liver, renal disease	Pointers of chronic disease

This can be plotted on sitting height and subischial leg length combined charts.

The US/LS ratio is 1.7:1 at birth. It gradually decreases reaching to a ratio of 1:2 at around 7 years and 1.1:1 at 10 years. It remains so till puberty when it further dips to 0.98:1 due to an earlier spurt in limb height as compared to the spine growth. Toward the end of puberty with an increase in spine height with a nearly stabilized limb length, the ratio again rises to 1:1, which persists thereafter.

Disproportionate short stature is seen in conditions wherein the growth of either the limbs or spine is more affected. In skeletal dysplasias, the limbs are more affected and the spine is spared. An exception is spondyloepiphyseal dysplasia wherein both the spine and limbs are affected. Spinal shortening is seen in storage disease such as mucopolysaccharidosis.

Clinical Pearl

- A short and thin child with weight most severely affected: think of chronic illness, syndromic short stature, and malnutrition
- A short and overweight child: think of endocrinopathy—growth hormone deficiency, hypothyroidism, and Cushing syndrome.

Clinical Examination

It includes a thorough examination to look for any pointers of a specific etiology of short stature. Facial dysmorphism adds important information. Few of these are listed below.

Evidence of anemia, cyanosis, jaundice, signs of chronic illness such as renal, liver, pulmonary disorders including asthma and nutritional deficiency, including features of malabsorption syndrome. Bony deformities including bow legs, knock knees, kyphosis, and scoliosis would indicate involvement of the skeletal system. A detailed systemic examination would add to the information.

Clinical Pearl

- Short stature with anemia should raise suspicion of celiac disease.

1st tier investigations

- Hemogram
- Biochemical investigations:
  - Serum creatinine (renal function)
  - Serum glutamic pyruvic transaminase (liver function)
  - Venous blood gas (if evidence of rickets to rule out renal tubular acidosis in case of rickets)
  - Thyroid function test
  - Anti-tissue transglutaminase (TTG) immunoglobulin A (IgA) (anti-TTG antibody, if low, reconfirm with total IgA levels and immunoglobulin G antibody)
  - Karyotype in a girl with unexplained short stature
- Radiological investigations: bone age [using Gruelich and Pyle, Tanner Whitehouse 3 (TW 3), Gilsanz and Ratib methods].

  Bone age is a useful, cheap, and invaluable investigation in the assessment of short children. In Gruelich and Pyle atlas, comparison of a radiograph of the left hand is done with that of standard age and gender specific radiographs. The age at which the radiograph in the atlas matches closest to the actual one of the patient in terms of maturity of ossification centers of bones, is the bone age of the

Box 2: Causes of proportionate and disproportionate short stature

Proportionate short stature
- Growth hormone deficiency
- Malnutrition
- Rickets
- Chronic illness
- Syndromic short stature
- Small for gestational age sequelae

Disproportionate short stature

Short upper segment
- Mucopolysaccharidosis
- Spondyloepimetaphyseal dysplasia

Short lower segment
- Achondroplasia, hypochondroplasia
- Osteogenesis imperfecta
- Hypophosphatemic rickets

patient. This is a fairly reliable method that can be used in day-to-day practice.

The TW 3 atlas is more exhaustive method, wherein 13 or 20 ossification centers in the hand are scored. The summation of these is then looked up in a table to give the final bone age. This is more of a research tool.

Gilsanz and Ratib have recently released their own atlas of bone age assessment which is very similar to Gruelich and Pyle method with an added advantage of digital processing.

Clinical Pearl

- Karyotype to rule out Turner syndrome is needed in all short girls even in the absence of stigmata.

Interpretation of Growth Velocity

Child has normal growth velocity with growth curve cruising below the 3rd percentile is a short normal child and needs continued monitoring. He/she may need 2nd level of investigations to rule out all causes before diagnosing as idiopathic short stature. Growth hormone has been used to treat short normal children who are below –2.5 SD and who are not likely to achieve normal adult stature.

Low Growth Velocity (Faltering Growth Curve)

Consider 2nd tier investigations:

- Anti-TTG IgA
- Growth hormone stimulation test: two provocation tests using clonidine, glucagon, insulin, dopamine, arginine, and growth hormone–releasing hormone (in India, clonidine, glucagon, arginine, and insulin are available)
- Magnetic resonance imaging brain: pituitary size, and congenital malformations of the brain
- Molecular testing for syndromes.

Idiopathic short stature if all tests are negative.

TABLE 2: Clinical signs indicating etiology

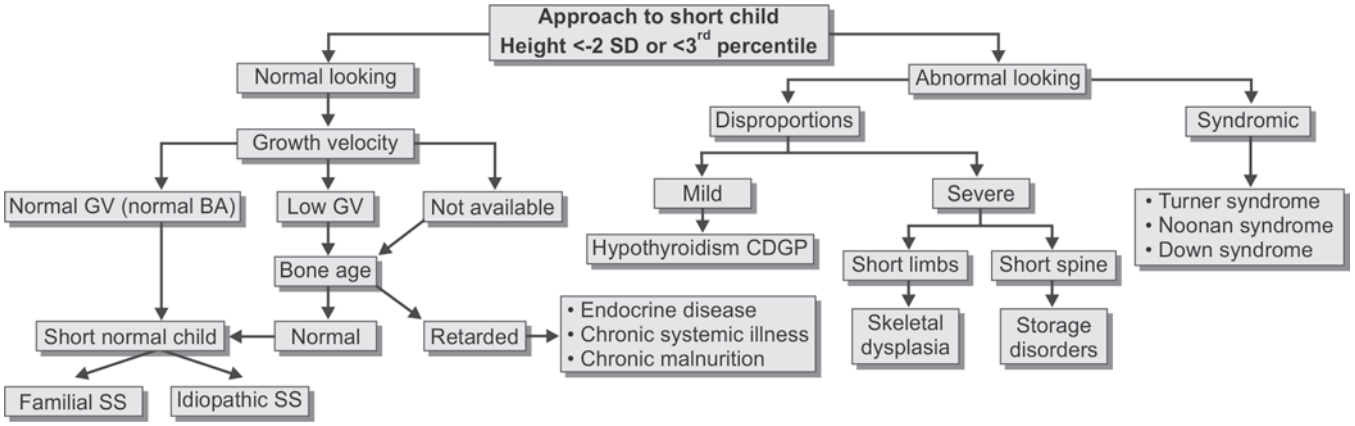
Clinical signs	Etiology
Immature facies with frontal bossing, depressed nasal bridge, midfacial hypoplasia, high pitched voice	Growth hormone deficiency
Mental slowing, coarse facies, puffy appearance, goiter	Hypothyroidism
Antimongoloid slant, low posterior hair line, webbed neck, short 4th/5th metacarpals, metatarsals, wide carrying angle, pigmented nevi, difference in upper limb lower limb blood pressure	Turner syndrome
Beak headed dwarfism, height less than -7 SD, developmental delay	Seckel syndrome
Small triangular facies with hemiatrophy	Russell-Silver syndrome
Almond shaped eyes, hypo-gonadism, obesity, behavioral problems, hyperphagia	Prader-Willi syndrome
Coarse facies, macrocephaly, short stubby fingers, rhizomelia	Skeletal dysplasia
Short 4th/5th metacarpal or metatarsal	SHOX gene defect, pseudopseudo-hypoparathyroidism, Turner syndrome

TABLE 3: Growth hormone dose

Underlying condition	Dose
Growth hormone deficiency	25–40 µg/kg/day
Turner syndrome	50–60 µg/kg/day
Small for gestational age sequelae	35–70 µg/kg/day
Prader-Willi syndrome	25–50 µg/kg/day
Idiopathic short stature	50 µg/kg/day

ALGORITHM 1

Short stature



SD, standard deviation; GV, growth velocity; BA, bone age; CDGP, constitutional delay in growth and puberty; SS, short stature.

Management Strategies

Treatment of the underlying condition usually leads to improvement in the growth velocity and catch up growth.

Growth Hormone

Growth hormone therapy is used in the following conditions:
Licensed indications:

- Growth hormone deficiency
- Small for gestational age sequelae
- Turner syndrome
- Prader-Willi syndrome
- Idiopathic short stature
- Chronic renal failure prior to renal transplant
- Glucocorticoid induced short stature

Conditions with doubtful benefit (under research at present):

- Hypochondroplasia
- Chronic inflammatory disorders like rheumatoid arthritis
- Noonan syndrome
- Other skeletal dysplasia.

Recombinant human growth hormone is given in the form of subcutaneous injections daily at bedtime for a period of at least 2 years, ideally till the final height is achieved. Growth hormone therapy is not useful once there is complete bony fusion. Response depends on indication for which it is used, age of starting therapy, duration of therapy, dose used, MPH, and bone age at onset.

Although adverse effects are rare, they may include: benign intracranial hypertension, hyperglycemia, worsening of scoliosis, slipped capital femoral epiphyses, gynecomastia, rash, and hives. Increased predisposition for neoplasia in those with increased chromosomal breakage syndromes has also been reported and is a contraindication to growth hormone therapy.

Androgens

Depot testosterone in small doses of 50 mg monthly for 3–6 months has been used in boys with CDGP. It is used to trigger the onset of pubertal spurt and usually results in attainment of satisfactory final height. In some conditions wherein the predicted adult height is less, it may be combined with growth hormone. The disadvantage of testosterone is that it aromatizes to estrogen and thus results in rapid bone maturation and fusion. Oxandrolone, a nonaromatizable androgen is a better alternative as it does not lead to early bony fusion.

Limb lengthening using Ilizarov may be offered for children with achondroplasia.

CONCLUSION

It is necessary to differentiate a short normal child from a short child with pathology. Treatment of only pathological short stature is warranted. Growth hormone therapy is indicated for special conditions, is usually for long term. The therapy aims at achieving genetic potential and depends on many factors, such as age at onset of therapy, etiology, degree of short stature, and duration of therapy, contrary to unrealistic expectations of most parents.

KEY POINTS

- ☞ Anthropometry and plotting of growth chart remains the most powerful tool for the diagnosis of short stature
- ☞ Longitudinal assessment of growth and growth velocity is much more important than a single time evaluation as it gives idea of growth pattern
- ☞ Bone age beyond 2 years of actual age on either side is considered abnormal and points toward an endocrine disease
- ☞ Adjusting height for midparental target height often reduces unnecessary investigations in short child
- ☞ A short and fat child has an endocrine disease, skeletal dysplasia, or syndrome whereas tall and fat child has nutritional obesity.

SUGGESTED READINGS

1. Bull RK, Edwards PD, Kemp PM, Fry S, Hughes IA. Bone age assessment: a large scale comparison of the Greulich and Pyle, and Tanner and Whitehouse (TW2) methods. Arch Dis Child. 1999;81:172-3.
2. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab. 2008;93(11):4210-7.
3. Gilsanz V, Ratib O. Hand Bone Age: A Digital Atlas of Skeletal Maturity. Berlin, Heidelberg: Springer-Verlag; 2005.
4. Khadilkar V, et al. 2007 Indian growth references. [online] Available from http://www.indiachildgrowth.com/growth-charts.html.
5. Khadilkar V, Khadilkar A. Growth charts: a diagnostic tool. Indian J Endocr Metab. 2011;15(Suppl 3):S166-71.
6. Khadilkar V, Phanse S. Growth charts from controversy to consensus. Indian J Endocrinol Metab. 2012;(16):S185-7.
7. WHO Multicentre Growth Reference Study standards. [online] Available from http://www.who.int/childgrowth/standards/en/[Accessed February, 2016].
8. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr. 2003;143(4):415-21.

CHAPTER 107

Childhood Obesity

Anurag Bajpai

INTRODUCTION

Childhood obesity has emerged as a global epidemic with doubling of prevalence over the last two decades. Studies from different parts of India have shown a rise in prevalence of overweight and obesity from 15 to 28%. The risk of numerous complications of early onset obesity imposes significant burden on the individual and society. Moreover, most obese children become obese adults. Timely evaluation and management of childhood obesity is, therefore, crucial.

WHAT IS OBESITY?

The term implies excessive body fat, not merely excess body weight. Thus, body weight alone is not a reliable marker of obesity. The gold standard for diagnosis is increased body fat measured by bioimpedance or dual energy enhanced X-ray absorptiometry. These methods are cumbersome, used mainly for research purposes. In practice, surrogate markers of adiposity using a combination of height and weight are used.

Body Mass Index

Body mass index (BMI) should be used for diagnosing obesity after 2 years of age. It takes into account the weight and height of the individual.

$$\text{BMI} = \text{Weight (kg)} \div \text{height (m)}^2$$

Body mass index correlates well with body fat and complications in children; however it may incorrectly diagnose obesity in muscular individuals, while underestimating adiposity in sedentary children with reduced muscle mass. Body mass index cutoffs for diagnosing obesity have been developed using statistical distribution (Centers for Disease Control and Prevention charts) or extrapolating from adult cutoffs (International Obesity Task Force). It varies with age, ethnicity, and gender. Thus, age and gender specific local charts should be used. Body mass index between 85th and 95th percentile for age indicates overweight, above the 95th percentile suggests obesity, and greater than 99th percentile (120% of 95th percentile) severe obesity.

For the same BMI, Indians have a greater risk of metabolic syndrome compared to their Western counterparts. As the aim of assessing BMI is to identify individuals at risk for metabolic complications, lower BMI cutoffs have been recommended for Indian adults (23 kg/m^2 for overweight and 28 kg/m^2 for obesity). The applicability of lower cutoffs in Indian children needs study.

Weight for Height

Weight for height should be used in children younger than 2 years of age. Weight for height more than 120% suggests obesity.

Waist Circumference

Waist circumference is a marker of abdominal obesity, a predictor of metabolic syndrome. Levels higher than 95th percentile for age and gender are abnormal.

WHAT CAUSES OBESITY?

In most children, obesity is not due to a disease, but related to lifestyle factors (constitutional obesity), while pathological causes account for less than 1% cases (Table 1). It is important to identify pointers to pathological obesity to avoid unnecessary workup in children with constitutional obesity.

Clinical Pearl

- Obesity implies increased body fat and not weight; body mass index may erroneously diagnose obesity in short, muscular individuals.

TABLE 1: Causes of obesity

Class	Etiology
Constitutional	Lifestyle issues
Endocrine	Cushing syndrome, hypothyroidism, growth hormone deficiency, Turner syndrome, pseudohypoparathyroidism
Dysmorphic syndromes	Prader-Willi, Lawrence-Moon-Biedl-Bardet, Cohen, Alstrom, Carpenter
Monogenic	Leptin deficiency, leptin resistance, melanocortin 4 receptor, proconvertase II
Drugs	Corticosteroids, olanzapine, risperidone, valproate

Constitutional Obesity

Constitutional obesity results from an imbalance between energy intake and expenditure. It is caused by a combination of genetic and environmental factors. Family history is common. Both low birth weight and high birth weight are associated with increased risk of obesity later in life. Dietary habits associated with childhood obesity include missing meals (especially breakfast), higher portion size, snacking, frequent eating out, and watching television while eating. Breastfeeding in infancy has a protective effect. Lack of activity and increased screen time are associated with obesity.

Clinical Pearl

- Childhood obesity is most commonly due to lifestyle factors.

Endocrine Causes

Endocrine diseases are rare but treatable causes of childhood obesity. They should be considered in the presence of clinical pointers, mainly growth failure and delayed puberty. Cushing syndrome presents with central obesity, high blood pressure, growth failure, and violaceous striae. Hypothyroidism is a rare cause of isolated obesity, usually associated with growth failure and developmental delay. In growth hormone (GH) deficiency and pseudohypoparathyroidism, growth retardation and hypocalcemia are dominant clinical features.

Dysmorphic Syndromes

Obesity is often a manifestation of dysmorphic syndromes. Many of these syndromes are associated with hypogonadism or hypotonia (Prader-Willi, Carpenter, Lawrence-Moon-Biedl-Bardet syndromes).

Hypothalamic Obesity

Hypothalamic obesity is caused by increased appetite due to a central nervous system (CNS) insult by surgery, radiation, tumors and trauma. These disorders are associated with excessive appetite, signs and symptoms of CNS involvement, and other hypothalamic-pituitary defects.

Monogenic Obesity

Single gene defects are a very rare cause of obesity, and should be suspected with early onset obesity, rapid weight gain and strong family history. Inefficient leptin action (deficiency or resistance) results in uncontrolled appetite and obesity. Abnormalities in mineralocorticoid receptor and proconvertase have also been associated with obesity. melanocortin 4 (MC4) receptor defects are the commonest monogenic form of obesity and are associated with growth acceleration.

Drugs

Commonly used drugs associated with obesity include corticosteroids, antipsychotics (olanzapine, risperidone), antidepressants (paroxetine), and antiepileptics (valproate, lamotrigine).

Clinical Pearl

- Think of pathological obesity in children with growth failure and/or developmental delay. Constitutional obesity is more likely if the child is tall and fat.

WHY BOTHER ABOUT OBESITY?

Childhood obesity is a predictor of a number of short- and long-term complications (Table 2).

Endocrine

Endocrine complications are the most important adverse effects of childhood obesity. Central to this is the development of insulin resistance (IR), caused by overspill of fat and its deposition in liver and skeletal muscle. Insulin resistance predisposes to the development of type 2 diabetes mellitus (T2DM), polycystic ovarian syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD). Hyperandrogenism is common in obese girls, as is accelerated growth, skeletal maturation, and early puberty.

TABLE 2: Complications of obesity

Category	Complications
Metabolic	Insulin resistance, type 2 diabetes mellitus, metabolic syndrome, hyperandrogenism
Cardiovascular	Hypertension, dyslipidemia, atherosclerosis
Gastrointestinal	Nonalcoholic fatty liver disease, gall stones, gastroesophageal reflux
Skeletal	Blount's disease, slipped capital femoral epiphysis, fractures
Respiratory	Obstructive sleep apnea, hypoventilation syndrome
Neurological	Benign intracranial hypertension

Cardiovascular

Obese children have a higher prevalence of dyslipidemia, hypertension, atherosclerosis, and increased risk of adult coronary disease. Importantly, hypertension may be masked, warranting repeated blood pressure measurements.

Central Nervous System

Benign intracranial hypertension is common in children with obesity and presents with headache and vomiting.

Orthopedic

These children have a higher risk of flat foot, Blount's disease, fractures, genu valgum, and osteoarthritis. The most debilitating complication is slipped capital femoral epiphysis, which presents with dull aching pain in the knee, hip or groin, with abnormal gait. Blount's disease (tibia vara) presents with progressive bowing of legs and knee pain. X-ray of knee and hip should be done in obese children with pain in hip or knee, or abnormal gait.

Respiratory

Obese children are at increased risk of respiratory distress and bronchial asthma. Obesity predisposes to the development of obstructive sleep apnea and hypoventilation syndrome.

Gastrointestinal

Obesity is associated with gastroesophageal reflux and NAFLD. Fatty liver is present in 40%, elevated transaminases in 25%, and gall stones in 2%. Rapid weight fluctuations are associated with gall stone disease, which should be suspected in an obese child with abdominal pain, jaundice, nausea, and intolerance to fatty foods.

Psychological

Obesity is associated with increased prevalence of mood disorders. This represents intrinsic effects of obesity on one hand and psychological effects of bullying on the other. It is important to assess the effect of an obese child, as depression increases the risk of obesity.

Clinical Pearl

- Obesity causes several short- and long-term complications, including insulin resistance, type 2 diabetes mellitus, polycystic ovarian syndrome, nonalcoholic fatty liver disease, dyslipidemia, hypertension, atherosclerosis, orthopedic problems, obstructive sleep apnea, and mood disorders.

HOW TO EVALUATE A CHILD WITH OBESITY?

Evaluation involves careful clinical assessment followed by focused investigations. The key questions are the cause of obesity and its effects.

What Is the Cause of Obesity?

Most obese children do not require investigations for the cause. It is important to identify the children who need workup by clinical examination (Table 3 and Algorithm 1).

Clinical Evaluation

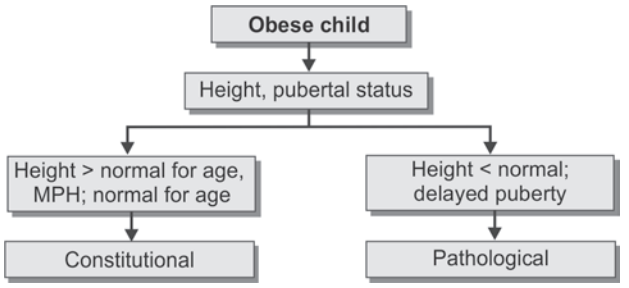
The clinical evaluation should include detailed history and examination. Pathological obesity should be considered with early onset of obesity, rapid weight gain, growth failure, dysmorphism, developmental delay, and pubertal delay. Pointers to specific disorders should be evaluated (Tables 4 and 5). Detailed dietary history, including duration of breastfeeding, age at weaning, meal pattern, calorie intake, snacking, consumption of junk food, and features of feeding disorders should be taken. Duration of activity and inactivity

TABLE 3: Differentiating features of constitutional and pathological obesity

Feature	Constitutional	Pathological
Pattern	Generalized	Central
Growth rate	Accelerated	Retarded
Skeletal maturation	Advanced	Retarded
Dysmorphic features	Absent	May be present
Endocrine features	Absent	May be present

ALGORITHM 1

Approach to a child with obesity



MPH, midparental height.

TABLE 4: Clues to diagnose obesity

Disorder	Features
Delayed puberty	Lawrence-Moon-Biedl-Bardet, Prader-Willi syndrome
Retinitis pigmentosa, polydactyly	Alstrom, Lawrence-Moon-Biedl-Bardet syndrome
Small hands and feet	Prader-Willi syndrome
Buffalo hump, striae	Cushing syndrome
Short 4th metacarpal	Pseudohypoparathyroidism, Turner syndrome
Developmental delay	Prader-Willi, hypothyroidism, pseudohypoparathyroidism

TABLE 5: Features of common causes of obesity

Disorder	Features
Prader-Willi syndrome	Infantile hypotonia, hyperphagia, almond like eyes, acromicria, hypogonadism, behavioral abnormalities
Lawrence-Moon-Biedl-Bardet syndrome	Hypogonadism, retinitis pigmentosa, polydactyly, renal abnormalities, mental retardation
Beckwith-Wiedemann	Organomegaly, ear lobe creases, hemihypertrophy
Cushing syndrome	Hirsutism, central obesity, growth retardation, striae, buffalo hump, hypertension, myopathy
Hypothyroidism	Growth retardation, coarse facies, developmental delay
Pseudohypopara-thyroidism	Tetany, round facies, short 4th metacarpal, cutaneous calcifications

should be looked into. Family history of consanguinity, T2DM, ischemic heart disease, and dyslipidemia should be inquired. Drug history should assess intake of steroids, valproate, antipsychotic, and any other drugs. History of CNS infection, trauma, radiation, tumor or surgery indicates hypothalamic obesity.

Examination should include assessment of growth parameters, pubertal status, and clues to diagnosis. Pubertal assessment may be challenging. Parents of obese girls are often concerned about premature thelarche. While this may reflect true precocious puberty caused by obesity, it is most likely due to increased fat and not true thelarche. To distinguish these conditions, approximate the thumb and index finger around the nipple: lack of resistance indicates lipomastia; breast nodule can be felt as an area of resistance. Obese boys frequently present with concerns of small penile size, which is usually due to penis being buried in the suprapubic pad. Stretched penile length should be measured after pressing the suprapubic pad of fat, to ascertain the actual size of penis.

Clinical Pearl

- Lipomastia may look like thelarche. Buried penis in suprapubic fat may give false impression of micropenis in obese boys.

Investigations

No workup for cause is required in children with normal growth, facies, development, and pubertal development. Thyroid profile and evaluation for Cushing (serum cortisol at 8 am after dexamethasone at 11 pm) should be done in the presence of growth failure and/or characteristic clinical features. The effect of obesity on endocrine function should be considered while assessing endocrine functions. Mildly elevated thyroid-stimulating hormone (TSH) levels with normal free thyroxine are common in obesity, and should not be treated unless TSH is persistently and significantly (>10 IU/mL) elevated. Similarly, cortisol levels may be mildly elevated and easily suppressed, and should not be mistakenly diagnosed as Cushing syndrome. Genetic testing for Prader-Willi syndrome should be done in the presence of facial features, history of infantile hypotonia, and growth failure. Monogenic causes of obesity should be considered only in the presence of clinical features or pointers to diagnosis.

What are the Complications of Obesity?

When to Evaluate?

Assessment of complications of obesity should be done in children with BMI above 95th percentile and those with BMI of 85th–95th percentile and family history of T2DM, hypertension, PCOS, or acanthosis nigricans.

Clinical Evaluation

History should inquire about symptoms of complications of obesity like headache, vomiting (benign intracranial hypertension), day time somnolence, respiratory distress, snoring (obstructive sleep apnea), abdominal pain (fatty liver, gall stone disease), acne, hirsutism, menstrual irregularity (PCOS), pain in hip and knee (slipped capital femoral epiphysis) or abnormal gait (Blount's disease). Examination should include measurement of blood pressure, acanthosis nigricans, hepatomegaly, cardiac examination and pedal edema (obstructive sleep apnea and cor pulmonale), and range of movement of knee and hip (slipped capital femoral epiphysis).

Investigations

Investigations should include an oral glucose tolerance test: blood sugars fasting and 2 hours after 1.75 g/kg glucose (maximum of 75 g), lipid profile, and liver function tests. Age appropriate cutoffs should be used for interpretation (Table 6). These tests should be repeated every 3 years if normal. Fasting insulin has limited role and is not routinely required; serum insulin 2 hours post glucose load may be raised, though there are no definite cutoffs in the pediatric age group. Mildly elevated liver transaminases are common in obesity; persistent elevation beyond twice the upper limit indicates nonalcoholic steatohepatitis. Children with elevated transaminases should undergo ultrasound abdomen and workup for other causes of hepatic dysfunction (hepatitis B and C, Wilson disease, and

TABLE 6: Pediatric cutoffs for investigations for assessment of obesity complications

Investigation	Normal	Borderline	Abnormal
Blood sugar fasting	<100 mg/dL	100–125 mg/dL	>126 mg/dL
Blood sugar 2 h after glucose load	<140 mg/dL	140–199 mg/dL	>200 mg/dL
Total cholesterol	<170 mg/dL	170–199 mg/dL	>200 mg/dL
LDL cholesterol	<110 mg/dL	110–129 mg/dL	>130 mg/dL
Triglyceride	<90 mg/dL	90–129 mg/dL	>139 mg/dL
HDL cholesterol	>45 mg/dL	40–45 mg/dL	<40 mg/dL
AST	<40 IU/L	40–80 IU/L	>80 IU/L

LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate aminotransferase.

autoimmune hepatitis). Sleep studies may be required in the presence of snoring, day time somnolence, or lethargy.

HOW TO MANAGE A CHILD WITH OBESITY?

Management is a big challenge, requiring a multidisciplinary approach involving physician, nutritionists, and physical trainers, with changes made by the entire family. The goal is to bring BMI as close to the normal range for age and gender as possible. Normalization may be difficult; excessive and rapid weight loss adversely affects the growth of the child and should be avoided. In most cases, weight stabilization is the initial aim. Weight loss should not exceed 1 kg every month in most children. The child and parents should be counseled that there is no quick fix solution, and the family would need to adhere to the modified lifestyle throughout life. The key focus is on changing the lifestyle of the child and family, with use of drugs and surgery in the rarest of rare cases.

Clinical Pearl

- Lifestyle measures should be adopted by the entire family, not just the child.

Lifestyle Measures

This is the cornerstone to management. The whole family is encouraged to follow a healthy lifestyle: focusing on the child alone is counterproductive.

Nutritional Therapy

The child should be advised to eat regular meals. Skipping meals and snacking between meals should be discouraged. The caloric intake should be reduced by 20%. Overzealous restriction and fad diets are not recommended. Food pyramid and traffic light approach for diet may be used to highlight healthy eating patterns, with special emphasis on fixed portion size, decreased junk food consumption, avoiding television viewing while eating, and increased fruit consumption.

Physical Activity

Periods of inactivity should be reduced and increased physical activity should be planned. Screen time (television, computer, and mobile devices) should be restricted to less than 1 hour a day. Increased routine activities (e.g., household chores, walking to school) should be encouraged. A minimum of 30 minutes daily of enjoyable activity like dancing, sports, and running should be ensured, avoiding weight bearing exercises and over regimented schedules.

Specific Management

Specific treatment is needed for hypothyroidism, GH deficiency, and Cushing syndrome. Mild elevations of TSH do not need treatment. Obese children with Prader-Willi Syndrome and growth failure may benefit from GH therapy. Octreotide is effective in hypothalamic obesity, leptin in leptin deficiency.

Treatment of Complications

Complications should be treated early to avoid long-term adverse effects. Metformin is indicated for IR, T2DM, NAFLD and PCOS; statins for persistent dyslipidemia. Treatment of NAFLD includes metformin, vitamin E, and pioglitazone. Girls with PCOS benefit from lifestyle modification, metformin, oral contraceptives, and antiandrogens. Medroxyprogesterone acetate is beneficial in children with obesity hypoventilation syndrome. Continuous positive airway pressure is needed in obstructive sleep apnea.

Medical Treatment for Obesity

Drugs used in the past have faced problems due to adverse effects. Orlistat is the only drug approved for use in children with obesity. It inhibits gastric lipase, resulting in reduced absorption of fat, with modest weight loss. Major side effects include abdominal pain, bloating, steatorrhea, and anal leakage of oil. It has to be combined with fat soluble vitamins. Newer agents in the pipeline include MC4 receptor modulators, glucagon-like peptide 1 analogs, and endocannabinoid agonists.

Surgical Management

Bariatric surgery should be considered only in severe obesity when other measures have failed, only after achievement of final height, due to potential adverse growth effects. It is a major surgical undertaking, to be viewed as potentially life-saving, not just a cosmetic procedure. Patients need to adhere to strict dietary restriction for life. In children, laparoscopic adjustable banding is the recommended procedure; malabsorptive procedures and gastric sleeve should not be done.

Clinical Pearl

- Medical and surgical treatment of childhood obesity should be considered only in severe cases associated with complications.

HOW TO PREVENT CHILDHOOD OBESITY?

Given the difficulties in management, prevention is the desirable goal. Though this is very challenging, the recent plateauing of childhood obesity rates in several states in the United States and some European countries is encouraging. This is proof that awareness and societal changes can reduce this important public health problem. Key measures include prevention and treatment of adult obesity (due to intergenerational effects of obesity), early identification and treatment of gestational diabetes mellitus, and increased consumption of healthy food. Exclusive breastfeeding should be done till 6 months, on a demand basis, not according to a schedule. Infants should be given the freedom to decide the frequency and amount of feeds. Saturated fats (e.g., full fat milk) should be restricted after age 2 years. Changes in dietary habits—eating food with family at regular times, avoiding snacking, avoiding television while eating, and fixed portion size, should be advised. The child is encouraged to play (moderate physical activity) for at least 60 minutes daily. The overall screen time should be limited to

less than 2 hours a day. Television should be removed from children's bedrooms, and avoided in children under 2 years.

KEY POINTS

- ☞ Childhood obesity is now a global epidemic, mainly due to lifestyle changes, pathologic causes are rare
- ☞ Body mass index after the age of 2 years, and weight for height in infants, and waist circumference, are used for routine diagnosis
- ☞ In constitutional obesity, the child is usually tall for age. Pathologic causes should be suspected in a child with growth retardation (i.e., short and fat) and/or delayed puberty
- ☞ Obesity leads to several health problems, so it should be taken seriously
- ☞ Most obese children require investigations not for the cause, but for the consequences of obesity
- ☞ Management involves lifestyle changes for the entire family, and treatment of consequences
- ☞ Management is difficult. Prevention is critical, at all levels, from individual to societal
- ☞ Lipomastia and buried penis require weight loss, and no other treatment.

SUGGESTED READINGS

1. Alemzadeh R, Rising R, Cedillo M, Lifshitz F. Obesity in children. In: Lifshitz F (Ed). Pediatric Endocrinology, 4th ed. New York: Marcel Dekker; 2003. pp. 823-58.
2. Barlow SE, Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 Suppl 4:S164.
3. CDC. (2013). Progress in Childhood Obesity. CDC vital signs. [online] Available from http://www.cdc.gov/vitalsigns/pdf/2013-08-vitalsigns.pdf. [Accessed May, 2015].
4. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5:S213.
5. Freemark F. Metabolic consequences of obesity and their management. In: Brook CGD, Clayton PE, Brown RS (Eds). Clinical Pediatric Endocrinology, 5th ed. London: Blackwell publishing; 2005. pp. 419-35.
6. Gillman MW, Ludwig DS. How early should obesity prevention start? N Engl J Med. 2013;369(23):2173-5.
7. Muglia LJ, Majzoub JA. Nutritional disorders. In: Sperling MA (Ed). Pediatric Endocrinology, 2nd ed. Philadelphia: WB Saunders; 2002. pp. 671-88.
8. Speiser PW, Rudolf MC, Anhalt H, Camacho-Hubner C, Chiarelli F, Eliakim A, et al. Childhood obesity. J Clin Endocrinol Metab. 2005;90(3):1871-87.

CHAPTER 108

An Approach to Hyperglycemia

Aspi J Irani

INTRODUCTION

Normoglycemia is defined as fasting venous plasma glucose between 70 and 100 mg/dL and a 2-hour postprandial or post glucose value less than 140 mg/dL. Corresponding values more than 126 and 200 mg/dL are used to define diabetes mellitus (DM).

Hyperglycemia is encountered by the pediatrician/neonatologist in five different settings:

1. Child or adolescent with typical symptoms of DM
2. Hyperglycemia as an incidental pick up (or during screening) in an obese (but asymptomatic) adolescent
3. Neonate or infant (below 6 months) with symptoms of hyperglycemia
4. Hyperglycemia during an acute illness in a child/adolescent [stress hyperglycemia (SH)]
5. Hyperglycemia in a sick neonate in the neonatal intensive care unit (NICU).

Hyperglycemia is due to a disturbed balance between insulin on one hand and the counter-regulatory hormones (adrenaline, glucagon, cortisol, and growth hormone) on the other. While insulin promotes utilization or storage of glucose entering the body, and promotes protein and fat anabolism, the counter-regulatory hormones promote catabolism of protein and fat and favor movement of glucose into the blood stream from storage sites (chiefly liver, muscle, and kidneys) by promoting gluconeogenesis and glycogenolysis.

Adverse effects of hyperglycemia include:

- Osmotic diuresis with dehydration and electrolyte derangements once the renal threshold has been exceeded
- Hyperosmolarity (An 18 mg/dL rise in blood glucose raises osmolarity by 1 mOsm/L) and osmotic shifts with brain cell dehydration and risk of intracranial bleeds
- Glucose overload in insulin independent endothelial cells (hepatic, immune, and nerve cells) with generation of oxygen free radicals and resultant mitochondrial dysfunction and enhanced apoptosis
- Impaired leukocyte phagocytic function predisposing to infections and leading to delayed clearing of infections
- In the NICU, an increased risk of severe retinopathy of prematurity, necrotizing enterocolitis (NEC) broncho-pulmonary dysplasia, septicemia, with longer duration of NICU stay, and a higher mortality
- In the long-term, persistent hyperglycemia can affect many organs by glycosylation of proteins/collagen.

CHILD OR ADOLESCENT WITH TYPICAL SYMPTOMS OF DIABETES MELLITUS

Polyuria, polydipsia, polyphagia, weight loss, and weakness (with or without a history of ants around the urine and of vaginal candidiasis) are typical symptoms due to hyperglycemia.

If ketosis has set in, there would be anorexia, abdominal pain, vomiting, abdominal distension, dehydration, acidotic breathing with a peculiar "acetone" odor to the breath, and drowsiness. Shock and coma may occur but are uncommon.

In the presence of typical symptoms of hyperglycemia with ketosis, single random blood glucose over 200 mg/dL is sufficient to clinch the diagnosis of DM. In this situation, an oral glucose tolerance test (OGTT) is not only unnecessary but can also be dangerous.

In an asymptomatic or mildly symptomatic child, a fasting blood glucose (done after 8 h of no calorie intake) of 126 mg/dL or above with 2-hour postprandial value 200 mg/dL or more on two occasions is diagnostic of DM. The OGTT should never be done if DM can be diagnosed from the fasting, random, or postprandial blood glucose values. A fasting blood glucose between 100 and 125 mg/dL is referred to as "impaired fasting glucose" while a post glucose reading between 140 and 199 mg/dL is labeled as "impaired glucose tolerance"; both these are considered as prediabetic states.

Having made the diagnosis of DM, the next step is to ascertain the type of DM. Type 1, is, by far, the commonest variety encountered in childhood. Presence of detectable pancreatic autoantibodies (common antibodies tested are to glutamic acid decarboxylase (GAD) 65, insulin, islet cell, and tyrosine phosphatase) with low C-peptide values in a child

with acute onset of symptoms of DM confirms the diagnosis of T1DM. One should look for associated autoimmune disorders, both endocrine (thyroid dysfunction, adrenal disease, and hypoparathyroidism) and nonendocrine (celiac disease, alopecia areata, vitiligo, autoimmune hepatitis, mucocutaneous candidiasis, and pernicious anemia).

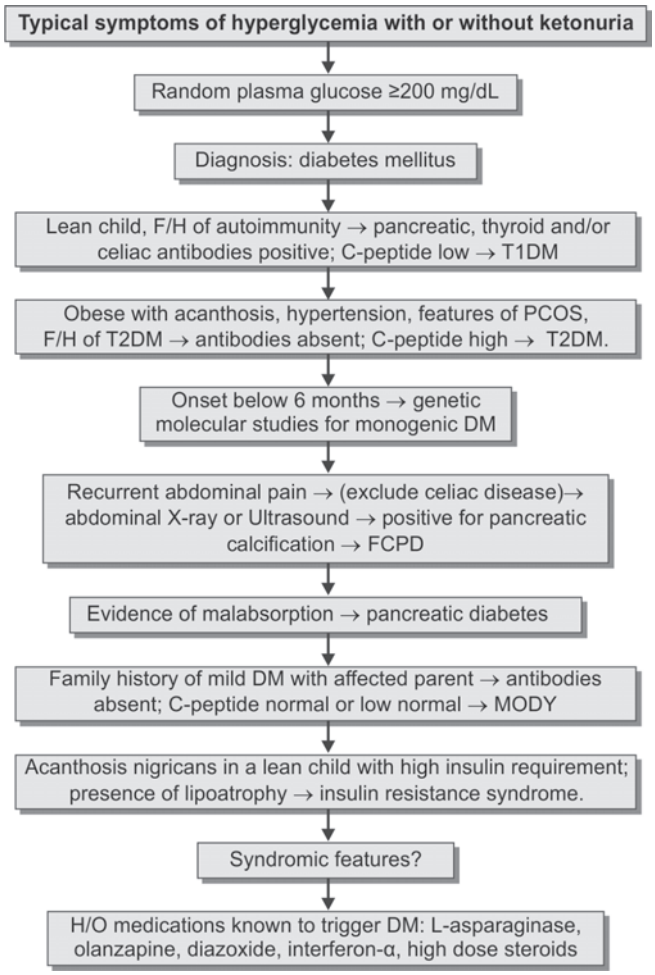
Type 2 DM (T2DM) is becoming commoner because of the increasing incidence of adolescent obesity. It must be suspected in any obese adolescent with a family history of T2DM, especially if there are associated features indicating insulin resistance [acanthosis nigricans, hypertension, hyperlipidemia, evidence of polycystic ovarian syndrome (PCOS)]. In such cases, absence of antibodies typical of T1DM with high C-peptide levels would confirm T2DM. It must be emphasized that diabetic ketoacidosis (DKA) at presentation does not exclude T2DM; 6–33% of T2DM present in DKA.

A nonobese adolescent with mild diabetes and a family history of DM in three generations, possibly has one of the varieties of maturity onset diabetes of the young. If there is optic atrophy or associated deafness or persistent polyuria despite good control of DM (pointing to an associated diabetes insipidus), the diagnosis would be "Wolfram syndrome". In a child with recurrent abdominal pain, the development of DM should initiate a search for pancreatic calculi (fibrocalculus pancreatic diabetes). Diabetes associated with sensorineural deafness and thiamine responsive megaloblastic anemia is referred to as "Roger syndrome". The clinician needs to look for any syndromic features in a child with DM as Mongolism, Turner syndrome, Prader-Willi, and Klinefelter syndromes (besides many others) can be associated with DM with a higher frequency than in the general population. Adolescents with thalassemia major tend to develop DM in the second decade of life due to iron loading in the pancreas (causing insulin deficiency) and in the liver (leading to insulin resistance). Algorithm 1 outlines the approach to a pediatric patient with typical symptoms of hyperglycemia with or without ketonuria.

Insulin is the mainstay of treatment for T1DM and also for initial treatment in T2DM with acute presentation. Metformin is the only approved oral drug for pediatric T2DM. All varieties of DM also require lifestyle change, meal planning, regular planned physical activity, counseling, and attention to comorbidities. All patients with DM must receive intensive and ongoing education in diabetes self-management.

ALGORITHM 1

Approach to a pediatric patient with typical symptoms of hyperglycemia with or without ketonuria



F/H, family history; T1DM, type 1 diabetes mellitus; PCOS, polycystic ovarian syndrome; T2DM, type 2 diabetes mellitus; FCPD, fibrocalculous pancreatic diabetes; MODY, maturity onset diabetes of the young; H/O, history of.

HYPERGLYCEMIA DETECTED ON SCREENING IN AN OBESE ASYMPTOMATIC ADOLESCENT

Children above the age of 10 years who have attained puberty must be screened for DM if they have any two of the following risk factors

- Obesity
- Family history of DM in a 1st or 2nd degree relative
- Evidences of insulin resistance(hypertension, acanthosis nigricans, dyslipidemia, fatty liver, and PCOS)
- *In utero* exposure to DM.

In these patients, a fasting and preferably also a 2-hour post glucose (1.75 g/kg to a maximum of 75 g) blood glucose should be checked once in every 2 years or whenever there are symptoms suggestive of hyperglycemia. Algorithm 2 outlines the diagnostic approach and classification of deranged glucose metabolism in these cases.

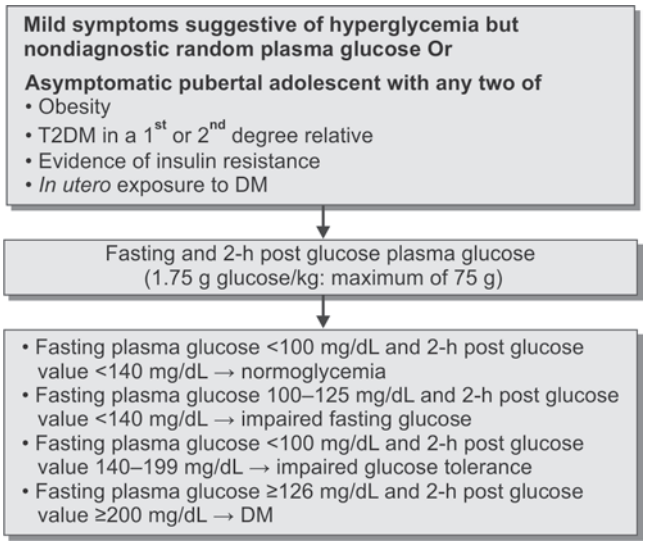
Clinical Pearl

- Obese adolescents with evidence of insulin resistance or a family history of diabetes mellitus (DM) or with *in-utero* exposure to DM must have a fasting blood glucose test every 2 years to screen for DM.

Early detection and treatment (lifestyle change and metformin) is very important as microvascular and macrovascular complications occur earlier and are more severe in adolescents than in adults with T2DM. Screening is very important as T2DM may remain asymptomatic and escape detection for a prolonged period of time. Some patients with T2DM may test positive for autoantibodies characteristic of T1DM; they are classified as having "latent autoimmune diabetes" and are likely to need insulin in the near future (usually in next 3 years).

ALGORITHM 2

Approach to a patient with mild symptoms suggestive of hyperglycemia and a patient with clinical picture/setting suggestive of type 2 diabetes mellitus



DM, diabetes mellitus; T2DM, type 2 diabetes mellitus.

NEONATE/INFANT (BELOW 6 MONTHS) WITH SYMPTOMS OF HYPERGLYCEMIA

The neonate/infant with diabetic hyperglycemia would present with irritability, polyuria, weight loss, failure to thrive, and dehydration with or without acidotic breathing and occasionally with candidiasis in the genital region. Important differentials include diabetes insipidus, renal tubular acidosis, diluted feeds, and hyperthyroidism. In patients presenting with hyperglycemia and metabolic acidosis, if there is lack of improvement with appropriate treatment of DKA, the possibility of certain inborn errors of metabolism must be kept in mind: these include methylmalonic acidemia, propionic acidemia, isovaleric acidemia, biotinidase deficiency, and cobolamine metabolism defects. If the diagnosis of DM is confirmed (as above), the two broad possibilities are: (1) transient neonatal diabetes mellitus (TNDM) and (2) permanent neonatal diabetes mellitus (PNDM).

Transient Neonatal Diabetes Mellitus

The presentation is soon after birth (median age 3 days). Most cases are below the 3rd percentile in weight (average weight 2 kg). Associated congenital anomalies reported include macroglossia in 20% and umbilical hernia in 10%. They show remarkable improvement with insulin therapy. This is a self-limited condition and resolves by 18 months (median age 12 weeks).

Abnormalities of chromosome 6q24 with overexpression of paternally expressed genes are seen in 65% of cases. The defect may be paternal uniparental isodisomy of chromosome 6, paternally inherited duplications within the long arm of chromosome 6, or loss of methylation within the TNDM critical region of chromosome 6 on the paternally inherited chromosome. Three novel heterozygous mutations in the KCNJ11 gene (G53S, G53R, and I182V) have been shown to result in TNDM in some patients who do not have abnormalities of chromosome 6q24. Some mutations in the ABCC8 gene and the HNF1β gene are also associated with this transient variety of DM.

Although these patients grow out of their insulin dependence by 18 months of age (usually earlier), 50–60% will have a recurrence of DM later in life (average age 14 years with a range of 4–25 years). On recurrence, most would require insulin though the dose is small or the requirement may be intermittent; some may be controlled with sulfonylureas. A few may display hyperglycemia only during intercurrent illnesses.

Thus, what is referred to as TNDM may actually be a permanent defect in β-cell insulin release with variable expression at different stages of development.

Permanent Neonatal Diabetes Mellitus

Permanent neonatal diabetes mellitus is a genetically heterogeneous disorder with at least nine different genetic etiologies reported till date. These genetic defects may be associated with either deranged β-cell function or reduced pancreatic mass with or without syndromic features. Thyroid, pancreas, liver, heart, brain, kidney, and skeletal abnormalities may be associated.

Approximately 95% of patients with monogenic causes of neonatal DM present within the first 6 months of life, with around 3% diagnosed between 6 and 12 months of age.

Clinical Pearl

- All patients diagnosed with diabetes mellitus before 6 months of age, as well as those patients diagnosed between 6 and12 months of age, who have no detectable pancreatic auto-antibodies, should undergo molecular genetic testing.

There are five genes known to be associated with nonsyndromic PNDM. The first two listed below have important therapeutic significance as they can be managed on sulfonylurea group of drugs and are not insulin requiring:

1. Heterogeneous activating mutations of the KCNJ11 gene which encodes one of the two protein subunits (Kir6.2) of the adenosine triphosphate sensitive K^+ (KATP) channel in the β-cells account for 30% of cases of PNDM. Low birth weight (LBW) is a consistent phenotypic marker but after insulin treatment, there is marked catch up growth followed by normal growth. Twenty percent have developmental delay and muscle weakness and 5% have epilepsy in association with neonatal diabetes (the so called DEND syndrome)
2. Mutation in the ABCC8 gene which encodes the other protein subunit (the SUR1 subunit) of the KATP channel constitutes another genetic etiology and is the cause in 19% of all PNDM
3. Mutations of the gene encoding insulin (INS gene) accounts for a further 20% of cases of PNDM: these babies are born at full term, have a better average birth weight (2.86 kg) and are diagnosed later (13 weeks as against 5–7 weeks) than those with defects in ABCC8 or KCJN11

4. Homozygous inactivating mutations of the gene encoding glucokinase must be suspected in PNDM with history of consanguinity especially if both parents have mild hyperglycemia. These cases present at birth with severe LBW. As a first test in any LBW baby born with neonatal diabetes, the parents blood glucose should be checked
5. Rarely, neonatal diabetes may be due to inactivating mutations of the PDX1 (IPF1) gene. This is associated with pancreatic agenesis or hypoplasia and hence with exocrine pancreatic insufficiency. These patients have the severest insulin deficiency and present early with significant LBW. Carrier parents would have mild adult onset diabetes.

Clinical Pearl

- Neonatal diabetes mellitus due to mutations of the KCNJ11 and ABCC8 genes do not require insulin therapy; these can be controlled with sulfonylurea group of drugs.

There are at least four syndromes associated with neonatal DM which can be suspected in a given case from their associated features:

1. GLIS3 gene mutation has PNDM due to pancreatic hypoplasia with severe congenital hypothyroidism, glaucoma, hepatic fibrosis, and cystic renal disease
2. PTF1α gene mutation of severe PNDM due to pancreatic agenesis or hypoplasia has associated exocrine pancreatic insufficiency, dysmorphic facies, microcephaly, and impaired cerebellar development with severe developmental delay and occasionally, gall bladder agenesis
3. FOXP3 gene mutation (the "IPEX syndrome") is a X-linked disorder of autoimmunity that occurs in males who present with neonatal diabetes, immune dysregulation, autoimmune thyroid disease, intractable diarrhea, exfoliative dermatitis, eczematous skin rash, and very high serum immunoglobulin E. Most die of overwhelming sepsis in the first months or years of life
4. Mutations of the EIF2AK3 gene lead to persistent neonatal diabetes and either multiple epiphyseal or spondyloepiphyseal dysplasia (Wolcott-Rallison syndrome). Transmission is autosomal recessive. Some may have progressive renal failure from glomerulonephritis. One-fourth patients have exocrine pancreatic insufficiency. They may also have recurrent hepatitis and mental retardation.

There is a case report of maternal enteroviral infection at the end of the first trimester leading to pancreatic hypoplasia with presence of GAD and anti-insulin antibodies and neonatal diabetes mellitus (NDM) presenting at or soon after birth.

It is often difficult to clinically distinguish TNDM from PNDM, however, patients with PNDM are usually born closer to term, have a higher birth weight, length and head circumference, a later age of presentation, and a higher insulin requirement. Presence of associated anomalies or syndromic features may be helpful in differential diagnosis. On follow-up, declining insulin requirement over weeks/months with return to normoglycemia off therapy clinches the diagnosis of TNDM.

MANAGEMENT OF NEONATAL DIABETES MELLITUS

Molecular genetic studies must be done in all infants presenting below 6–12 months of age with diabetes. A search for the KCNJ11 and ABCC8 mutations should be urgently undertaken as it has important therapeutic implications. An ultrasound or preferably computed tomography or magnetic resonance imaging scan of the abdomen should be obtained to look for hypoplastic/absent pancreas. Appropriate tests to detect associated hypothyroidism, cerebellar hypoplasia, renal cysts, skeletal defects, agenesis of the gall bladder, or deranged liver function should be undertaken in selected cases. Screening of the parents for undiagnosed diabetes and gene mutations is essential.

At presentation, if the infant is dehydrated with or without ketoacidosis, intravenous fluids and insulin infusion would be required as per the DKA protocol.

For long-term management, insulin injections (coupled with a high calorie intake) are crucial to achieve normal catch up growth and sustained weight gain. Rapid and short acting insulin preparations should be avoided as the risk of hypoglycemia is high (these are used only in babies started on the "insulin pump"). It is best to prescribe two or three injections of neutral protamine Hagedorn insulin subcutaneously each day. The average dose would be 0.5–1.0 units/kg/day but this must be periodically adjusted on basis of home blood glucose monitoring results. Glargine insulin with its flat pharmacokinetic profile might prove useful but is not licensed for use in this age group. Continuous subcutaneous insulin infusion (the "insulin pump") has been successfully tried in neonates with 30% of the total dose given as a continuous basal infusion and 70% as boluses divided equally between the total daily feeds.

In the first 6 months, the infant needs to be exclusively breastfed at frequent intervals. If the mother is not in a position to breastfeed, a milk formula may be offered. Frequent small feeds are preferred in order to prevent swings in blood glucose. When weaning foods are introduced, one should prefer foods with a low glycemic index.

Regular home monitoring of blood glucose (checked 2–3 hours after a feed and immediately before a feed) should be done and the recommended target blood glucose is between 100 mg and 200 mg/dL. It should be remembered that prevention of hypoglycemia is an important priority in the first 3 years of life as it can have a permanent detrimental effect on brain development.

Patients with NDM owing to KCNJ11 and ABCC8 mutations can be successfully shifted to oral treatment with sulfonylureas after initial stabilization with insulin. Glibenclamide appears to be more effective than other sulfonylureas. Doses required are usually higher than those used in adult patients with T2DM (0.33 mg/kg/day for a 60 kg adult). The median dose in NDM is 0.45 mg/kg/day (range 0.1–1.5 mg/kg/day). Glycemic control tends to improve with time, and the dose of sulfonylurea can subsequently be decreased. Transient diarrhea and yellow or grayish staining of deciduous teeth may occur, but other adverse effects are rare.

Pancreatic enzyme replacement therapy is required for those with exocrine deficiency.

STRESS HYPERGLYCEMIA

Stress hyperglycemia refers to transiently elevated blood glucose during an illness. The American Diabetic Association has defined SH as any blood glucose more than 140 mg/dL in a hospitalized nondiabetic patient. About 3.8% of children presenting to the emergency department would have SH. Fever more than 39.5°C, febrile seizures, traumatic brain injuries, burns, sepsis, pancreatitis, and dehydration are the most common acute situations associated with SH. The more severe the illness, the greater is the likelihood of SH. A glycosylated hemoglobin test would help in excluding the possibility of hitherto undetected DM as the cause for hyperglycemia.

Stress hyperglycemia is caused by changes in glucose metabolism, due to increase in counter-regulatory hormones, leading to increased glycogenolysis, neoglucogenesis, and development of insulin resistance both central (in the liver) and peripheral (in muscle and fat). Proinflammatory cytokines tumor necrosis factor-α [increased free fatty acid (FFA) causing insulin resistance], interleukin (IL)-1 (increased gluconeogenesis), and IL-6 (increased glycogenolysis) also contribute. Interleukin-10 and transforming growth factor-β may also be involved. Intensive care unit (ICU) procedures (particularly, mechanical ventilation), use of vasoactive agents, prolonged immobilization, and nutritional practices in the ICU further add to SH.

Modest hyperglycemia (<180 mg/dL) may be beneficial (an adaptive response) by providing additional energy to meet the increased metabolic demand of the brain, red blood cells, and other cells; but if prolonged or severe, it has been associated with higher morbidity and mortality. Both the peak and the duration of hyperglycemia affect prognosis. Stress hyperglycemia is more dangerous than hyperglycemia without stress. In the former, the glucose transporters are over-expressed. Hence, more glucose enters the cells. This leads to altered cell metabolism with increased reactive oxygen species generation which causes altered mitochondrial function and apoptosis. Stress hyperglycemia also impairs macrophage and neutrophil function and complement activity.

Does stress hyperglycemia need to be treated and if so, what is the best approach? There is no conclusive answer to this question in adult and in pediatric studies conducted till date. Two major trials addressing this issue are underway. Trials concluded so far in the pediatric population using insulin infusion to achieve tight blood glucose control have given conflicting results. The duration of hospital stay may be reduced with tight blood glucose control but the incidence of hypoglycemia also goes up significantly. Thus, it may be reasonable to try and maintain the blood glucose at levels of 140–180 mg/dL rather than aggressively controlling blood glucose to lower levels. When insulin is used, it should be given as a continuous infusion of regular human insulin with close monitoring of blood glucose.

Clinical Pearl

- Stress hyperglycemia needs treatment with insulin infusion, only if blood glucose is more than 180 mg/dL with glycosuria; the target blood glucose should be 140–180 mg/dL, with all efforts to prevent hypoglycemia.

Are children with SH more likely to develop DM in future? Studies have reported an incidence of later diabetes ranging from 0–33% in patients with a history of SH. In one detailed study only 2.1% developed DM during 42 months of follow-up; all of these had human leukocyte antigen types or autoimmune markers known to be associated with T1DM, or an abnormal OGTT on recovery from the acute illness. Those with hyperglycemia during relatively minor illnesses have a higher risk than those who develop SH during major illnesses.

HYPERGLYCEMIA IN NEONATAL INTENSIVE CARE UNIT

Hyperglycemia in neonates, defined historically as a whole blood glucose more than 125 mg/dL or serum glucose more than 150 mg/dL, is common in critically ill neonates and in the very low birth weight (VLBW) premature babies. Its occurrence is inversely related to gestational age and birth weight and directly related to the severity of any accompanying illnesses.

Pathophysiology and Causes

Lower and delayed insulin production in response to glucose load is reported in the VLBW neonates, due to smaller beta cell mass, preferential release of inactive proinsulin instead of insulin, and lack of enteral feeding which eliminates the boosting effect of gut incretins on insulin release. Glucose utilization is further limited because of their small mass of insulin dependent tissues: fat and muscle. Sick preterm babies have increased insulin resistance due to increased inflammatory markers, cytokines, and catecholamines.

Hyperglycemia could result from:

- Excess/rapid exogenous glucose delivery (iatrogenic)
- Stress (serious illness especially septicemia, respiratory distress, or NEC; pain; surgical procedures)
- Therapy with certain drugs (corticosteroids, theophylline, caffeine, phenytoin, or use of diazoxide in mother)
- Cerebral pathology with large damaged areas having reduced metabolism and thus, decreased glucose utilization (trauma, hypoxemic-ischemic lesions, hemorrhage, meningitis, and encephalitis)
- Total parenteral nutrition can also affect blood glucose status.

Intralipid infusion raises blood glucose as it stimulates gluconeogenesis by supplying FFA and glycerol. Intralipid supplies nearly three times more energy than glucose, hence when a neonate is started on intralipid, there is no need to give glucose at higher than physiological rate of 6–8 mg/kg/min. Aminoacids also support gluconeogenesis but to a lesser extent than intralipid. High amounts of aminoacid infusion, however, may help by increasing insulin secretion and glucose utilization.

Management

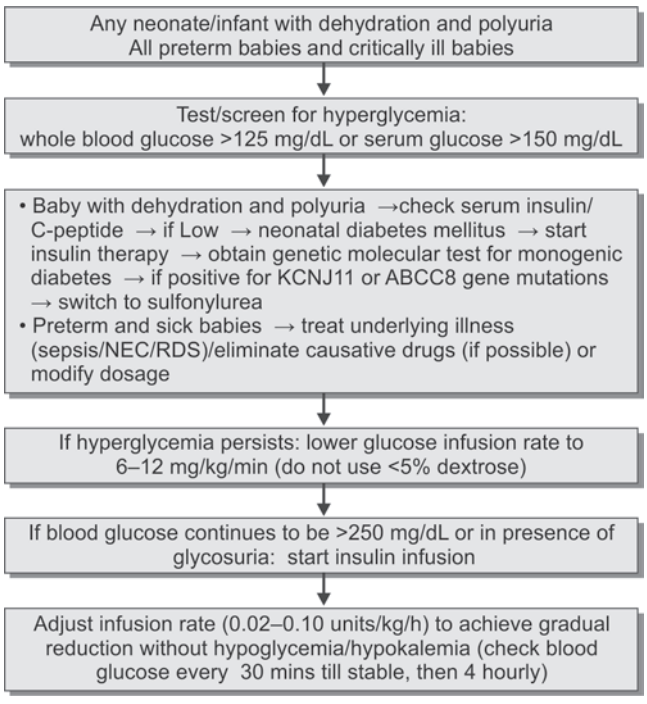
- Anticipate and monitor for hyperglycemia: all susceptible neonates must have blood glucose screening. Heel prick or fingers prick blood glucose at bedside though inaccurate is very useful in screening for hyperglycemia. The results must be confirmed with laboratory estimation of plasma

glucose. The continuous glucose monitoring system measures interstitial tissue glucose level every 5 minutes; it has been successfully used in the NICU. Urine should be checked for glycosuria as this is likely to be accompanied with changes in serum osmolarity

- Any underlying cause of hyperglycemia must be sought out and addressed first (such as sepsis, TNDM and PNDM, specific illnesses, or hyperglycemia inducing drugs)
- Consider limited reduction of glucose infusion rate: When hyperglycemia is detected, the first intervention is to reduce the glucose infusion rate to 6–12 mg/kg/min; stable preterms need a glucose supply of 6 mg/kg/min, an ill preterm would require more glucose. A lower rate would not meet the basic glucose requirement. A higher rate than 12 mg/kg/min would be detrimental as the maximal glucose oxidative capacity is exceeded and beyond this level, conversion to fat occurs. Further, high glucose rates increase carbon dioxide production which is undesirable in respiratory compromised infants. Dextrose solutions with concentration less than 5% should never be used as these would be hypo-osmolar and can cause hemolysis and hyperkalemia. Total parenteral nutrition should be started as soon as possible in LBW babies; certain aminoacids can stimulate insulin release
- Insulin therapy: it should be started when the blood glucose exceeds 250 mg/dL or when there is glycosuria despite above measures. Blood glucose should be brought down slowly to avoid rapid fluid shifts. Insulin is given as an infusion at a rate of 0.02–0.1 units/kg/h. At the outset, it is important to run off about 50 mL of the insulin infusion to saturate binding sites on the tubing. The infusion should be changed every 24 hours. Large inter-subject variation in response is common, thus blood glucose must be checked every 30–60 minutes initially till it has stabilized and thereafter every 4 hours for titration of insulin dose. Some studies have shown insulin to be safe and beneficial and others report risks and problems. A threefold increased lactate concentration and significant acidosis is reported when insulin is given with high glucose infusion rate. Careful monitoring is required to minimize risks of hypokalemia and hypoglycemia which are known complications of insulin therapy. Algorithm 3 outlines the approach to a neonate with symptoms of hyperglycemia or who is susceptible to hyperglycemia.

ALGORITHM 3

Approach to a neonate with suspected hyperglycemia or susceptible to hyperglycemia



NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome.

KEY POINTS

- Diabetes mellitus (DM) must be considered in any child presenting with polyuria, polydipsia, polyphagia, weight loss, and weakness or with secondary enuresis, ants around the urine, or recurrent vaginal candidiasis
- All pubertal adolescents with obesity and a family history of type 2 diabetes mellitus or evidence of insulin resistance or with history of *in utero* exposure to DM must be screened for DM every 2 years
- Neonates/infants with irritability, polyuria, weight loss, failure to thrive, and dehydration with or without acidotic breathing or genital candidiasis must have a blood glucose test; if diagnosed to have diabetes, they should undergo genetic molecular testing for monogenic diabetes
- Preterm babies, very low birth weight babies, and critically ill neonates must be screened for hyperglycemia and measures should be instituted to keep the blood glucose below a level at which there is significant glycosuria.

SUGGESTED READINGS

1. Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocr Rev. 2008;29(3): 265-91.
2. Guven A, Cebeci N, Dursun A, Aktekin E, Baumgartner M, Fowler B. Methylmalonic acidemia mimicking diabetic ketoacidosis in an infant. Pediatr Diabetes. 2012;13(6):e22-5.
3. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. [online] Available from: www.ispad.org.
4. Khadilkar VV, Khadilkar AV, Kapoor RR, Hussain K, Hattersley AT, Ellard S. KCNJ11 activating mutation in an Indian family with remitting and relapsing diabetes. Indian J Pediatr. 2010;77(5):551-4.
5. Pati NK, Maheshwari R, Chellani H, Salhan RN. Transient neonatal hyperglycemia. Indian Pediatr. 2001;38(8):898-901.
6. Pearson ER, Flechtner I, Njølstad PR. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006;355:467-77.
7. Preissig CM, Hansen I, Roerig P, Rigby MR. A protocolized approach to identify and manage hyperglycemia in a pediatric critical care unit. Pediatr Crit Care Med. 2008;9:581-8.
8. Preissig CM, Rigby MR. Pediatric critical illness hyperglycemia: risk factors associated with development and severity of hyperglycemia in critically ill children. J Pediatr. 2009;155(5):734-9.
9. Rafiq M, Flanagan SE, Patch AM, Shields BM, Ellard S, Hattersley AT. Effective treatment with oral sulfonylurea in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. Diabetes Care. 2008;31(2):204-9.
10. Sellers EAC, Moore K, Dean HJ. Clinical management of type 2 diabetes in indigenous youth. Pediatr Clin North Am. 2009;56(6):1441-59.
11. Srinivasan V. Stress hyperglycemia in pediatric critical illness: the intensive care unit adds to the stress! J Diabetes Sci Technol. 2012;6(1):37-47.

CHAPTER 109

Gynecomastia in Children

Raghupathy Palany

INTRODUCTION

Gynecomastia is a benign enlargement of the male breast due to proliferation of the glandular component. The condition may occur in one or both breasts and begins as a small firm lump beneath the nipple, which may be tender and later extend concentrically. If the breast enlargement is soft in consistency, then it indicates fat deposition which is termed as pseudogynecomastia (lipomastia), and there is no glandular proliferation.

Physiologic gynecomastia is seen in newborns and in pubescent males. In newborns, breast development in both sexes may be associated with milk flow (galactorrhea). This condition usually lasts for a couple of weeks, but in rare cases may last until the child is 2 years old.

Pubertal gynecomastia is quite common and occurs in nearly two-thirds of pubertal boys. It appears around 12 years, and regresses in around 18–24 months. Obese boys appear to be more affected and may improve when adipose tissue becomes less on weight reduction. Gynecomastia is stated to be caused by relatively increased aromatization or higher than normal adult values of estrogen- testosterone ratio in this period, or through episodic elevations of estrogen, although many studies failed to document these changes conclusively. Increased sensitivity of the breast tissue to estrogens may be operative.

Pathologic causes of gynecomastia should be sought carefully as they require to be treated appropriately.

The histology of the male and female breast tissue being similar, exposure to estrogen in both sexes induces ductal epithelial hyperplasia, ductal elongation and branching, proliferation of the periductal fibroblasts, and an increase in vascularity.

Increased estrogen production and/or action can occur at the testicular level or at the periphery and is characterized as follows:

- From peripheral conversion: this can be due to increased substrate or increased activity of aromatase, as in chronic liver disease, malnutrition, hyperthyroidism, adrenal tumors, and familial gynecomastia
- From the testes: this can be due to testicular tumors or to ectopic production of human chorionic gonadotropin, as is reported with carcinoma of lung, kidney, gastrointestinal tract, and extragonadal germ cell tumors.

Pathologic gynecomastia can be caused by:

- Increase in the production and/or action of estrogen
  - Increased aromatization of androgens to estrogens
  - Increased androgenic precursors [dehydroepiandrosterone (DHEA) and androstenedione]
  - Increased sex hormone-binding globulin (SHBG)—binds testosterone with higher affinity than estrogen favoring greater peripheral estrogen action
  - Estrogen receptor agonism.
- Decrease in the production and/or action of testosterone
  - Decreased production
    - Primary hypogonadism—Klinefelter syndrome
      - Congenital anorchia
      - Enzymatic defect in testosterone biosynthesis
      - Infection (viral orchitis)
      - Infiltrative disorders
      - Testicular trauma
    - Secondary hypogonadism—hypothalamic or pituitary disorder
      - Low testicular production of testosterone/estriol—adrenal androgens are aromatized—estrogen/androgen imbalance
      - Kallmann syndrome with anosmia
  - Androgen insensitivity syndrome
  - Increased SHBG—binds testosterone with greater affinity than estrogen favoring greater peripheral estrogen action
- Androgen receptor antagonism
- Idiopathic
- Drug use (Box 2).

Box 1: Clinical approach for evaluation of gynecomastia

History

- Duration of symptoms, undescended testis, mumps
- Intake of medications
- Symptoms of psychological stress
- Local symptoms, palpable mass, tenderness and enlargement of breasts, nipple discharge

Physical examination

- Height, weight
- Feminizing signs, Tanner staging
- Breast and overlying skin
- Regional lymph nodes
- Undescended testes, testicular mass
- Chronic renal or hepatic disease

Box 2: Drugs known to cause gynecomastia

Antiandrogens/inhibitors of androgen synthesis

- Cyproterone acetate
- Flutamide, bicalutamide, nilutamide
- Finasteride, dutasteride
- Ketoconazole
- Spironolactone

Chemotherapeutic drugs

- Alkylating agents
- Methotrexate
- Vinca alkaloids
- Imatinib

Cardiac drugs and antihypertensives

- Calcium channel blockers (verapamil, nifedipine, diltiazem)
- ACE Inhibitors (captopril, enalapril)
- Digoxin
- Alpha-blockers
- Amiodarone
- Methyldopa
- Reserpine
- Nitrates

Hormones

- Anabolic steroids
- Androgens
- Estrogens
- Chorionic gonadotropin

Psychoactive drugs

- Haloperidol
- Diazepam
- Tricyclic antidepressants
- Phenothiazines

Anti-infective agents

- Antiretroviral therapy for HIV/AIDS (e.g., indinavir)
- Isoniazid
- Ethionamide
- Griseofulvin
- Minocycline
- Metronidazole
- Ketoconazole

Drugs of abuse

- Amphetamines
- Heroin
- Methadone
- Alcohol
- Marijuana

Miscellaneous

- Theophylline
- Omeprazole
- Auranofin
- Diethylpropion
- Heparin
- Domperidone
- Penicillamine
- Sulindac

HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; ACE, angiotensin converting enzyme.

SIGNS AND SYMPTOMS

- History of mumps, testicular trauma, or drug use should be obtained
- Thorough examination of the size and consistency of the breasts and to differentiate from lipomastia is essential
- Examination of the testes, with attention to size and consistency, as well as nodules or asymmetry
- Dimpling of the skin, nipple retraction and discharge, and axillary lymphadenopathy are suggestive of breast carcinoma.

DIAGNOSIS

Patients with physiologic, asymptomatic, and pubertal gynecomastia do not require further evaluation and should be re-evaluated in 6 months. Further evaluation is necessary in the following situations:

- Breast size greater than 5 cm (macromastia)
- A lump that is tender, of recent onset, progressive, or of unknown duration
- Signs of malignancy (e.g., hard or fixed lymph nodes or positive lymph node findings).

Laboratory Tests

- Serum chemistry panel
- Free or total testosterone, luteinizing hormone, estradiol, and DHEA levels
- Thyroid stimulating hormone and free thyroxine levels.

Imaging Studies

- Mammography, if one or more features of breast cancer are apparent upon clinical examination, followed by fine needle aspiration or breast biopsy as appropriate
- Testicular ultrasonography: indicated if the serum estradiol level is elevated and the clinical examination findings suggest the possibility of a testicular neoplasm
- Breast ultrasonography (though the positive predictive value of imaging in males is low).

Clinical Pearl

- The diagnosis of pathologic gynecomastia must be made only after ruling out lipomastia and physiological breast enlargement.

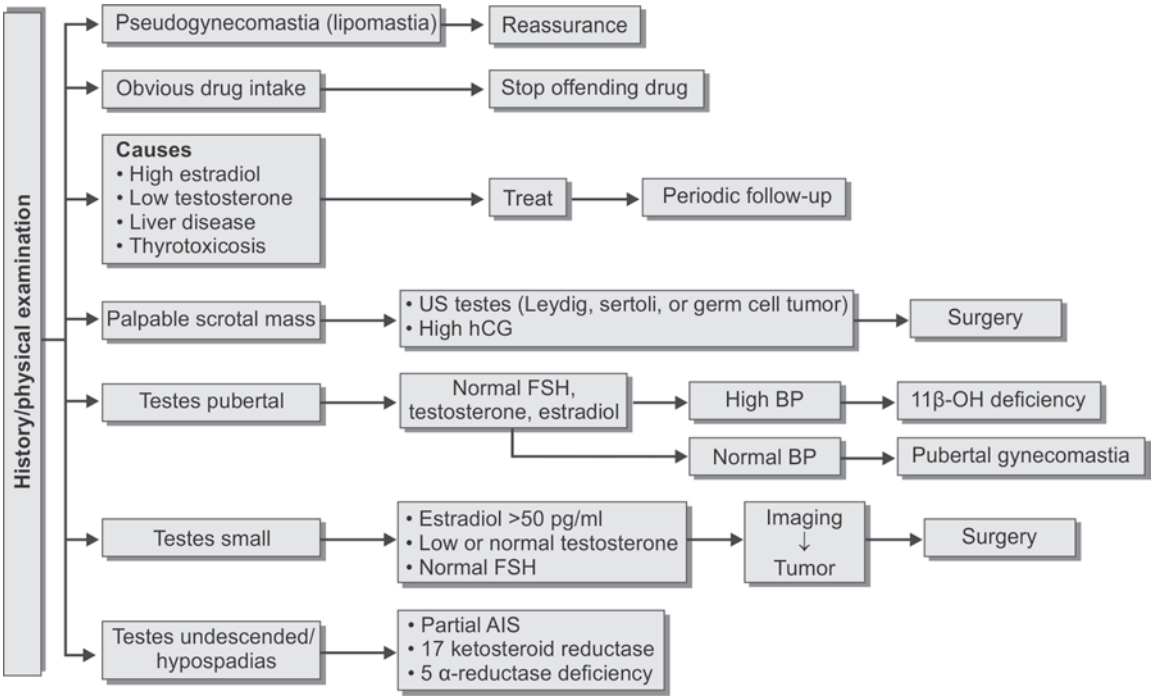
MANAGEMENT

- No treatment is required for physiologic gynecomastia
- Pubertal gynecomastia resolves spontaneously within several weeks to 2 years in most patients; therapy must be considered if remission has not occurred in 2 years
- Breasts larger than 4 cm in diameter may not regress completely
- Identifying and managing an underlying primary disorder often alleviates breast enlargement
- For patients with idiopathic gynecomastia or with residual gynecomastia after treatment of the primary cause, medical or surgical treatment may be considered
- In pathologic causes of gynecomastia, medical therapies should be tried early after onset.

Medical therapy involves the following drugs, but controlled studies are lacking:

ALGORITHM 1

Approach to gynecomastia estrogen excess, androgen deficiency, or androgen/estrogen imbalance



US, ultrasound; hCG, human chorionic gonadotropin; BP, blood pressure; 11β-OH, 11β-hydroxylase; FSH, follicle-stimulating hormone; AIS, androgen insensitivity syndrome.

- Clomiphene
- Tamoxifen or
- Danazol (less frequently used).

Aromatase inhibitors are also currently being tried.

Surgical excision of glandular and adipose tissues by circumareolar approach leaving minimal scarring is the best form of treatment for those requiring treatment, in macromastia, long-standing gynecomastia, or failed medical therapy, as well as for cosmetic reasons. Liposuction may not be as safe and successful.

PATIENT EDUCATION

Patients with physiologic gynecomastia should be reassured regarding the benign nature of their condition, and informed that most cases spontaneously resolve.

PROGNOSIS

In approximately 90% of cases, pubertal gynecomastia resolves within a period of months to several years. However, macromastia seldom resolves completely and often requires surgery.

Gynecomastia that occurs secondary to an underlying, treatable cause (e.g., drug-induced gynecomastia) usually responds to treatment or removal of the primary cause. Men with Klinefelter syndrome have a 10–20-fold increased risk for breast cancer.

Clinical Pearls

- Dimpling of the skin, nipple retraction and discharge, and axillary lymphadenopathy are suggestive of breast carcinoma
- Enlarged lymph nodes, hard or fixed lymph nodes are suggestive of malignant changes.

KEY POINTS

- ☞ Lipomastia needs to be distinguished from gynecomastia
- ☞ Accurate diagnosis is essential for planning appropriate therapy
- ☞ Medical therapy must be tried first, prior to advising surgical excision.

SUGGESTED READINGS

1. Carlson HE. Approach to the patient with gynecomastia. J Clin Endocrinol Metab. 2011:96:15-21.
2. Hormone Foundation. Patient information page. Gynecomastia. J Clin Endocrinol Metab. 2011;96:0.
3. Laituri CA, Garey CL, Ostlie DJ, St Peter SD, Gittes GK, Snyder CL. Treatment of adolescent gynecomastia. J Pediatr Surg. 2010;45:650-4.
4. Mahoney CP. Adolescent gynecomastia. Differential diagnosis and management. Pediatr Clin North Am. 1990;37:1389-404.
5. Nordt CA, DiVasta AD. Gynecomastia in adolescents. Curr Opin Pediatr. 2008;20:375-82.

CHAPTER 110

Precocious Puberty

Puthezhath SN Menon, Madhava Vijayakumar

INTRODUCTION

Precocious puberty (PP) is characterized by the appearance of markers of pubertal development at an age earlier than the usual pattern. Tremendous advances in the understanding of the pathophysiology have resulted in paradigm shifts in the current management. Precocious puberty represents a significant diagnostic, psychosocial, and therapeutic challenge for the pediatrician. Most cases in girls are an exaggeration of the normal physiological process, whereas in boys half the cases are pathological. In general, younger the age, more is the chance of detecting an organic pathology. Early diagnosis and treatment is pivotal since, if left untreated, PP leads to eventual short stature and also causes psychological stress in the affected children. Some of the underlying causes (e.g., tumors) may even be fatal.

PHYSIOLOGY OF PUBERTY

The pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the pituitary gland to secrete the gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Luteinizing hormone stimulates the Leydig cells of testes which secrete testosterone, initiating the pubertal changes in boys. Follicle-stimulating hormone stimulates spermatogenesis by the seminiferous tubules. Luteinizing hormone and FSH stimulate the ovaries to secrete estrogen which initiates the onset of puberty in girls and leads to the development of secondary sexual characters as well.

The secretion of GnRH is regulated by the "hypothalamic pulse generator" constituted by the neurons in the arcuate nucleus of the hypothalamus, which expresses several neurotransmitters, including kisspeptin and neurokinin B. The gonadal sex steroids exert a negative feedback regulation of gonadotropin secretion through the hypothalamic neurons.

Adrenarche is the increased production of the adrenal androgens—dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), associated with the development of the zona reticularis of the adrenal cortex and is independent of gonadal maturation.

NORMAL PUBERTY

Testicular enlargement from 3 to 4 mL is the first sign of puberty in boys, followed by enlargement of penis, pigmentation of scrotum, and growth of pubic and axillary hair. The various stages of puberty are graded as Tanner stages 1–5 (sexual maturity rating; Table 1). Peak growth velocity occurs in the later stages of puberty (Table 2). Onset of puberty is closely related to skeletal maturation.

Breast development is the first sign of puberty in girls, followed by growth acceleration, pubic hair development, and menarche (Tables 3 and 4). Onset of breast development usually occurs at a bone age of 10 years and menarche at 12.5 years, irrespective of the chronological age. Peak growth velocity occurs in the initial 2 years, before menarche.

DEFINITION OF PRECOCIOUS PUBERTY

Puberty is considered precocious when signs of puberty appear before the age of 9 years in boys and 8 years in girls. The onset of menarche before 9.5 years is also termed as precocious.

TYPES OF PRECOCIOUS PUBERTY

- Central precocious puberty (CPP) or gonadotropin-dependent precocious puberty is caused by early release of gonadotropins (FSH and LH) from the pituitary, which in turn stimulate the testes to produce testosterone, or ovaries to produce estrogen. In CPP, the sequence of pubertal changes mimics normal puberty, but begins at an earlier age
- Peripheral precocious puberty (PPP) or gonadotropin-independent precocious puberty is caused by secretion of sex steroids from any organ which is outside the hypothalamic-pituitary-gonadal axis and independent of

TABLE 1: Classification of sexual maturity rating (Tanner's staging) in boys

Pubertal stage	Genital development	Pubic hair development	Axillary hair development
1	Prepubertal: testes size 1–3 mL	Nil	Nil
2	Testes size ≥4 mL in volume or ≥2.5 cm in length Early penile growth Scrotal skin thin and pink	Minimally pigmented hair at base of penis	Few axillary hair
3	Testes enlarge to 10–15 mL in volume or ≥3.3–4 cm in length Penis grows in length Scrotal thickening and pigmentation	Darker, coarser, and curled hair extending to mons pubis	Adult pattern
4	Testes enlarge to 15–20 mL in volume or ≥4–4.5 cm in length Penis grows in breadth; glans increases in size	Thicker adult pattern of hair not yet extending to medial surface of thighs	
5	Adult genitalia; testes 25 mL in volume or >4.5 cm in length	Adult distribution spreading to medial side of thighs	

TABLE 2: Normal pubertal development in boys

Onset of pubertal changes	Mean age (years)	Range (years)
Testicular enlargement begins	11–12	9–14
Penile enlargement begins	12	9–14
Pigmentation of scrotum	12	9–14
Pubic hair appears	12–13	11–14
Acceleration of growth	13–14	12–16
Axillary hair appears	14	12–16

TABLE 3: Classification of sexual maturity rating (Tanner's staging) in girls

Pubertal stage	Breast development	Pubic hair development	Axillary hair development
1	Prepubertal	Nil	Nil
2	Appearance of breast buds and slight areolar enlargement	Minimally pigmented hair on labia	Few axillary hair
3	Further enlargement of breast and areola	Darker, coarser, and curled hair extending to mons pubis	Adult pattern
4	Areola and nipple (papilla) form a secondary mound above the level of the breast	Thicker but not yet adult pattern	
5	Areola part of breast contour, projection of nipple only	Adult distribution extending to medial surface of thighs	

the hypothalamic pulse generator. Here, the sequence of puberty does not follow the normal pubertal pattern.

Premature thelarche is the early development of breasts, without other signs of puberty such as rapid linear growth or pubic hair development. Premature adrenarche is the early development of pubic hair without other pubertal changes. Both are normal physiologic variants.

TABLE 4: Normal pubertal development in girls

Onset of pubertal changes	Mean age (years)	Range (years)
Breast development (thelarche)	10–11	8–15
Acceleration of growth	10–11	8–15
Pubic hair appears (pubarche)	11–12	9–15
Menarche	12–13	10–16

CAUSES OF PRECOCIOUS PUBERTY

Box 1 lists the common causes of precocious puberty. Idiopathic precocity is rare in boys. Organic causes account for a majority of cases in younger girls, whereas idiopathic causes are more common after the age of 6 years.

APPROACH TO DIAGNOSIS

History

Note the age at onset of the first signs of puberty and its progress over time. The growth spurt or peak growth velocity is important, as the acceleration of linear growth results in tall stature initially, but eventually the affected children become short adults since fusion of bones occur early. Onset of puberty in early childhood (below age 6 years) is highly suggestive of organic central nervous system (CNS) pathology, particularly hypothalamic hamartoma, or McCune-Albright syndrome (MAS). Inquire about details of childbirth, perinatal insults, head trauma, CNS infections, tumors, and craniospinal radiation. History of headache, vomiting, and visual disturbances suggests an intracranial tumor. Gelastic epilepsy is a characteristic feature of hypothalamic hamartoma. Prematurity, intrauterine growth retardation, and adoption may be associated with PP. Developmental delay and behavioral disturbances are associated with CNS involvement as

Box 1: Etiology of precocious puberty

Central isosexual precocious puberty in girls and boys

- Idiopathic (common in girls): sporadic, familial
- Genetic: KISS1, GPR54, and MKRN3 mutations
- Neurogenic:
  - Hypothalamic hamartoma (common)
  - Central nervous system tumors: glioma, astrocytoma, ependymoma, pineal tumors, craniopharyngioma
  - Central nervous system infections: neurotuberculosis, post-meningitis/encephalitis
  - Central nervous system insults: trauma, neurosurgery, cranial irradiation, perinatal asphyxiation
  - Central nervous system malformations: arachnoid cyst, hydrocephalus, septo-optic dysplasia, neurofibromatosis, neural tube defects, cerebral dysgenesis
- Miscellaneous: adoption, intrauterine growth retardation, Russell-Silver syndrome, endocrine disruptor syndrome

Peripheral precocious puberty in girls

- Hypothyroidism
- Ovarian causes
  - McCune-Albright syndrome (more common in girls)
  - Benign follicular cysts
  - Tumors: granulosa-theca cell tumors, arrhenoblastoma, teratoma
- Adrenal causes: feminizing adrenal neoplasia
- Exogenous estrogen exposure: medications, phytoestrogens

Peripheral precocious puberty in boys

- Adrenal causes
  - Congenital adrenal hyperplasia (CAH): 21-hydroxylase and 11β-hydroxylase deficiency
  - Adrenal tumors: virilizing adenoma, carcinoma
- Testicular causes
  - Tumors: Leydig cell tumor, adrenal rest tumor
  - Apparent luteinizing hormone excess: familial male-limited precocious puberty (FMPP or testotoxicosis)
- Human chorionic gonadotropin-secreting tumors: intracranial (germinoma or teratoma), ectopic (hepatoblastoma, teratoma, choriocarcinoma)
- Exogenous androgen/testosterone exposure: testosterone creams and medications

Combined peripheral and central precocious puberty

- Prolonged undertreated precocious puberty (CAH, McCune-Albright syndrome, FMPP)

Heterosexual precocity

- Virilization in girls: CAH, virilizing ovarian/adrenal neoplasia, polycystic ovarian syndrome
- Feminization in boys: estrogen secreting adrenal tumor, exogenous estrogens/drugs

Variations in pubertal development

- Premature thelarche
- Premature pubarche/adrenarche
- Premature menarche

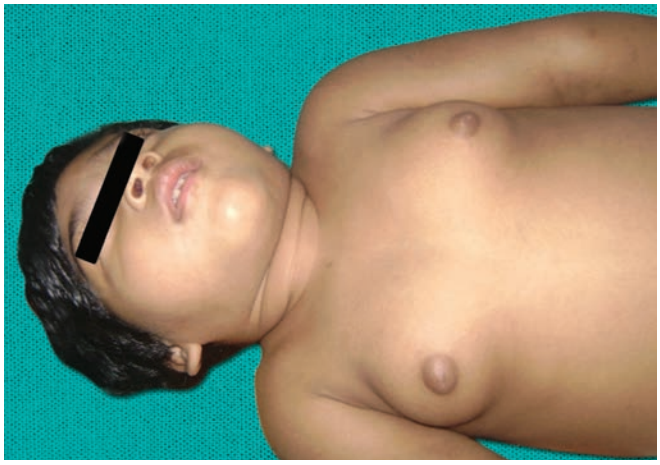


Fig. 1: Premature thelarche due to gonadotropin-dependent precocious puberty in a 4-year-old girl with spastic quadriplegia with seizures on anticonvulsant therapy

in cerebral palsy, hamartoma, and CNS malformations (Fig. 1). A detailed family history of early puberty and consanguinity is helpful to diagnose constitutional forms, familial male-limited precocious puberty (FMPP or testotoxicosis) and congenital adrenal hyperplasia (CAH). Carefully elicit the history of drugs or creams consumed/applied by the child or parents/other family members, including illicit drug use (anabolic steroids, estrogen creams, androgen, and phytoestrogens). Possibility of sexual abuse, foreign body or vaginal infection must be probed in girls with isolated vaginal bleeding. Ask for any previous height measurements (pediatrician/school).

Physical Examination

The height, weight, span, and body proportions should be measured carefully and plotted on growth charts. It is important to measure the height of father and mother to calculate the midparental height, which is plotted on the right side of the growth chart. Compare with previous height measurements to assess growth velocity. Note the development of acne, pubic, axillary and facial hair, as well as appearance of hair in unusual areas. Look for voice change and muscle development. Skin should be checked for texture (hypothyroidism), macules (neurocutaneous syndromes), neurofibromas, and café-au-lait spots (neurocutaneous disorders and MAS; Fig. 2). It is important to look for skeletal deformities (e.g., MAS). Hyperpigmentation of mucosa and skin is a common feature of CAH. Check for other clinical stigmata of hypothyroidism, e.g., weight gain with decreased linear growth, puffiness, lethargy, constipation, or coarse skin. Precocious puberty is characterized by rapid growth rate, deepening of voice (in boys), and enlargement of genitalia. However, PP associated with hypothyroidism is characterized by growth faltering and absence of pubarche.

Pubertal development should be assessed according to Tanner's stages. In boys, assess testicular volume using an orchidometer and measure the stretched penile length (from the base of the shaft of the penis to the tip, excluding

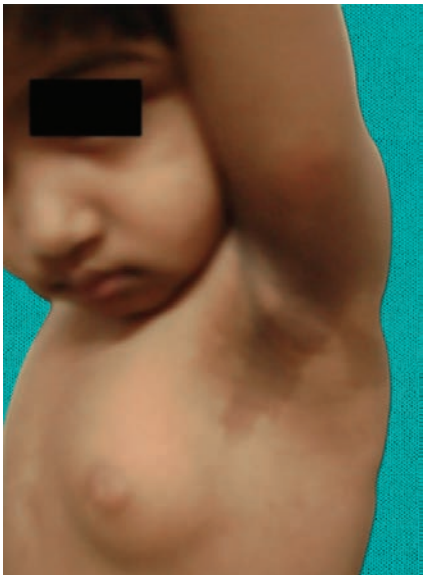


Fig. 2: McCune-Albright syndrome in a 4-year-old girl. Note the premature thelarche and the large café-au-lait pigmented macule in the axilla

the foreskin). In children with CPP (e.g., hypothalamic hamartoma), penile enlargement is associated with increase in testicular volume (>4 mL, or diameter >2.5 cm). In PPP (e.g., CAH), testicular volume remains prepubertal (<4 mL). In testotoxicosis and human chorionic gonadotropin (hCG)-secreting tumors, testes are modestly and symmetrically enlarged (3–4 mL). Asymmetrical or unilateral enlargement of testis is seen in Leydig cell tumors or adrenal rests.

Clinical Pearl

- Measuring testicular volume carefully narrows down the possibilities, thus reducing the cost and number of investigations and the time taken for establishing the etiology.

In girls, evaluation of the breast as well as genital examination in an appropriate position is important. Vaginal mucosa should be examined in good light for signs of estrogen effect (e.g., pale pink color instead of glistening red prepubertal mucosa). Presence of vaginal secretions and menstruation should be noted. Clitoral size should be evaluated. Vaginal bleeding without breast development may indicate sexual abuse: marks of injury should be looked for. Virilization without signs of estrogen effect indicates androgens from the adrenal or rarely, the ovary or an androgen-secreting tumor. Rapid virilization may suggest androgen-secreting tumors of adrenal gland or ovary. Breasts should be carefully examined for nodules and galactorrhea.

In a boy with true precocious puberty, an organic cause is far more likely, unlike in girls older than 6 years, where most investigations are likely to be normal. All young children with precocious puberty should be evaluated for an underlying CNS disorder. This should include the signs of raised intracranial pressure and examination of optic fundi. Blood pressure may be high in children with 11β-hydroxylase deficiency or adrenal tumor. Abdominal examination may reveal adrenal or ovarian mass as well as enlarged uterus. Firm hepatomegaly may be a manifestation of hCG-secreting tumors such as hepatoblastoma.

If breast development is the only clinical feature, without growth acceleration and pubic hair development, the condition is labeled as premature thelarche. Premature adrenarche is the likely diagnosis if signs of virilization (pubic hair, axillary hair, facial hair, or acne) appear without breast development, growth acceleration, or advanced bone age. These children should be followed up regularly, to look for later development of growth spurt and other pubertal changes. A fluctuating course is suggestive of intermittent estrogen production by ovarian cysts. Discordant puberty (e.g., vaginal bleeding within short duration of thelarche) indicates withdrawal bleeding following removal of the source of estrogen production as with ovarian cyst, hypothyroidism, or MAS.

Investigations

Investigations should be directed to confirm PP and find out the etiology. Bone age should be assessed accurately, using a Greulich-Pyle or Tanner-Whitehouse atlas, and pelvic ultrasound done in girls by an ultrasonologist experienced in pediatrics. Precocious puberty is associated with advanced bone age except in hypothyroidism. If the bone age advancement is appropriate for the height age, it is likely that the precocity is benign, probably a normal variant that needs only careful follow-up and no treatment. An advanced bone age, coupled with pubertal changes on pelvic ultrasound, suggests the need for an endocrine evaluation.

Hormonal investigations are recommended in very young children with advancing puberty—if more than one sign of puberty is present; if a new sign of puberty appears during follow-up; if the growth rate is accelerated; or if bone age is advancing rapidly. Serum estradiol in girls, and testosterone in boys in early morning samples confirm the diagnosis. Serum levels of estradiol less than 10 pg/mL and testosterone less than 25 ng/dL rule out CPP. However interpretation of the results, especially for serum estradiol, might be difficult as the sensitivity of most available assays is much above these levels.

Basal level of serum LH in a pooled or midnight sample (since the secretion of LH is pulsatile) is the best screening test to diagnose CPP. Luteinizing hormone is more useful than FSH: levels less than 0.1 IU/L by a very sensitive assay indicate prepubertal state, while those above 0.6 IU/L suggest pubertal levels. In premature adrenarche, gonadotropin levels are prepubertal, while in PPP, they are suppressed.

Gonadotropin-releasing hormone stimulation test or GnRH agonist analog stimulation test is required if baseline gonadotropin levels are inconclusive.

The GnRH stimulation test is performed by collecting 3–7 blood samples at 30-minute intervals after injection of intravenous or subcutaneous GnRH (2.5 μg/kg; maximum 100 μg). Normal prepubertal children show a peak increment of 3–4 IU/L of LH and 2–3 IU/L of FSH. Pubertal LH levels

(>6 IU/L) and LH to FSH ratio greater than 0.9 are diagnostic of CPP. A predominant FSH response is seen in premature thelarche. However, this test is difficult to do, due to the limited availability of GnRH and the higher number of samples, which makes it more invasive and expensive.

Gonadotropin-releasing Hormone Agonist Analog Test

Gonadotropin-releasing hormone agonist analog test is, therefore, the preferred test now. A single sample is taken 60 minutes after a subcutaneous injection of leuprolide acetate 10–20 μg/kg (maximum of 500 μg) or of triptorelin 0.1 mg. A stimulated LH level of 6 IU/L or more is consistent with CPP.

Clinical Pearl

- Luteinizing hormone level in a pooled serum sample is the best screening test for central precocious puberty; gonadotropin-releasing hormone stimulation test is confirmatory.

Other Hormones

Estimation of serum total testosterone is useful in girls to differentiate between premature adrenarche and virilization, and in polycystic ovarian syndrome. Serum free testosterone is not a useful test. Pubertal levels of DHEAS characterize premature adrenarche, while greatly elevated level of DHEAS is seen in virilizing adrenal tumors.

Elevated unstimulated plasma 17-hydroxyprogesterone levels are seen in CAH. If the levels are inconclusive, an adrenocorticotropic hormone stimulation test is performed.

Testosterone levels are very high in tumors. Pubertal testosterone levels with suppressed gonadotropins are seen in FMPP (testotoxicosis). Human chorionic gonadotropin and often α-fetoprotein are elevated in patients with hCG-secreting tumors. In girls, increased estrogen with suppressed gonadotropins is seen in conditions causing autonomous secretion of estrogen such as functional ovarian cysts, ovarian tumor, or MAS.

Serum thyroid stimulating hormone and thyroxine levels should be checked if the bone age is delayed, especially with slow height velocity. Serum prolactin levels should be estimated in the presence of galactorrhea.

Imaging

Plain X-rays of the Skull

They may show sellar enlargement, calcification, and evidence of raised intracranial pressure, but are almost always of little utility. A skeletal survey should be done if clinical features suggest fibrous dysplasia (MAS).

Pelvic Ultrasound

It helps in girls to arrive at a diagnosis by visualizing the uterus, adrenals, and ovaries. Ovarian volume more than 1–2 mL, with multiple cysts (>6 cysts and greater than 4 mm diameter) is characteristic of a peripubertal state. The pubertal ovarian volume is usually above 3 mL. Large ovarian cysts are often seen in girls with hypothyroidism: these regress with thyroxine replacement, and do not require surgery. In the uterus, the earliest feature of estrogenization is a change in the shape from prepubertal tubular shape (diameters of fundus and cervix are equal) to pubertal pear shape (diameter of the fundus is more than that of cervix). Endometrial thickness of 6–8 mm indicates menarche is imminent.

Abdominal Ultrasound

It is useful in diagnosing adrenal tumors and ultrasound of testes is used to diagnose testicular tumors. Computed tomography (CT) or magnetic resonance imaging (MRI) of abdomen may be confirmatory in adrenal tumors.

Neuroimaging

High resolution MRI of hypothalamus and pituitary helps to detect lesions such as hypothalamic hamartoma, glioma, astrocytoma, and structural malformations like septo-optic dysplasia. Magnetic resonance imaging should be done in all boys, and in girls below 6 years, since the chance of finding an organic cause is high. In girls above 6 years, since most will be idiopathic, MRI should be individualized, e.g., it should be done if the pubertal progression is very rapid or there is other evidence of a CNS pathology. Further hormonal evaluation of the hypothalamic-pituitary axis may be indicated if an abnormality is detected.

Clinical Pearl

- An organic etiology is more likely in a young boy with central precocious puberty, unlike an older girl where most investigations are likely to be normal.

Algorithm 1 summarizes the approach to the diagnosis of PP in girls where as algorithm 2 details the approach to the diagnosis of PP in boys.

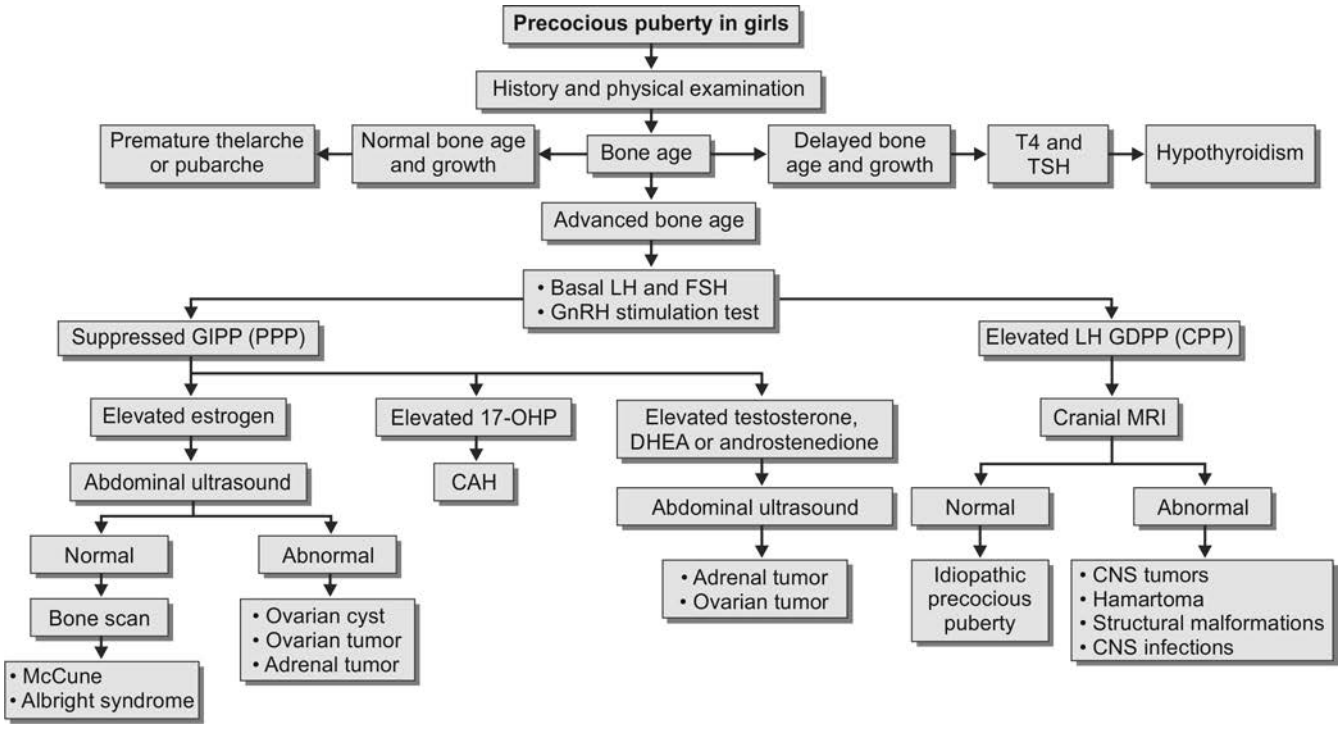
MANAGEMENT

Untreated PP leads to early pubertal maturation with advancement of bone age and early epiphyseal fusion, leading to tall stature in childhood, but short stature in adulthood, and psychological problems. Treatment is aimed at arresting the progression of puberty, identifying and managing the underlying cause, increasing the prospects for better adult height, and providing psychosocial support to affected children and their families.

Tumors of the brain, gonads, adrenals, or ectopic sites may require surgery, radiotherapy, or chemotherapy. Ovarian cysts more than 3 cm in diameter, which are persistent or have a solid component, may need exploration and excision. Smaller cysts are monitored by frequent estrogen estimations and ultrasounds. Congenital adrenal hyperplasia is managed with hydrocortisone (15–20 mg/m^2) and fludrocortisone. Hypothyroidism is managed with thyroxine replacement.

ALGORITHM 1

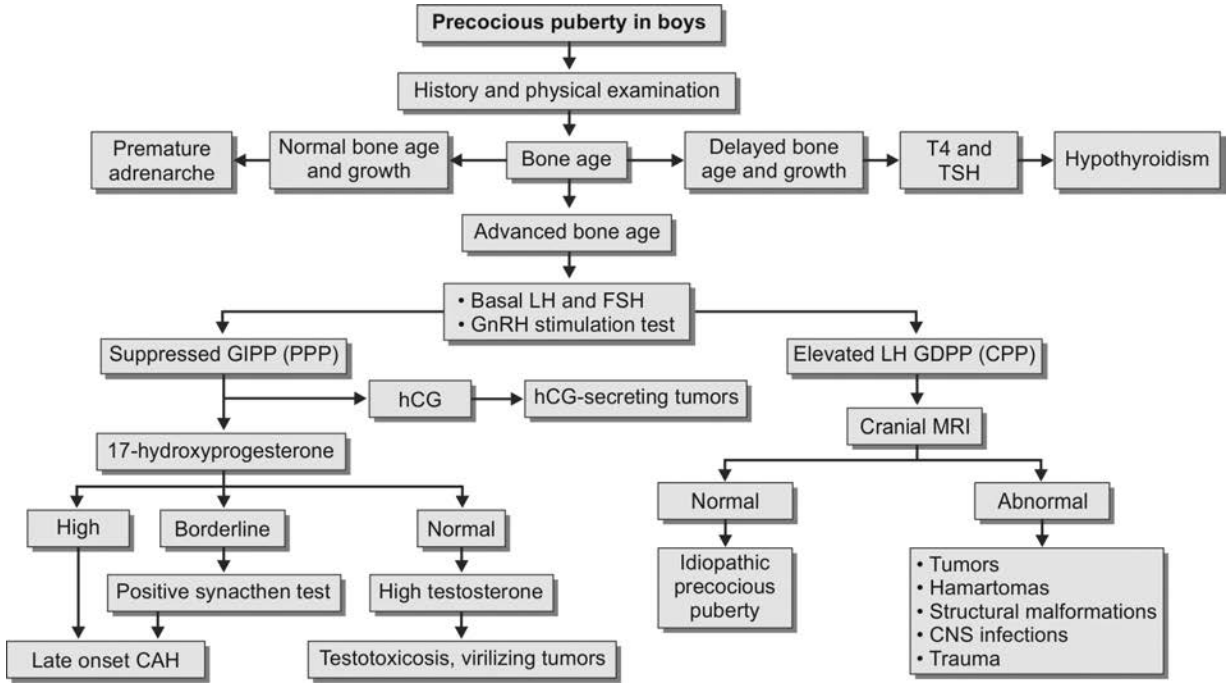
Approach to the diagnosis in a girl with precocious puberty



T4, thyroxine; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GDPP, gonadotropin-dependent precocious puberty; CPP, central precocious puberty; GIPP, gonadotropin-independent precocious puberty; PPP, peripheral precocious puberty; 17-OHP, 17-hydroxyprogesterone; CNS, central nervous system; DHEA, dehydroepiandrosterone.

ALGORITHM 2

Approach to the diagnosis of precocious puberty in boys



T4, thyroxine; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GDPP, gonadotropin-dependent precocious puberty; CPP, central precocious puberty; GIPP, gonadotropin-independent precocious puberty; PPP, peripheral precocious puberty; CAH, congenital adrenal hyperplasia; MRI, magnetic resonance imaging; CNS, central nervous system; hCG, human chorionic gonadotropin.

In CPP, long-acting GnRH analogs are the mainstay of treatment. They decrease the episodic release of GnRH due to their continued high levels, causing desensitization of gonadotropin-producing cells of the pituitary. They slow down rapid skeletal maturation and linear growth, which remain unaffected by other forms of therapy. Depot preparations are preferred. These include leuprolide (3.75 and 11.25 mg), triptorelin (3.75 and 11.25 mg), and goserelin (3.6 mg). Treatment should be continued till the child reaches the normal pubertal age (10–11 years). The effectiveness of therapy is monitored by clinical evaluation of puberty, growth, and hormone evaluation. The sex steroids should revert to normal prepubertal levels for age. An effective dose is one where the gonadotropin response to exogenous GnRH is obliterated. This can be done by testing serum LH 60 minutes after the depot injection. Gonadotropin-releasing hormone analog treatment in girls with CPP has no long-term deleterious effects on reproductive function or bone mineralization.

In patients with autonomous gonadal steroid production such as MAS and FMPP, therapy is aimed at reducing sex steroid production or its effects, thereby arresting acceleration of growth and progression of puberty. Medroxyprogesterone acetate and cyproterone acetate interfere with sex steroid synthesis, but have no beneficial effect on final height outcome. Aromatase inhibitors prevent testosterone conversion to estrogens or block the receptors for testosterone and dihydrotestosterone. Medical management of peripheral precocity has not been generally successful, in contrast to the success of GnRH analogs for CPP.

KEY POINTS

- ☞ Central precocious puberty (CPP) is idiopathic in 90% girls, but only 10% boys. Hence careful search for a cause, including neurological imaging, is warranted in boys and girls less than 6 years of age
- ☞ Genital maturation without testicular enlargement rules out CPP in boys
- ☞ Serum luteinizing hormone level (pooled sample) is the best screening test for CPP; gonadotropin-releasing hormone stimulation test is confirmatory
- ☞ Untreated precocious puberty is associated with short final height
- ☞ Gonadotropin-releasing hormone analog is the treatment of choice for CPP
- ☞ Hypothyroidism is the only condition which causes precocious puberty associated with growth delay and retarded bone age.

SUGGESTED READINGS

1. Bajpai A, Sharma J, Kabra M, Gupta A, Menon PS. Precocious puberty: clinical and endocrine profile and factors indicating neurogenic precocity in Indian children. J Pediatr Endocrinol Metab. 2002;15:1173-81.
2. Bajpai A, Menon PS. Contemporary issues in precocious puberty. Indian J Endocrinol Metab. 2011;15:S172-9.
3. Bajpai A, Sharma J, Kabra M, Gupta AK, Menon PS. Long-acting GnRH analogue therapy in central isosexual precocious puberty. Indian Pediatr. 2002;39:633-9.
4. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009;123:e752-62.
5. Chalumean M, Hadjiathanasiou CG, Ng SM, Cassio A, Mul D, Cisternino M, et al. Selecting girls with precocious puberty for brain imaging: validation of European evidence-based diagnosis rule. J Pediatr. 2003;143:445-50.
6. Dattani MT, Tziaferi V, Hindmarsh PC. Normal and abnormal puberty. In: Brook CG, Clayton PE, Brown RS (Eds). Clinical Pediatric Endocrinology, 6th ed. Chichester: Wiley-Blackwell; 2009. pp. 183-210.
7. Lee PA, Houk CP. Puberty and its disorders. In: Lifshitz F (Ed). Pediatric Endocrinology, 5th ed. New York: Informa Healthcare; 2007. pp. 207-324.
8. Rosenfield RL, Cooke DW, Radovick S. Puberty and its disorders in female. In: Sperling MA (Ed). Pediatric Endocrinology, 3rd ed. Philadelphia: Saunders Elsevier; 2008. pp. 530-600.
9. Sathasivam A, Rosenberg HK, Shapiro S, Wang H, Rapaport R. Pelvic Ultrasonography in the Evaluation of Central Precocious Puberty: Comparison with Leuprolide Stimulation Test. J Pediatr. 2011;159:490-5.
10. Vijayakumar M, Menon PS. Precocious puberty—Perspectives in diagnosis and management. Indian J Pediatr. 2014;81:76-83.

CHAPTER 111

Persistent Hypoglycemia in Newborns and Infants

Ganesh S Jevalikar

INTRODUCTION

The neonatal period marks the transition of continuous supply of glucose from maternal circulation in intrauterine life to interrupted availability of glucose in extrauterine life. Hypoglycemia is a significant threat to the developing brain and if inadequately treated, can lead to permanent brain damage. This chapter discusses causes and approach to treatment of persistent hypoglycemia in infants. Transient hypoglycemia is more common, particularly in preterm, low birth weight, and sick newborns and is discussed in the later section.

DEFINITION OF HYPOGLYCEMIA

A single cut-off to define normal plasma glucose is not possible as specific brain responses to low glucose depend on several factors like the duration of low glucose and the availability of alternative fuels. The Whipple's triad used to define hypoglycemia in older children and adults cannot be used in infants, due to the inability to communicate symptoms and the nonspecific nature of the symptoms. Recognition of hypoglycemia may therefore require confirmation by repeated measurements of plasma glucose.

Due to the possible risks of hypoglycemia to the developing brain, evaluation and management is recommended in infants whose plasma glucose concentrations are documented by laboratory quality assays to be below the normal threshold for neurogenic responses (<60 mg/dL). This is especially applicable beyond the first 2-3 hours of life. Plasma glucose values are 10–15% higher than whole blood values and appropriate corrections should be made before interpreting the values.

A single cut-off to define normal plasma glucose is not possible as specific brain responses to low glucose depend on several factors like duration of low glucose and the availability of alternative fuels. The Whipple's triad used to define hypoglycemia in older children and adults cannot be used in infants due to the inability to communicate symptoms and the nonspecific nature of the symptoms. , Recognition of hypoglycemia may therefore require confirmation by repeated measurements of plasma glucose.

Due to possible risks of hypoglycemia to the developing brain evaluation and management is recommended in infants whose plasma glucose concentrations are documented by laboratory quality assays to be below the normal threshold for neurogenic responses (<60 mg/dL). This is especially applicable beyond first 2-3 hours of life. Plasma glucose values are 10–15% higher than whole blood values and appropriate corrections should be made before interpreting the values.

Low values obtained on capillary testing should be confirmed by laboratory assessment, since capillary assessments are not accurate enough (particularly in the low range) to diagnose hypoglycemia. Samples for blood glucose must be analyzed immediately as delayed processing decreases values.

Clinical Pearls

- Diagnosis of hypoglycemia should be based on a level in a venous sample, not capillary glucose by finger stick
- Plasma glucose values are 10–15% higher than whole blood
- Delay in processing of sample causes drop in measured glucose.

GLUCOSE HOMEOSTASIS IN FETUS AND NEWBORN

Fetal blood glucose remains around 54 mg/dL over most of gestation, especially after 20 weeks of pregnancy. In the first 1–2 hours after birth, blood glucose drops to as low as 30 mg/dL. This stimulates glycogenolysis, gluconeogenesis, and ketogenesis, mediated by hormonal changes [suppression of insulin and release of counter-regulatory hormones: catecholamines, glucagon, and growth hormone (GH)], changes in hormone receptors, and expression of key enzymes of glucose production, which increase the blood glucose to

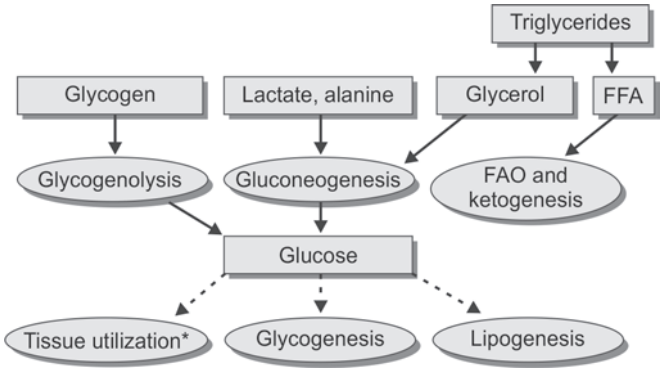
greater than 45 mg/dL by 12 hours of birth. Initiation of feeding after birth maintains ongoing supply of energy substrates. Breastfed newborns have lower blood glucose and higher ketone concentrations (principal alternative fuel for brain) compared to formula-fed newborns.

GLUCOSE HOMEOSTASIS IN OLDER CHILDREN

Understanding glucose homeostasis in the fed and fasting states is important to understand the causes of hypoglycemia. Although the mechanisms of control are analogous to adults, children have lesser tolerance to fasting due to lesser glycogen stores and lesser muscle mass. In the fed state, insulin promotes glucose utilization by insulin-dependent tissues (utilization by brain is insulin independent) and promotes glycogenesis and lipogenesis, the storage forms of energy. In the fasting state, a drop in blood glucose is prevented by suppression of insulin and release of counter-regulatory hormones (catecholamines, glucagon, GH, and corticosteroids) which mediate glycogenolysis, gluconeogenesis, and lipolysis. Lipolysis generates alternative fuels through fatty acid oxidation and formation of ketone bodies. These mechanisms come into play at different intervals of fasting, with glycogenolysis being the immediate mechanism and gluconeogenesis the principal mechanism after depletion of glycogen stores. Insulin has an inhibitory effect on fatty acid breakdown and ketogenesis. Figure 1 illustrates glucose homeostasis in the fasting state in a simplified way.

Interruption of normal homeostatic mechanisms maintaining blood glucose levels causes hypoglycemia.

Glucose entry into β-cells through glucose transporter 2 initiates the process of insulin secretion (Fig. 2). Upon entry, glucose is metabolized to glucose-6-phosphate by glucokinase which is further metabolized, leading to generation of adenosine triphosphate (ATP). Increase in intracellular ATP/

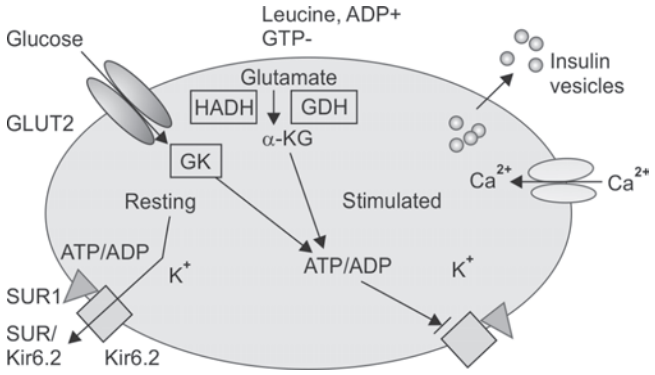


Dashed arrows indicate actions mediated by insulin which are inhibited in a fasting state, whereas weighted arrows indicate actions which maintain plasma glucose level or provide alternate fuel in fasting state. These are mediated by counter-regulatory hormones. Insulin is inhibitory to fatty acid breakdown and ketogenesis.

*Important reactions involved in glucose homeostasis

FFAs, free fatty acids; FAO, fatty acid oxidation.

Fig. 1: Glucose homeostasis in fasting state



GLUT2, glucose transporter 2; GK, glucokinase; GDH, glutamate dehydrogenase; SUR, sulfonylurea receptor α-KG , α-ketoglutarate; ATP, adenosine triphosphate; ADP,adenosine diphosphate; GTP, guanosine triphosphate.

Fig. 2: Physiology of insulin secretion. Diagram of β-cell of pancreas showing major steps in insulin secretion

adenosine diphosphate ratio closes ATP sensitive potassium (KATP) channels [which consist of inward rectifying K^+ channel Kir 6.2, surrounded by sulfonylurea receptor (SUR)]. This causes depolarization and opening of voltage-gated calcium channels. Increased intracellular calcium causes exocytosis of insulin vesicles. Glutamate dehydrogenase (GDH) catalyzes glutamate oxidation leading to formation of ATP and further cascade of reactions leading to insulin release. Leucine is an allosteric activator of GDH action.

TRANSIENT HYPOGLYCEMIA OF NEWBORN

As noted above, blood glucose less than 45 mg/dL may be observed in 5–15% healthy term newborns. Some newborns are at risk for transient hypoglycemia (Box 1). In some of these conditions, hypoglycemia may be recurrent or persistent over first few weeks (e.g., in small for gestational age babies), therefore needing evaluation as persistent hypoglycemia.

PERSISTENT HYPOGLYCEMIA IN NEWBORNS, INFANTS, AND CHILDREN

Persistent hypoglycemia can result from conditions (Box 2) which interfere in normal glucose homeostasis (Fig. 1)

Box 1: Causes of transient hypoglycemia in neonatal period

- Preterm appropriate for gestational age
- Small for gestational age (term or preterm)
- Birth asphyxia
- Neonatal sepsis
- Systemic diseases: liver disease, cardiac failure/ cyanotic heart disease
- Polycythemia
- Cold injury
- Transient hyperinsulinism
  - Infant of diabetic mother
  - Small for gestational age
  - Birth asphyxia
  - Rh incompatibility
  - Exchange transfusion
  - Syndromic causes: Beckwith-Wiedemann, Turner, Kabuki, and trisomy 13 syndromes

Box 2: Etiology of persistent hypoglycemia in newborns, infants, and children

Hyperinsulinism

- Congenital hyperinsulinism
  - ABCC8, KCNJ11, GDH, glucokinase, HADH, HNF4α, HNF1α, SLC16A1, UCP2, PGM1, HK1
  - Syndromic: Beckwith-Wiedemann, trisomy 13, Kabuki, and Costello syndromes
- Insulinoma (sporadic or MEN1 associated)
- Dumping syndrome
- Exogenous insulin administration
- Sulfonylurea ingestion

Hormone deficiencies

- Adrenocorticotropic hormone/cortisol deficiency
- Growth hormone deficiency
- Catecholamine deficiency (rare as isolated entity)

Carbohydrate disorders

- Glycogen storage diseases
- Galactosemia
- Hereditary fructose intolerance
- Other disorders of gluconeogenesis

Fatty acid disorders

- Carnitine transporter deficiency
- Carnitine palmitoyltransferase-1/2 deficiency
- Carnitine translocase deficiency

Very long/long/medium/short chain acyl-coenzyme A dehydrogenase deficiency

Amino acid disorders

- Methylmalonic acidemia
- 3-hydroxy-3-methylglutaric aciduria
- Maple syrup urine disease
- Tyrosinemia type 1

Increased utilization

- Sepsis
- Systemic disease: liver disease, heart failure, falciparum malaria

Miscellaneous

- Ketotic hypoglycemia
- Congenital disorders of glycosylation
- Insulin antibodies
- Drugs*: quinine, pentamidine, salicylates, alcohol

*Except insulin and sulfonylurea.

including alterations in hormones, or deficiencies of enzymes of glycogenolysis, gluconeogenesis, and fatty acid oxidation.

Congenital Hyperinsulinism

Congenital hyperinsulinism (CHI) [previously called nesidioblastosis, persistent hyperinsulinemic hypoglycemia of infancy (PHHI), or leucine sensitive hypoglycemia] is the most common cause of persistent hypoglycemia in neonates and infants. Insulin secretion is inappropriate (rather than excessive) at the time of hypoglycemia (normally with low blood glucose, insulin gets totally suppressed). It poses more risk to the brain than other causes, as unsuppressed insulin also prevents ketogenesis (alternative fuel for the brain). In spite of significant recent advances in molecular genetics, in nearly 40–50% of cases of CHI, precise genetic mechanisms remain unknown. Mutations causing CHI generally increase intracellular ATP, leading to persistent closure of KATP channels and uninhibited insulin release. Most commonly, these are mutations in subunits of KATP channels (SUR1 receptor coded by ABCC8 gene and Kir6.2 channel coded by KCNJ gene). Autosomal recessive (AR) mutations present earlier, are associated with macrosomia, and are more commonly unresponsive to diazoxide. Autosomal dominant (AD) mutations are generally milder and diazoxide responsive. Other types include activating mutations of glucokinase, GDH (characterized by hyperammonemia and leucine sensitivity, macrosomia is unusual), short chain hydroxylacyl-coenzyme A (CoA) dehydrogenase, SLC16A1 (characterized by exercise-induced hyperinsulinism), and recently described mutations in several newer genes (Box 2)

Histologically, focal and diffuse types are seen. Focal forms are due to paternally inherited recessive mutations of KATP channel and somatic loss of heterozygosity in maternal chromosome 11, and can be completely cured by selective pancreatectomy.

Clinically, CHI can be divided into diazoxide responsive and unresponsive. Genetic studies can be helpful in predicting response to treatment and need for surgical management, and must be attempted in all cases presenting with CHI.

Clinical Pearls

- Congenital hyperinsulinism is the most common cause of persistent neonatal hypoglycemia
- Insulin secretion is inappropriate rather than excessive
- Genetic analysis may be helpful in deciding the line of treatment and must be attempted in all cases.

Hormone Deficiencies

Growth hormone (GH) and/or adrenocorticotropic hormone (ACTH) deficiency can present as neonatal hypoglycemia. It is more common with multiple pituitary hormone deficiencies than with isolated hormone deficiencies. Microphallus, conjugated hyperbilirubinemia, and midline defects are clinical clues to these deficiencies. Low serum free thyroxine can be suggestive. The diagnosis is suspected if GH and/or cortisol levels are low in a hypoglycemic blood sample, keeping in mind that persistent or recurrent hypoglycemia per se can impair GH and cortisol responses. Primary adrenal insufficiency can cause hypoglycemia, e.g., neonates with congenital adrenal hyperplasia, but usually other clinical features dominate (genital ambiguity, salt wasting crisis). Hypoglycemia due to hormone deficiencies responds to appropriate hormone replacement.

Disorders of Carbohydrate Metabolism

Glycogen storage disorders (GSDs) are AR enzyme deficiencies of glycogen metabolism. Ketotic hypoglycemia is commonly seen in types I, III, VI, and IX GSD. Although they can present in the newborn period, more often they manifest when the interval between feeding and the duration of fasting increases. Failure to thrive, short stature, hepatomegaly, and doll-like facies are clinical clues. In some, skeletal or cardiac muscle involvement may be present but is usually asymptomatic in childhood. Renal tubular dysfunction can be seen in type 1 GSD, and hypophosphatemic rickets in Fanconi-Bickel syndrome. Biochemical evaluation shows elevated lactate, uric acid, triglycerides, and hepatic transaminases (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase). Lactate and uric acid are usually elevated in type 1 GSD. Glycemic response to glucagon tends to be absent or poor. Definitive diagnosis can be established by genetic analysis or enzyme studies in liver biopsy specimen. Treatment of hypoglycemia usually consists of frequent carbohydrate feeding and supplementation with uncooked cornstarch.

Defects in gluconeogenesis (phosphoenolpyruvate carboxykinase deficiency, fructose-1,6-biphosphatase deficiency) present with fasting hypoglycemia, high lactate and alanine levels, and fatty infiltration of liver and other organs. Hereditary fructose intolerance presents on exposure to fructose containing food (sucrose, fruits, and juices), with hypoglycemia, vomiting, failure to thrive, hepatomegaly and renal tubular dysfunction.

Classic galactosemia [galactose-1-phosphate uridyltransferase (GALT) deficiency] presents in neonates and infants with hypoglycemia, cholestatic jaundice, vomiting, and *Escherichia coli* sepsis. Urine tests positive for non-glucose reducing substances and diagnosis is confirmed by GALT assay.

Fatty Acid Oxidation Disorders

Hereditary or acquired defects of fatty acid oxidation impair ketogenesis and produce nonketotic hypoglycemia, liver dysfunction, cardiomyopathy, and encephalopathy. Manifestations can be of variable severity, including risk of sudden death. Episodes of decompensation are usually triggered by fasting or intercurrent illnesses. Treatment includes avoidance of fasting, frequent feeding, high carbohydrate (up to 70% of energy intake)-low fat diet, use of cornstarch, and carnitine supplementation (not useful in long chain hydroxyacyl CoA dehydrogenase).

Aminoacidopathies

Aminoacidopathies (Box 2) present with ketotic hypoglycemia, repeated vomiting, and developmental delay. Seizures, encephalopathy, and hepatomegaly can be present. Hyperammonemia is seen in organic acid disorders. Diagnosis depends on finding of specific organic acids in urine and analysis of liver biopsy or cultured fibroblasts.

Insulinoma

Islet cell adenoma (insulinoma) is a rare cause of hypoglycemia in children. Diagnosis is based on magnetic resonance imaging or functional scanning of pancreas. If present, it should prompt evaluation for features of MEN1 in the child.

Accelerated Hypoglycemia (Ketotic Hypoglycemia)

This condition usually presents at 1.5–5 years of age, typically as early morning lethargy and difficulty in getting up in the morning, associated with ketonemia/ketonuria. These children have relatively lesser concentrations of alanine and less tolerance to fasting. Spontaneous improvement is seen after 8–9 years of age.

SYMPTOMS OF HYPOGLYCEMIA

Symptoms of hypoglycemia in neonates (Box 3) can be nonspecific and caused by other etiologies like sepsis, asphyxia, and electrolyte disturbances.

Symptoms are usually divided into those resulting from autonomic system activation and those resulting from neuroglucopenia (Table 1). However, in newborns, in poorly controlled type 1 diabetes mellitus, and in those with autonomic dysfunction, autonomic symptoms may be absent. The threshold blood glucose value at which symptoms appear can be variable.

CLINICAL EVALUATION

Careful history and examination is the first step in diagnosis. Clues to diagnosis on history and examination are listed in Tables 2 and 3, respectively.

Box 3: Symptoms of hypoglycemia in newborns

- Seizures
- Jitteriness
- Apathy
- Cyanosis
- Apnea or tachypnea
- Hypothermia
- Limpness
- Lethargy
- Poor suck/feeding
- Eye rolling
- Sudden pallor, mottling
- Cardiac arrest

TABLE 1: Symptoms of hypoglycemia in children

Autonomic symptoms	Neuroglucopenic symptoms
Tremors	Headache
Palpitations, tachycardia	Lightheadedness
Anxiety	Sensation of warmth
Restlessness	Fatigue, weakness
Sweating	Inability to think, inappropriate behavior
Hunger	Emotional lability
Paresthesias	Blurring of vision
Pallor	Seizures
Increased systolic blood pressure	Transient focal neurological deficits (diplopia, hemiparesis, etc.) , unconsciousness, brain damage and death if prolonged untreated episode

TABLE 2: Clues to diagnosis of persistent hypoglycemia in children

Points in history	Diagnostic clues
Age of onset	• Early onset in hyperinsulinism (severe forms) • Onset after gaps between feeds increase (GSD)
Gestational age and birth weight	• Transient hyperinsulinism in SGA • Macrosomia (infant of diabetic mother, hyperinsulinism) • Prematurity
Relation of hypoglycemia to feeding	• In fed and fasting state—hyperinsulinism • In early hours of fasting—defects in glycogen metabolism • In later hours of fasting—defects in gluconeogenesis, FAO disorders
Relation of specific feeds	• Protein (leucine) exposure—hyperinsulinism • Fruits—hereditary fructose intolerance • Milk—galactosemia
Antenatal history	• Gestational diabetes (infant of diabetic mother, HNF4α mutations) • Medications (tocolytics in mother) • Blood group (Rh incompatibility)
Perinatal history	• Prolonged labor in macrosomia • Birth asphyxia
Family history	• Consanguinity (autosomal recessive disorders) • Affected siblings • Neonatal/sudden deaths (hyperinsulinism, FAO disorders)
Associated symptoms	• Jaundice (hypopituitarism, galactosemia, other inborn errors of metabolism) • Features of sepsis/cardiac failure or other systemic disease • Recurrent vomiting (metabolic disease, adrenal insufficiency) • Abnormal odors (aminoacidopathies) • Genital ambiguity (congenital adrenal hyperplasia)
Drug history	Potential exposure to insulin/sulfonylurea

GSD, glycogen storage disorder; SGA, small for gestational age; FAO, fatty acid oxidation.

Diagnostic Algorithm

Evaluation of the hypoglycemic infant starts with an accurate blood glucose, obtained by laboratory analysis. Plasma blood glucose less than 50 mg/dL during infancy, and less than 60 mg/dL beyond infancy is consistent with the diagnosis, especially when associated with symptoms. At all ages, cases with persistent hypoglycemia must be referred urgently to centers having expertise in managing CHI. Prolonged fruitless attempts at making diagnosis can lead to irreversible brain damage. Diagnostic sampling at the time of hypoglycemia is most important; this critical sample taken before administering medication, of blood and urine (passed after the hypoglycemic episode) needs to be analyzed for tests mentioned in Table 4. In any sick neonate/child, a sample of blood should be taken and stored, so further tests can be decided depending on further clues and detecting the cause of the seizure/coma (e.g., hypoglycemia/hypocalcemia/hyponatremia/other). Alongside diagnosis, hypoglycemia has to be managed, especially if neuroglucopenic symptoms (like seizures) are present. High IV glucose requirement (>8 mg/kg/min) is a strong pointer in favor of CHI. Criteria for diagnosis of hyperinsulinism are mentioned in Box 4.

Growth hormone levels greater than 20 ng/mL in neonates (>10 ng/mL in children) and cortisol greater than 20 µg/dL in the critical sample rule out GH and cortisol deficiency, respectively. Lower values in the hypoglycemic sample need confirmation by definitive testing unless hypopituitarism/adrenal insufficiency is obvious clinically. High insulin with low C-peptide indicates exogenous insulin administration.

A commonly used algorithm (Algorithm 1) for diagnosis of persistent hypoglycemia is given below.

TABLE 3: Clues to diagnosis of persistent hypoglycemia on physical examination

Clinical feature	Possible diagnosis
Short stature	GSDs, hypopituitarism
Macrosomia	Infant of diabetic mother, hyperinsulinism
Hepatomegaly	GSDs, FAO disorders*, galactosemia, other metabolic diseases
Midline defects (midline cleft lip, single central incisor), micropenis, nystagmus	Hypopituitarism
Hyperpigmentation	Adrenal insufficiency
Hyperventilation	Metabolic acidosis (inborn errors of metabolism)
Gallop rhythm	Cardiomyopathy in FAO disorders
Dysmorphism	Beckwith-Wiedemann and other syndromes

*Hepatomegaly may be present only in decompensated stage
GSD, glycogen storage disorder; FAO, fatty acid oxidation.

TABLE 4: Tests to be done on critical sample collected during hypoglycemia

Blood	Urine
• Glucose (fluoride vial) • Insulin • Cortisol • Growth hormone • β-hydroxybutyrate • Plasma acylcarnitine profile • Ammonia (heparinized sample on ice) • Lactate (fluoride vial)	• Ketones • Urinary organic acids • Urine acylglycines

A serum and urine sample is preserved for subsequent analysis.

Box 4: Criteria for diagnosis of hyperinsulinism

Glucose infusion rate >8 mg/kg/min laboratory plasma blood glucose <50 mg/dL with

- Detectable insulin concentration (>2 mIU/L)*
- Suppressed/low ketones (serum/urine)
- Suppressed/low serum fatty acids†
- Supportive criteria (when diagnosis is in doubt)
- Positive glycemic response to IM/IV glucagon
- Positive glycemic response to SC/IV octreotide
- Low IGFBP-1

*Depends on sensitivity of the assay used.

†Not commonly available at many centers in India.

IGFBP-1, insulin-like growth factor binding protein-1; IM, intramuscular; IV, intravenous; SC, subcutaneous.

A fasting challenge may be occasionally required for diagnosis, but should be done only at experienced centers under careful supervision of pediatric endocrinologists. It may be particularly risky for infants with fatty acid oxidation disorders.

MANAGEMENT

Acute symptomatic hypoglycemia should be treated with a 2 mL/kg IV 10% dextrose bolus, followed by continuous infusion of 10% dextrose at the rate of 6–8 mg/kg/min. Frequent monitoring of capillary glucose is required initially to judge the required concentration to maintain blood glucose greater than 60 mg/dL. Real-time continuous glucose monitoring can be a useful tool. Efforts to start and maintain enteral feeds can then be done, and if successful, IV glucose tapered gradually. Breastfeeding should be encouraged, as it favors ketogenesis. Frequent feeding, including at night, is important, and may require tube feeding. Raw cornstarch (1–2 g/kg/day) can be added to feeds for children older than 1 year of age. It can be given at bedtime to prevent morning hypoglycemia. Glucose polymers (polyjoule, maxijoule, etc.) can be useful for infants as a source of complex carbohydrates, but are not easily available in India. Higher concentrations should be avoided as they increase the risk of necrotizing enterocolitis.

Inability to start or maintain enteral feeds/persistent hypoglycemia is managed with increasing the concentration of IV glucose. Glucose infusion rates greater than 8 mg/kg/min should prompt consultation with a pediatric endocrinologist to rule out CHI (such infants often require rates >10–15 mg/kg/min). Glucose boluses reflexly stimulate insulin secretion and should be avoided after the initial bolus. A patent IV access must always be ensured and higher concentrations of glucose (>10–12%) given through central vascular access.

Specific Treatment for Congenital Hyperinsulinism

After documenting high glucose requirement, a trial of diazoxide is given for infants with proven or suspected CHI, usually started at 7–10 mg/kg/day in three divided doses orally, and increased up to 20 mg/kg/day. A trial of at least 5–7 days is needed before labeling a patient diazoxide unresponsive. Common side effects include fluid retention, tachycardia, and hypertrichosis (reversible on stopping). Diazoxide is not freely available and costs up to Rs 50–60 per tablet. Diazoxide unresponsive hypoglycemia can be medically managed with injection octreotide or glucagon. Nifedipine and chlorothiazide may help as add-on oral agents but should not be used alone (Table 5).

Diazoxide unresponsive patients need mutation analysis and 18F-fluorodihydroxyphenylalanine positron emission tomography/positron emission tomography-computed tomography (^{18}F DOPA PET/PET-CT) to differentiate focal and diffuse forms of disease. Selective pancreatectomy can be curative in cases with the focal form. The diffuse form can be managed with long-term octreotide if response to treatment is present and resources permit. Use of long acting octreotide preparations and sirolimus has been recently described in some cases. Other cases are managed with near-total pancreatectomy which is associated with development of diabetes mellitus in the postoperative period.

Specific Treatment of Other Causes of Persistent Hypoglycemia

General principles of management of persistent hypoglycemia are described in box 5.

Growth hormone/cortisol deficiencies are treated with specific hormone replacement. Galactosemia and fructose intolerance require avoidance of milk or lactose-containing substances/fruits, honey, and sucrose-containing foods, respectively. Frequent feeds, nocturnal cornstarch, and avoidance of fasting are the treatment for many of the metabolic diseases. Carnitine supplementation can be useful in some fatty acid oxidation (FAO) disorders.

PROGNOSIS

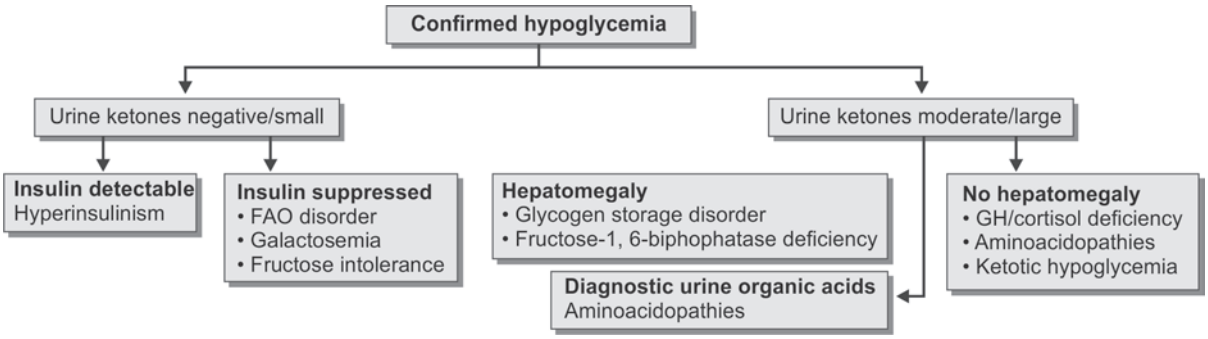
Persistent hypoglycemia and hyperinsulinism are a major risk for neurologic damage, resulting in sequelae like psychomotor retardation and epilepsy. All children should have periodic neurodevelopmental evaluation. Early referral to experienced centers, aggressive treatment of hypoglycemia, and timely decision of surgery in diazoxide unresponsive cases can help prevent brain damage in hyperinsulinism. Surgical treatment for diffuse hyperinsulinism results in diabetes mellitus.

Box 5: Principles of management of persistent hypoglycemia

- Early recognition and aggressive treatment of hypoglycemia
- Frequent/continuous glucose monitoring
- Early referral to pediatric endocrinologist
- Intravenous glucose treatment through patent central/peripheral line
- Regular enteral feeds, addition of glucose polymer/cornstarch if necessary.
- Specific treatment of underlying cause

ALGORITHM 1

Diagnostic algorithm for persistent hypoglycemia



FAO, fatty acid oxidation; GH, growth hormone.

TABLE 5: Medications used in management of hyperinsulinism

Medication	Route	Dose	Mechanism	Side effects
Diazoxide	Oral	5–20 mg/kg/day 3 doses/day	ATP sensitive K^+ channel agonist	Fluid retention Hypertrichosis
Chlorothiazide (used with diazoxide)	Oral	7–10 mg/kg/day 2 doses/day	ATP sensitive K^+ channel agonist	Hyponatremia Hypokalemia
Nifedipine	Oral	0.25–0.5 mg/kg/day	Calcium channel blockade	Hypotension (uncommon)
Glucagon	SC/IV infusion	1–20 µg/kg/h	Gluconeogenesis and glycogenolysis	Vomiting, rebound hypoglycemia
Octreotide	SC/IV infusion or 6–8 hourly divided	5–25 µg/kg/day	Multiple actions	GI side effects, cholelithiasis

GI, gastrointestinal; SC,subcutaneous; IV, intravenous.

KEY POINTS

- ☞ Persistent hypoglycemia, especially in the newborn/infant, can permanently damage the developing brain
- ☞ Early diagnosis and aggressive management is important to prevent brain damage
- ☞ Neonatal hypoglycemia is usually defined as <47 to <50 mg/dL beyond the first 2–3 hours of life. Low values obtained on capillary testing should be confirmed by laboratory assessment
- ☞ A critical sample of blood and urine must be collected in any sick baby before starting medication
- ☞ Congenital hyperinsulinism (CHI) is the most common cause of persistent nonketotic hypoglycemia in neonates and infants. Genetic analysis must be done to look for mutations
- ☞ In CHI due to focal nesidioblastosis, selective pancreatectomy is curative
- ☞ Diazoxide and other drugs may give long-term control of hypoglycemia. In diazoxide unresponsive babies, total pancreatectomy may be needed, and results in diabetes
- ☞ Hormone deficiencies (growth hormone and/or adreno-corticotropic hormone deficiency) and inborn errors of metabolism need specific treatment.

SUGGESTED READINGS

1. Committee on Fetus and Newborn. Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127:575-9.
2. Hay WW, Raju TN, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. J Pediatr. 2009;155:612-7.
3. Kapoor RR, Flanagan SE, James C, Shield J, Ellard S, Hussain K. Hyperinsulinaemic hypoglycaemia. Arch Dis Child. 2009;94:450-7.
4. Desai MP, Khatri JV. Persistent hyperinsulinemic hypoglycaemia of infancy. Indian Pediatr. 1998;35:317-28.
5. Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fékété C, De Lonlay-Debeney P, et al. Practical management of hyperinsulinism in infancy. Arch Dis Child Fetal Neonatal Ed. 2000;82:F98-F107.
6. Wolfsdorf JI, Weinstein DA. Hypoglycemia in children. In: Lifshitz F (Ed). Pediatric Endocrinology (Volume 1), 5th edition. USA: Informa Healthcare; 2007.
7. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, Levitsky LL, Murad MH, Rozance PJ, Simmons RA, Sperling MA, Weinstein DA, White NH, Wolfsdorf JI; Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015;167:238-45.
8. Stanley CA. Perspective on the Genetics and Diagnosis of Congenital Hyperinsulinism Disorders. J Clin Endocrinol Metab. 2016;101:815-26.
9. Vora S, Chandran S, Rajadurai VS, Hussain K. HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/26713990" Hyperinsulinemic Hypoglycemia in Infancy: Current Concepts in Diagnosis and Management. Indian Pediatr. 2015;52:1051-9.

CHAPTER 112

Approach to a Child with Disorder of Sex Development

Vijaya Sarathi

INTRODUCTION

Disorders of sex development (DSDs) are defined as congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical. A 2006 Consensus Conference suggested that the potentially pejorative terms "pseudohermaphroditism" and "intersex" be replaced by the diagnostic category "disorders of sex development". The most common presentation of DSDs is with abnormalities of the external genitalia (ambiguous genitalia), usually detected at birth. Abnormalities of external genitalia sufficient to prompt evaluation (Box 1) occur in approximately 1 in 4,500 live births. Early evaluation of a child with ambiguous genitalia is of utmost importance due to the association with life-threatening disorders like congenital adrenal hyperplasia (CAH) and early assignment of appropriate sex. Some DSDs are not characterized by genital ambiguity (Turner syndrome, Klinefelter syndrome). Some others will have apparently normal genitalia at birth, and get diagnosed at an older age. Presentation in older individuals may include genital ambiguity unrecognized at birth, inguinal hernia, delayed/incomplete puberty, primary amenorrhea, virilisation in an apparent female, breast development or gross hematuria in an apparent male.

Box 1: Problems in newborns that merit evaluation for disorders of sex development

- Ambiguous genitalia
- Apparent female genitalia with
  - Enlarged clitoris
  - Posterior labial fusion
  - Inguinal/labial mass
- Apparent male genitalia with
  - Nonpalpable testes
  - Isolated perineoscrotal hypospadias
  - Severe hypospadias, undescended testi(e)s, micropenis
- Family history of DSD, such as complete AIS
- Discordance between genital appearance and prenatal karyotype

DSD, disorder of sex development; AIS, androgen insensitivity syndrome.

Clinical Pearl

- Isolated penile hypospadias or isolated micropenis does not merit evaluation for disorders of sex development.

CAUSES AND CLASSIFICATION

Ambiguous genitalia usually results due to virilization of a female fetus (XX DSD), undervirilization of a male fetus (XY DSD), or mixed sex chromosome disorders. An example of classification of DSDs is shown in table 1.

Virilization of a female fetus occurs due to androgen exposure during some critical periods of development. Fetal androgen exposure between 8 weeks and 12 weeks of fetal life leads to urogenital sinus (single opening at introitus) and labioscrotal fusion. Androgen exposure after 12 weeks of gestation will lead to isolated clitoromegaly. Significant undervirilization of a male fetus occurs due to low or absent fetal androgen exposure during the critical developmental period. Low or absent androgen after this critical developmental period will cause isolated micropenis.

EVALUATION OF A CHILD WITH AMBIGUOUS GENITALIA

Evaluation of an infant or a child with ambiguous genitalia is challenging. Most virilized 46XX infants have CAH; however, only 50% of undervirilized 46XY patients receive a definitive diagnosis.

History

A detailed history and thorough physical examination have a pivotal role in the evaluation of a child with ambiguous genitalia. History should include family history of DSDs,

TABLE 1: An example of classification of disorder of sex development

Sex chromosome DSD	46, XY DSD	46, XX DSD
• 45,X (Turner syndrome and variants) • 47,XXY (Klinefelter syndrome and variants) • 45,XO/46,XY (Mixed gonadal dysgenesis) • 46,XX/46,XY (Chimeric ovotesticular DSD)	• Disorders of gonadal development ○ Gonadal dysgenesis ○ Ovotesticular DSD • Disorders of androgen synthesis or action: ○ Androgen biosynthesis defect (e.g., 17α hydroxylase deficiency, 3β hydroxysteroid dehydrogenase deficiency, 5αRD2 deficiency and star mutations) ○ Defect in androgen action (e.g., CAIS, PAIS) ○ Luteinizing hormone receptor defects (e.g., Leydig cell hypoplasia, aplasia) • Disorders of anti-Mullerian hormone and anti-Mullerian hormone receptors (persistent Mullerian duct syndrome)	• Disorders of gonadal (ovarian) development ○ Ovotesticular DSD ○ Testicular DSD (e.g. SRY, duplicate SOX9) ○ Gonadal dysgenesis • Androgen excess ○ Fetal (e.g., 21-hydroxylase deficiency, 11-hydroxylase deficiency) ○ Fetoplacental (aromatase deficiency, P450 oxidoreductase deficiency); and ○ Maternal (luteoma, exogenous, etc.) • Others ○ Cloacal exstrophy ○ Vaginal atresia ○ MURCS (Mullerian, renal, cervico-thoracic somite abnormalities) ○ Other syndromes

DSD, disorder of sex development; CAIS, complete androgen insensitivity syndrome; PAIS, partial androgen insensitivity syndrome; StAR, steroidogenic acute regulatory protein; 5αRD2, 5-alpha-reductase type 2.

TABLE 2: Clinical pointers towards etiology of disorder of sex development

Maternal virilization during pregnancy	Placental aromatase deficiency, luteoma of pregnancy, maternal androgen secreting tumors, maternal androgen intake
Early sibling death	CAH with salt wasting
Failure to thrive, hypotension, hyperkalemia	CAH with salt wasting, SF-1 mutation
Hypertension, hypokalemia	11β-hydroxylase deficiency, 17α-hydroxylase deficiency
Hyperpigmentation	CAH, SF-1 mutation
Peripheral precocity	21-hydroxylase deficiency, 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency, gonadal dysgenesis with gonadoblastoma
Inguinal hernia in a baby girl	Complete androgen insensitivity, testosterone synthetic defects, Leydig cell aplasia
Bilateral well palpable gonads with ambiguous genitalia	Androgen insensitivity syndrome, 5α-reductase deficiency, testosterone synthetic defects, Leydig cell hypoplasia
Asymmetric genitalia	Mixed gonadal dysgenesis, ovotesticular DSD
Apparent male external genitalia with no palpable gonads	Severely virilized CAH female, hypogonadotrophic hypogonadism, testicular regression syndrome
Cyclical hematuria	Ovotesticular DSD
Virilization at puberty	Partial androgen insensitivity syndrome, 5α-reductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency, partial gonadal dysgenesis
Gynecomastia	Partial androgen insensitivity syndrome, partial gonadal dysgenesis, 17β-hydroxysteroid dehydrogenase deficiency
Progressive postnatal virilization	CAH, aromatase deficiency (at puberty)
Primary amenorrhea, severe oligohypomenorrhea	Complete androgen insensitivity, pure gonadal dysgenesis, 17α-hydroxylase deficiency, aromatase deficiency

CAH, congenital adrenal hyperplasia; DSD, disorder of sex development.

previous perinatal or neonatal deaths in siblings or other family members, consanguinity, maternal drug (androgen, alcohol or progesterone) intake during pregnancy, and maternal history of virilization during pregnancy. In an infant, history of vomiting, dehydration, inadequate weight gain, and dark pigmentation of oral mucosa and/or genital mucosa should be asked for. In a newborn boy with marked pigmentation of the scrotum, CAH should be ruled out. In an older child, history should also focus on postnatal progression of virilization (increasing clitoral size, premature pubarche, or precocious puberty), pubertal events (virilization of an apparent girl at puberty, gynecomastia, delayed or absent puberty), gross or cyclical hematuria in a boy, and response to hormonal therapy, especially to testosterone in boys. Certain key pointers in history and physical examination provide useful clues towards the etiological diagnosis and are listed in table 2.

Physical Examination

Physical examination should include measurement of blood pressure with appropriate sized cuff, an accurate and objective assessment of genitalia, and evaluation for any dysmorphic features. While 21-hydroxylase deficiency is characterized by hypotension with dyselectrolytemia and hypoglycemia due to adrenal insufficiency, presence of hypertension raises the possibility of 11β-hydroxylase deficiency.

Dysmorphic Features

A thorough evaluation should be done in all children with ambiguous genitalia, so that if it is part of a syndrome, the diagnosis can be made.

Clinical Pearl

- All infants with ambiguous genitalia and nonpalpable gonads should be considered to have congenital adrenal hyperplasia and closely monitored until proven otherwise.

Gonads

The scrotum, labia majora, and inguinal area should be carefully palpated to identify the presence, position, size, and consistency of the gonads. Palpable gonads in the scrotum or inguinal canal are almost always testes or rarely ovotestes; hence, suggest 46XY DSD or ovotesticular DSD. Pigmentation and rugae of the labioscrotal folds and presence of epididymis should also be evaluated. Non-palpable gonads suggest either XX DSD (most likely CAH) or XY DSD with gonadal dysgenesis or cryptorchidism.

Phallic Length

Penile/clitoral length is measured from the pubic ramus to the tip of the glans (excluding any excess foreskin) after stretching the penis to the point of increased resistance. The ruler should be pressed down against the ramus to completely depress the suprapubic fat pad. Normal values for stretched penile length and clitoris are available and vary among different ethnic populations. In general, a penile length of less than 2.5 cm suggests micropenis whereas a clitoral length of greater than or equal to 1 cm suggests clitoromegaly in term infants.

Clinical Pearl

- Normal preterm female infants may appear to have clitoromegaly since they have larger clitoral breadth compared to body size.

Anogenital Ratio

In apparently female external genitalia, mild degree of virilization in the form of posterior labial fusion can be evaluated with measurement of anogenital ratio. This is the ratio of the distance from the anus to the posterior fourchette, and the distance from the anus to the base of the clitoris. A ratio of greater than 0.5 suggests virilization with some posterior labial fusion.

Urethral Opening

It may be present anywhere from the tip of the phallus to the perineum and should be assessed by careful examination of the ventral aspect of the phallus for grooves. A single opening at the base of the phallus may be either an incompletely fused penile urethra (hypospadias) or a virilized urogenital sinus (e.g., internal connection between the vagina and urethra). Accordingly, these findings must be confirmed either by cystoscopy/vaginoscopy or radiographically, because the physical examination can be misleading.

Prader Stages

Degree of genital ambiguity does not differentiate between 46XX DSD and 46XY DSD. It merely provides information about the extent of abnormality once the karyotype is known. Prader staging is commonly used to describe the degree of virilization in 46 XX DSDs. Different Prader stages are depicted in figure 1. Stage 1 is otherwise normal looking female genitalia with isolated phallic enlargement, stage 2 is further phallic enlargement and posterior labial fusion without urogenital sinus, stage 3 is significant phallic enlargement with almost complete fusion of labioscrotal folds and urogenital sinus with single perineal opening, stage 4 is phallus with penile appearance with complete labioscrotal fusion and urogenital sinus opening at the base or ventral surface of the phallus, and stage 5 is phallus with the appearance of well-developed penis with completely fused labioscrotal folds and urogenital sinus opening at the body or glans of the phallus.

Laboratory Evaluation

First line laboratory testing, especially in newborns, includes karyotyping with SRY detection (even when prenatal karyotype is available), imaging (abdomino-pelvic ultrasound), and measurement of 17-hydroxyprogesterone, testosterone, gonadotropins, anti-Mullerian hormone, and electrolytes. The results of these investigations are generally available within 48 hours and will be sufficient for making a working diagnosis. To minimize psychological distress during evaluation, the patient/family should be informed exactly what will be done and why. Congenital adrenal hyperplasia is always a possibility in an infant with ambiguous genitalia. Hence, throughout the evaluation period, careful monitoring of the infant for weight, vitals, and blood chemistry (blood glucose, sodium and potassium) should be carried out to start early treatment if the findings suggest CAH.

Karyotype

Karyotype is performed, usually using peripheral leukocytes. Because of the possibility of mosaicism, it is suggested that at

Fig. 1: Prader's staging to describe the degree of virilization in female infant

least 200 cells should be examined. The results of the karyotype permit classification of the infant into one of three diagnostic categories (XX DSD, XY DSD, and mixed sex chromosome DSD) that guide further evaluation.

Fluorescence *In Situ* Hybridization

Fluorescence *in situ* hybridization using Y specific (SRY) and X specific probes will provide results within hours compared to conventional karyotype which takes days to provide results.

Adrenal Steroids

Measurement of 17-hydroxyprogesterone should be done promptly in all infants presenting with genital ambiguity or marked genital pigmentation, to exclude CAH due to 21-hydroxylase deficiency. It should be measured on or after day 3–4 of life since maternal steroid may result in spuriously high values if determined during day 1–2. Levels of 17-hydroxyprogesterone (17-OHP) should be interpreted using gestational age matched reference ranges to avoid spurious diagnosis of CAH. It should also be noted that stress responses like sepsis may falsely elevate 17-OHP levels. Other tests for adrenal evaluation include serum cortisol, plasma adrenocorticotrophic hormone, plasma renin activity, 17-hydroxypregnenolone, 11-desoxycortisol, and dehydroepiandrosterone.

Clinical Pearls

- Measurement of 17-hydroxyprogesterone (17-OHP) should be avoided during first 2 days of life
- Levels of 17-OHP may be falsely elevated in infants with sepsis and prematurity and should be interpreted with caution.

Gonadal Steroids

Gonadal steroid assessment during the prepubertal period requires a human chorionic gonadotropin (hCG) stimulation test. However, in infants between 1 month and 6 months, transient activation of hypothalamic-pituitary-adrenal axis may provide an opportunity for gonadal steroid assessment without hCG stimulation.

Human Chorionic Gonadotropin Stimulation Test

There are many protocols for hCG stimulation test. The most widely used one is the short hCG stimulation test. Human chorionic gonadotropin (500–1,500 IU/day) is administered intramuscularly on 3 consecutive days; 24 hours after the last dose, blood sample is collected and analyzed for testosterone, dihydrotestosterone, and androstenedione.

Normal or high testosterone levels suggest androgen insensitivity or 5α-reductase deficiency. An elevated testosterone to dihydrotestosterone ratio (T/DHT) suggests 5α-reductase deficiency. However, a recent study has suggested that the use of T/DHT ratio has poor sensitivity for the diagnosis of 5α-reductase deficiency. Hence, molecular studies are essential for appropriate diagnosis of these conditions. Low testosterone values suggest gonadal dysgenesis, Leydig cell hypoplasia, or testosterone biosynthetic defect. The most common testosterone biosynthetic defect, 17β-hydroxysteroid dehydrogenase (17β-HSD) deficiency, is diagnosed by decreased testosterone to androstenedione ratio.

Imaging

Ultrasonography of the abdomen and pelvis by an ultrasonologist experienced in neonatal work is important to determine the presence of gonads, a uterus, and/or a vagina. Retrograde urethrogram may be necessary, although most surgeons find direct visualization by cystoscopy/vaginoscopy under general anesthesia to be the single best method of assessing the urethral and vaginal anatomy. In some complicated cases (particularly those infants with elements of male and female gonads/internal reproductive structures), laparoscopic visualization may ultimately be required to completely delineate reproductive anatomy and this allows for simultaneous gonadal biopsy for histologic/genetic evaluation.

Urinary steroid profile by gas chromatography/mass spectrometry is useful when rarer forms of CAH are suspected. Specific genetic analyses may be helpful in reaching the exact diagnosis.

Given the spectrum of findings and diagnoses, no specific single evaluation protocol can be used. Evaluation of each case must be individualized. In this chapter, author provides a practical decision-making algorithm based on karyotype of the child (Algorithm 1). A simplified practical algorithm to approach a child with apparently male genitalia and undescended testes is depicted in algorithm 2. A detailed algorithmic approach to a child with XX DSD and XY DSD are depicted in algorithm 3 and algorithm 4 respectively.

MANAGEMENT

The primary aim in managing an infant with DSD should be to achieve a diagnosis, sex assignment, and management plan as quickly as possible. This requires involvement of an experienced multidisciplinary team. Ideally, the team includes pediatric endocrinologist, pediatric surgeon, child psychologist/psychiatrist, gynecologist, geneticist, neonatologist, medical social worker, and medical ethics specialist.

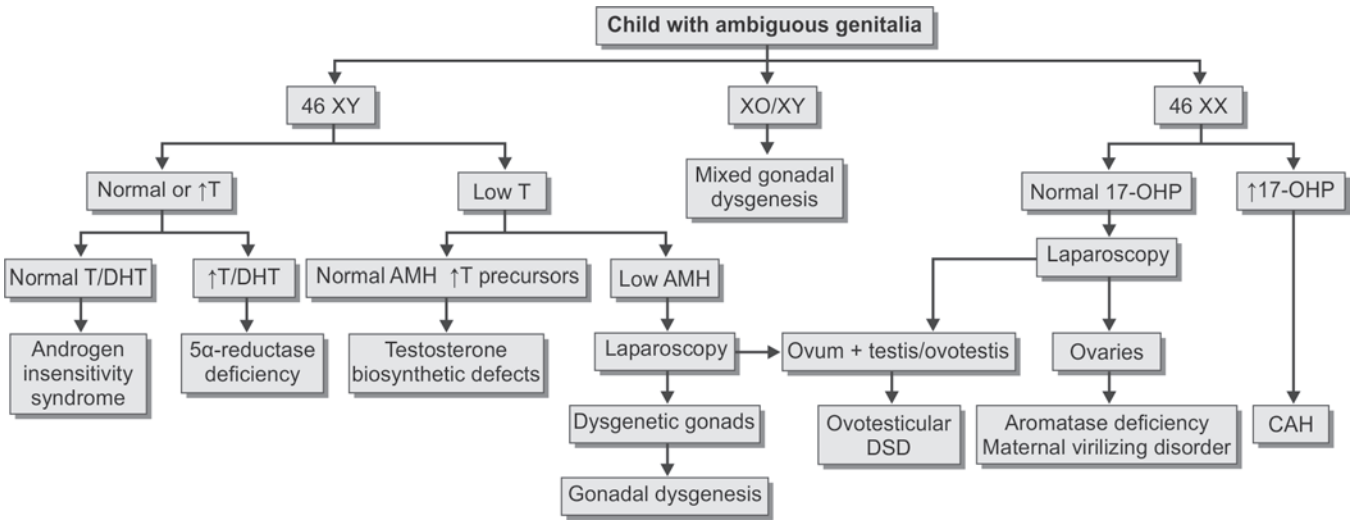
Newborn Gender Assignment

Infants with 46XY complete androgen insensitivity syndrome (CAIS) and 46XX CAH should be reared as females, whereas for those with 5α-reductase deficiency or 17β-HSD3 deficiency, a male assignment should be strongly considered. In other cases, factors that influence gender assignment include diagnosis, genital appearance, surgical options, need for lifelong replacement therapy, potential for fertility, views of the family, and, sometimes, circumstances relating to cultural practices.

Feminizing genital surgery involves external genitalia reconstruction and vaginal exteriorization, with early separation of the vagina and urethra. Clitoral reduction is considered with severe virilization (Prader III–V) and preferably, performed in conjunction with common urogenital sinus repair. Procedures

ALGORITHM 1

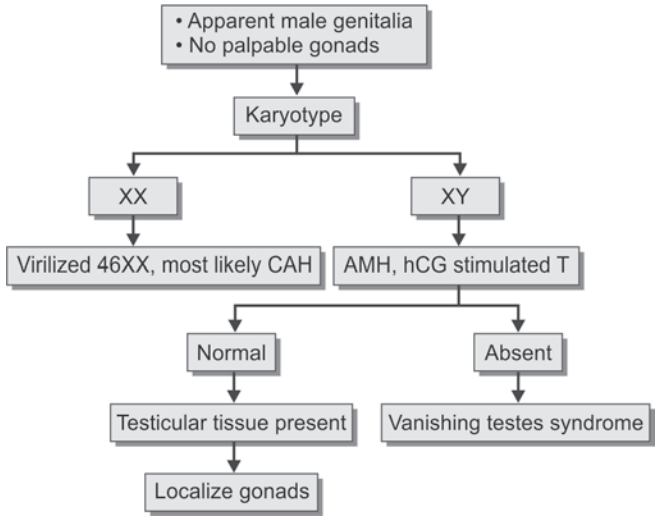
A simplified practical algorithmic approach to a child with ambiguous genitalia



17-OHP, 17-hydroxyprogesterone; AMH, anti-Mullerian hormone; CAH, congenital adrenal hyperplasia; DHT, dihydrotestosterone; DSD, disorder of sex development; T, testosterone.

ALGORITHM 2

Algorithm to approach a child with apparently male genitalia and undescended testes



AMH, anti-Mullerian hormone; CAH, congenital adrenal hyperplasia; hCG, human chorionic gonadotropin; T, testosterone.

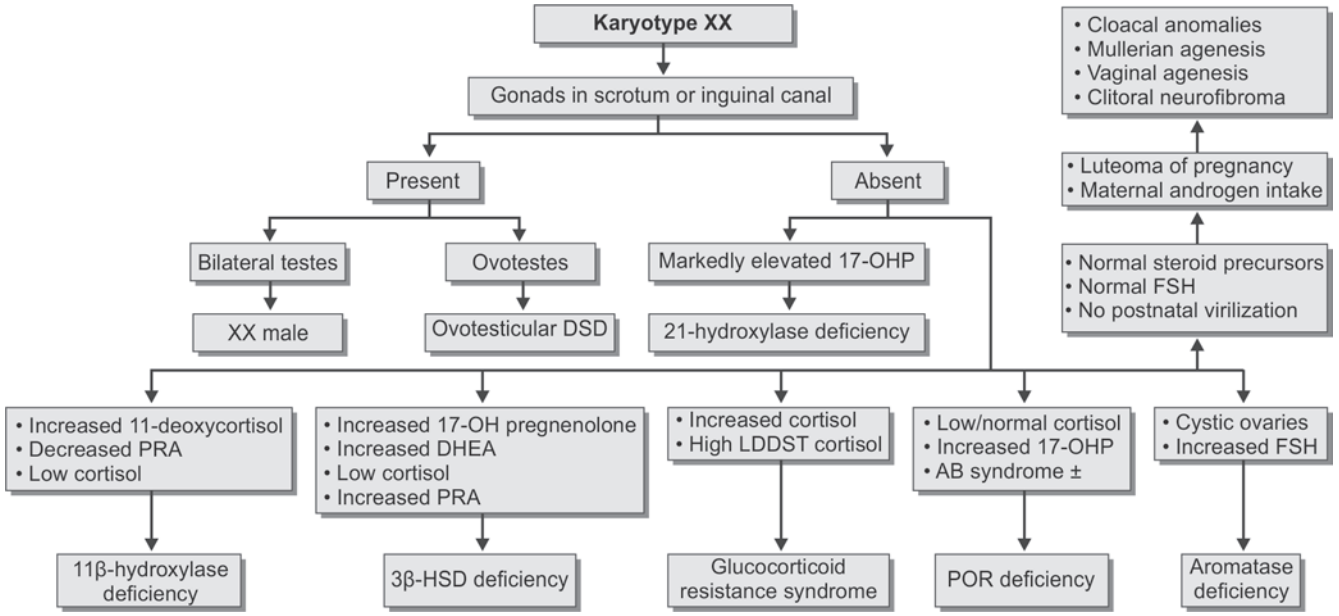
should emphasize functional cosmetic appearance and be designed to preserve erectile function and enervation. Vaginoplasty should be performed in the teenage years. Masculinizing genital surgery involves more surgical procedures and urologic difficulties than feminizing genitoplasty. Standard surgical repair involving hypospadias includes chordee correction, urethral reconstruction, and judicious testosterone supplementation. If needed, adult-sized testicular prostheses should be inserted after sufficient pubertal scrotal development. For XY DSD individuals (except for CAIS) who have been assigned female gender, gonadectomy should be performed before puberty. Patients with GBY-positive gonadal dysgenesis and partial androgen insensitivity syndrome (PAIS) with intra-abdominal testis, and Turner syndrome with Y chromosome have high risk of germ cell malignancy and should undergo gonadectomy before puberty.

Hypogonadism is common in patients with dysgenetic gonads, defects in sex-steroid biosynthesis, and resistance to androgens. Intramuscular depot injections of testosterone esters are commonly used in males. Other options include oral testosterone undecanoate, and transdermal preparations. Patients with PAIS may require supraphysiologic doses of testosterone for optimal effect. Females with hypogonadism require estrogen supplementation to induce pubertal changes and menses. For women with a uterus, a progestin is usually added after breakthrough bleeding develops or within 1–2 years of continuous estrogen.

Amongst all causes of DSD, CAH is the most important condition that needs to be promptly diagnosed and treated. Most commonly it manifests with a salt wasting crisis during the 2nd week of life and if untreated may cause death. During infancy, initial reduction of markedly elevated adrenal sex hormones may require hydrocortisone up to 25 mg/m^2 per day, but typical dosing is 10–15 mg/m^2 per day divided three times daily. Mineralocorticoid should be replaced in the form of fludrocortisone (100–200 μg/day). Sodium chloride supplements are often needed in infancy (1–3 g/day) distributed in several feedings. During period of sickness or surgery, stress doses of hydrocortisone should be supplemented.

ALGORITHM 3

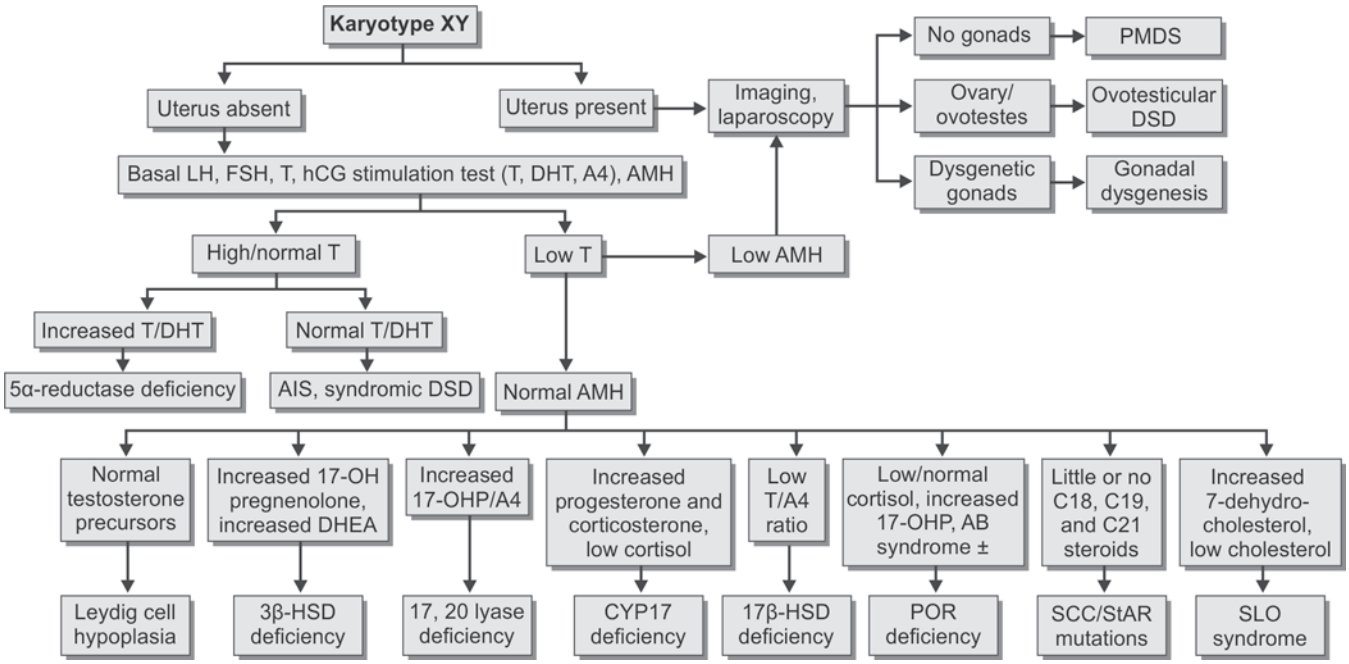
Approach to a child with XX disorder of sex development



DSD, disorder of sex development; 17-OHP, 17-hydroxyprogesterone; FSH, follicle-stimulating hormone; PRA, plasma renin activity; DHEA, dehydroepiandrosterone; 3β-HSD, 3β-hydroxysteroid dehydrogenase; LDDST, low-dose dexamethasone suppression test; AB, Antley-Bixler; POR, P450 oxidoreductase.

ALGORITHM 4

Approach to a child with XY disorder of sex development



LH, luteinizing hormone; FSH, follicle-stimulating hormone; T, testosterone; hCG, human chorionic gonadotropin; DHT, dihydrotestosterone; AMH, anti-Mullerian hormone; PMDS, persistent Mullerian duct syndrome; DSD, disorder of sex development; DHEA, dehydroepiandrosterone; 17-OHP, 17-hydroxyprogesterone; HSD, hydroxysteroid dehydrogenase; SCC, side-chain cleavage enzyme; SLO syndrome, Smith-Lemli-Opitz syndrome; A4, androstenedione; AIS, androgen insensitivity syndrome; POR, P450 oxidoreductase; StAR, steroidogenic acute regulatory protein.

KEY POINTS

- ☞ The most common presentation of disorders of sex development (DSD) is with abnormalities of the external genitalia (ambiguous genitalia), usually detected at birth (1 in 4500 live births)
- ☞ Most virilized 46XX infants have congenital adrenal hyperplasia (CAH) which may lead to death if untreated
- ☞ Only 50% of undervirilized 46XY patients receive a definitive diagnosis. The common diagnoses include androgen insensitivity syndrome, 5α-reductase deficiency, gonadal dysgenesis, and testosterone biosynthetic defects
- ☞ Degree of genital ambiguity (Prader staging) does not differentiate between 46XX DSD and 46XY DSD. It merely provides information about the extent of abnormality once the karyotype is known
- ☞ First line investigations of an infant with ambiguous genitalia should include karyotyping with SRY detection, pelvic ultrasound, and measurement of 17-hydroxyprogesterone (day 3 onwards)
- ☞ All infants with suspected CAH should be closely monitored for weight, serum electrolytes, and blood glucose
- ☞ Management of an infant with ambiguous genitalia requires involvement of an experienced multidisciplinary team. Ideally, the team includes pediatric endocrinologist, pediatric surgeon/urologist, child psychologist/psychiatrist, gynecologist, geneticist, neonatologist, medical social worker, and medical ethics specialist
- ☞ Infants with 46XY complete androgen insensitivity syndrome and 46XX CAH should be reared as females, whereas for those with 5α-reductase deficiency or 17β-HSD3 deficiency, a male assignment should be strongly considered
- ☞ Patients with GBY-positive gonadal dysgenesis and partial androgen insensitivity syndrome with intra-abdominal testis, Turner with Y chromosome have high risk of germ cell malignancy and should undergo gonadectomy before puberty.

SUGGESTED READINGS

1. Carillo AA, Damian M, Bercovitz G. Disorders of sexual differentiation. In: Lifshitz F editor. Pediatric Endocrinology. Vol 2. 5th ed. London: Informa Healthcare; 2007. pp. 365-413.
2. Houk CP, Hughes IA, Ahmed SF, Lee PA; Writing Committee for the International Intersex Consensus Conference Participants. Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. Pediatrics. 2006;118(2):753-7.
3. Lambert SM, Vilain EJ, Kolon TF. A practical approach to ambiguous genitalia in the newborn period. Urol Clin North Am. 2010;37(2):195-205.

CHAPTER 113

Approach to Thyroid Disorders in Children

Anju Virmani

INTRODUCTION

Thyroid disorders are common in childhood, and can cause significant morbidity. Symptoms may be confusing or misleading, but diagnosis and treatment are becoming easier with increasing availability of reliable hormone and other tests, and wide availability of inexpensive medication. Yet this increases the responsibility of the pediatrician to take timely and correct decisions. This chapter will discuss the approach to the following:

- Universal thyroid screening
- Hypothyroidism
- Hyperthyroidism.

CONGENITAL HYPOTHYROIDISM

Of the various thyroid disorders, congenital hypothyroidism (CH) is the most important as it needs early diagnosis based on lab screening and early treatment, if permanent brain damage is to be prevented. Congenital hypothyroidism is the most common cause of preventable mental retardation. Because 90% of affected newborns look normal, the cost-effectiveness of screening each and every newborn is undoubted. Worldwide incidence is reported as 1 in 3,000–4,000 newborns, but in India, it may be much higher. Several hospitals now screen all newborns, and some states have also begun programs for universal screening.

Clinical Pearl

- All newborns must get thyroid function tested, not just those whose mothers have thyroid disorders. If not done at birth, it should be done whenever the baby is first seen (e.g., for vaccination).

International recommendations for mass newborn screening advise taking a heel prick sample on special filter papers on day 3–5 of age (or at time of discharge). This timing is meant to reduce the impact of the neonatal thyroid-stimulating hormone (TSH) surge, and allow for screening of other disorders like phenylketonuria which cannot be done in cord blood. If only CH screening is planned, to avoid problems due to early discharge of mothers, cord blood can be collected, as was done in early studies in the 1970s. This has several logistic advantages: it is easily done in 100% deliveries, no needle prick is needed, the report is available by the time the baby is discharged, hence in those newborns in whom confirmation by repeat testing and start of replacement is required, it is easily done well in time.

The primary TSH method is most widely used, with a sensitivity of 97.5% and specificity of 99%; the best method is combined TSH and thyroxine (T4) screening, which is somewhat more expensive (higher cost of testing, lesser cost of recall and confirmation). Most programs use a cutoff for TSH of greater than 20–25 mU/mL. The American Academy of Pediatrics suggests a cutoff of greater than 40 mU/mL. Any level above this should be confirmed by an urgent repeat venous sample for T4 and TSH, so that replacement can be started within 1–2 weeks of life. Once the diagnosis is confirmed (usually TSH is >50 mU/mL), if it is conveniently possible, a Tc-99m thyroid scan should be done: this would help in diagnosing dysgenesis (agenesis, hypoplasia, and ectopia, i.e., lingual thyroid). Treatment should not be delayed just to obtain a scan.

Initial doses of thyroxine are 10–15 μg/kg, i.e., usually 25–50 μg given orally as a once-daily dose, to allow for rapid normalization of serum T4. Doses should be titrated on the basis of serum T4 (keep in the upper half of normal range) and TSH, done after 2 weeks of starting, then every 1–2 months for the first 6 months, then every 3–4 months till age 3 years. It must be remembered that up to age 3–4 months, normal TSH levels are up to 9 mU/mL.

Clinical Pearl

- Congenital hypothyroidism confirmation should be done urgently, so that thyroxine can be started as soon as possible. This should preferably begin by age 2 weeks, to ensure normal brain development.

If a cause of permanent CH is found, e.g., dysgenesis, parents are explained that treatment is needed lifelong. Otherwise, to confirm if CH is permanent or transient, thyroxine is discontinued at the age of 2.5–3 years for 4–5 weeks, and T4, TSH (and if necessary, thyroid scan) repeated. If the TSH rises, thyroxine replacement is reinstituted (monitored by T4 and TSH every 6–12 months), and the family explained that replacement would be needed lifelong.

Periodic training of staff and validation of correctness of sample collection and lab performance is essential, especially with filter paper samples.

HYPOTHYROIDISM IN THE OLDER CHILD

Symptoms and signs of hypothyroidism are variable and often subtle, so a high index of suspicion is needed. These may be slow height gain, unexplained weight gain, decreased academic performance, dullness, fatigue, lethargy and increased sleep, cold intolerance, constipation, puffy pale face, dry skin and hair, irregular and/ or heavy periods, bradycardia, hoarse voice, and thinning of sides of eyebrows. The most common causes are chronic lymphocytic thyroiditis and iodine deficiency; rarer causes include CH (diagnosed late), pituitary disorders, surgery, or radioiodine ablation. Children with Turner syndrome, Down syndrome, and autoimmune disorders like type 1 diabetes mellitus or celiac disease, are more prone to primary hypothyroidism, and should be screened periodically.

Diagnosis is relatively straightforward: serum levels of T4 and TSH. Sampling should preferably be done in the morning, as TSH levels decrease in the evening. Serum triiodothyronine (T3) rarely contributes to the diagnosis. Thyroid antibodies are expensive, and do not alter the management. In addition, they may be present in 5–10% of the normal population, and raised antibodies in themselves do not justify any medication. Increased TSH with low T4 is diagnostic of primary hypothyroidism. Low T4 with normal, low, or even mildly increased TSH is diagnostic of secondary/ tertiary hypothyroidism, which is much rarer. Secondary hypothyroidism should be thought of if there is any reason to suspect pituitary or hypothalamic disorders. Indian normative data for thyroid hormones is comparable with that elsewhere.

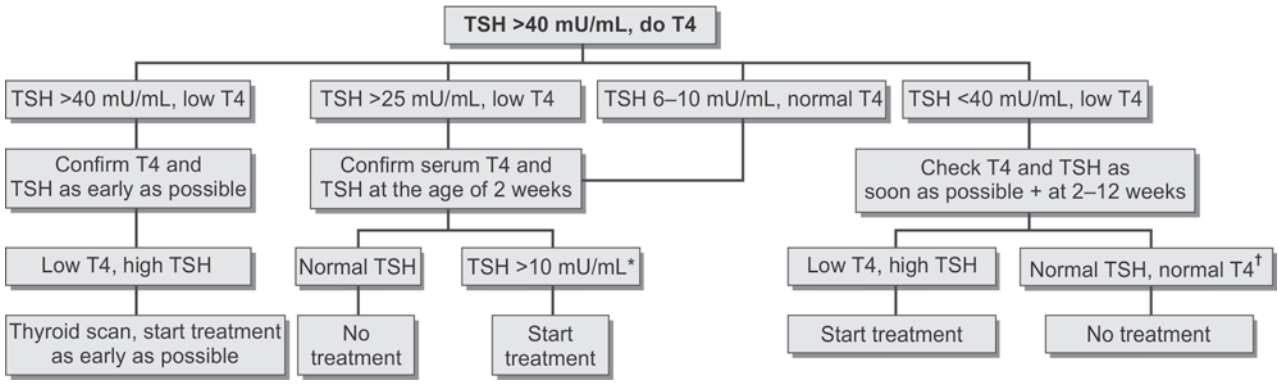
Clinical Pearl

- Hypothyroidism must be confirmed by lab testing. Treatment started on clinical suspicion alone is not justified.

Replacement is also quite straightforward: with oral thyroxine. Even if iodine deficiency is suspected or proven, iodine should not be given for treatment. Thyroxine is started as a once daily oral dose of 2–10 µg/kg. Higher doses are needed in young children; with age, the dose/kg reduces, such that the total daily dose is not very different across different ages. Iron, soya, and calcium can interfere with absorption of thyroxine, and should not be given within a few hours of medication. Doses are titrated on the basis of serum TSH (which takes 4–5 weeks to normalize) and T4. Thus, testing should be done after 6 weeks of a dose change, and every 3–6 months if no dose change is needed. Testing TSH too soon after a dose change can be misleading. Growth and puberty should be monitored, and should proceed normally if replacement is adequate. Once growth is complete, a trial of stopping thyroxine can be offered: thyroxine is stopped for 4–5 weeks and then TSH tested. If the TSH rises, thyroxine is reinstituted (monitored by T4 and TSH every 6–12 months), and the family explained that replacement would be needed lifelong.

ALGORITHM 1

Approach to thyroid function at birth



*Possibilities: delayed maturation, thyroid hormone resistance, Down syndrome.

†Possibilities: transient intrauterine exposure to drugs or maternal antibodies, iodine deficiency, pre- or postnatal exposure to iodides.

TSH, thyroid-stimulating hormone.

Clinical Pearl

- Thyroid stimulating hormone takes 4–6 weeks to change. Testing too soon after a dose change may be misleading.

Thyroid stimulating hormone levels of less than 10 mU/mL with normal T4 levels are considered compensated or biochemical hypothyroidism, and ordinarily may not merit replacement with thyroxine. Obese children often have mildly raised TSH, and should not be labeled hypothyroid unless they are short (cf. midparental height) or growing slowly. In most obese children, the cause is related to excess calories in diet and inadequate exercise: such children tend to be tall, which is not compatible with hypothyroidism. However, replacement may be considered if symptoms are significant or if growth velocity is subnormal. In a child with slow height gain, evaluation of growth hormone status should only be done after normalizing thyroid status. In this situation also, treatment of compensated hypothyroidism may be considered.

Clinical Pearl

- All obese children are not hypothyroid. Start treatment if the TSH is >10, and/or the T4 is low, and the child is short for age and midparental height, or growing slowly.

Box 1: Thyroid function in hypothyroidism

- High TSH, low T4
  - Primary hypothyroidism
- High TSH, high T4
  - Primary hypothyroidism with poor compliance with treatment
- Normal/borderline high/low TSH, low T4
  - Central (secondary/tertiary) hypothyroidism
- Borderline TSH, normal T4
  - Biochemical hypothyroidism

TSH, thyroid stimulating hormone.

Box 2: Treatment of hyperthyroidism

- Graves' disease
  - Medical: neomercazole + β-blockers (i.e., delete rarely)
  - Definitive treatment: lifelong thyroxine replacement needed
    - Radioiodine ablation: no anesthesia/scar. Not if nodular or large goiter; ophthalmopathy
    - Surgical: thyroidectomy—immediate relief, no worsening of ophthalmopathy. But, risk of hypoparathyroidism/injury to recurrent laryngeal nerve
- Thyroiditis
  - Symptomatic relief with β-blockers
- Thyroid nodule
  - Surgical excision

HYPERTHYROIDISM

Hyperthyroidism is uncommon in children, and symptoms and signs are even more variable and confusing, so a high index of suspicion is needed. These may be unexplained weight loss often in spite of increased appetite, decreased academic performance, irritability, palpitations, sweating, nervousness, fatigue, poor sleep, and heat intolerance. Goiter is almost always present. Signs include nervousness, fine tremors, warm sweaty palms, tachycardia, and exophthalmos. The most common causes are Graves' disease (GD), initial stages of thyroiditis, or an autonomous thyroid nodule. Serum T4 and T3 are high, and TSH is suppressed; antibodies may be positive. Rarely, T3 may be raised with normal T4 (T3 toxicosis). A thyroid scan is useful to distinguish GD, which shows increased uptake, from thyroiditis, (put comma) which will show decreased, patchy uptake, or from a nodule, which shows up as a discrete lesion.

Clinical Pearl

- Thyroid scan is useful in distinguishing the cause of hyperthyroidism, and in guiding which treatment is appropriate.

Treatment of GD can be with drugs, radioactive iodine (RAI) ablation, or surgery. Thyroiditis merely needs symptomatic relief with β-blockers till hypothyroidism sets in. An autonomous nodule needs surgical excision.

Usually, GD is initially treated with antithyroid drugs, usually neomercazole. Doses are titrated on the basis of serum TSH and T4. Beta-blockers are needed for symptomatic relief. Remissions can be seen in up to two-thirds of patients, but over half of them later relapse. In those with allergy to antithyroid drugs, or prolonged therapy (no remission, or relapse), ablation with RAI or surgery may be needed.

In general, RAI ablation is preferred as there is no risk of anesthesia or scarring. However, RAI ablation is contraindicated if the patient is pregnant, and does not work well if the gland is nodular or very large, when surgery is needed. If ophthalmopathy is present, it may get aggravated, so surgery is preferable. Thyroidectomy gives immediate relief, but common complications include transient or permanent hypoparathyroidism and injury to the recurrent laryngeal nerve. Risks are lower in experienced hands, so it should be done in centers with considerable experience.

THYROID NODULE

The biggest concern with a thyroid nodule is whether it is malignant or benign. Thyroid cancer, uncommon in general, is even rarer in children. Most nodules are picked up incidentally by family or physician, or on radiologic examination. A history of previous thyroid disease or radiation to the head/neck region, or family history of thyroid disease is important. A multinodular goiter is usually due to thyroiditis and/or iodine deficiency, and almost always benign. A single nodule or palpable lymph nodes are more worrying. During work-up, apart from TSH and T4, a careful ultrasound should look at the size of the gland, the number, size, and appearance of

nodules and cervical lymph nodes. A fine needle aspiration cytology (FNAC) to look for malignancy should be done from a nodule which is single, suspicious looking, or increasing in size. If the cells are follicular, since adenoma and carcinoma cannot be distinguished on FNAC, the entire nodule would have to be surgically removed (lobectomy). If a papillary carcinoma is detected, or FNAC is suspicious for malignancy, a total thyroidectomy should be done. If the TSH is suppressed, a Tc-99m thyroid scan would be useful as a "hot" autonomously functioning nodule is less likely to be malignant.

KEY POINTS

- ☞ Screening for congenital hypothyroidism (CH) must be offered to every single newborn, since it is the most common cause of preventable mental retardation
- ☞ Screening for CH can be done in cord blood, or in a filter paper heel prick sample on day 3–5 of age
- ☞ Primary thyroid stimulating hormone (TSH) method is most widely used worldwide for screening
- ☞ High levels should be urgently confirmed, and replacement started within 7–14 days of birth
- ☞ Initial treatment is with high doses of oral thyroxine (10–15 µg/kg/day), titrated with serum thyroxine (T4) and TSH
- ☞ In older children, a high index of suspicion is needed. High TSH and low T4 confirm hypothyroidism
- ☞ Children at risk of primary hypothyroidism should be screened every 1–2 years
- ☞ Treatment is with oral thyroxine, doses to be titrated with TSH and if needed, T4 levels every 3–12 months
- ☞ Compensated or biochemical hypothyroidism (TSH <10 mU/mL, normal T4) may not need treatment, just follow-up
- ☞ Hyperthyroidism is characterized by suppressed TSH, and raised triiodothyronine (T3) and T4 (rarely only T3). A thyroid scan helps decide treatment
- ☞ Treatment of Graves' disease is with drugs, or radioactive iodine ablation, or surgery. Thyroiditis needs only symptomatic treatment
- ☞ Malignancy should be ruled out in solitary thyroid nodules.

SUGGESTED READINGS

1. American Academy of Pediatrics, Rose SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006;117(6):2290-303.
2. Manglik AK, Chatterjee N, Ghosh G. Umbilical cord blood TSH levels in term neonates: a screening tool for congenital hypothyroidism. Indian Pediatr. 2005;42(10):1029-32.
3. Marwaha RK, Tandon N, Karak AK, Gupta N, Verma K, Kochupillai N. Hashimoto's thyroiditis: countrywide screening of goitrous healthy young girls in postiodization phase in India. J Clin Endocrinol Metab. 2000;85(10):3798-802.
5. Sanghvi U, Diwakar KK. Universal Newborn Screening for Congenital Hypothyroidism. Indian Pediatr 2008; 45:331-332.
4. Virmani A. Neonatal Thyroid Screening, IAP Recommendations & Guidelines. [online] Available from www.iapindia.org. [Accessed November, 2015].

CHAPTER 114

Endocrine Hypertension in Children

Sudha R Chandrashekhar

INTRODUCTION

Systemic hypertension is a leading cause of morbidity and mortality in adults and is an emerging public health concern. Hypertension in childhood and adolescence tracks into adulthood. The prevalence of hypertension increases with age from 15% in young adults to 60% in persons older than 65 years of age. The reported prevalence of hypertension in children is around 5% and hence, routine measurement of blood pressure (BP) in children is recommended to pick up this silent killer disease. In infants and younger children, systemic hypertension is almost always secondary to an underlying disease process and hence, careful and thorough evaluation is essential. Endocrine hypertension in children is less common than renovascular or cardiovascular causes.

Diagnosis of hypertension depends on accurate measurement of BP which is a difficult and time-consuming part of clinical examination. Blood pressure is measured in a calm and quite child, may be in parent's lap, with a cuff size completely encircling upper part of the arm and an inflatable bladder covering two-thirds of upper arm length and encircling at least three-fourths of the circumference. Although Doppler or oscillometric methods are useful, sphygmomanometry happens to be the gold standard and the time of appearance of the first sound and complete disappearance of Korotkoff sound is taken as systolic and diastolic BP, respectively. Mean of at least three BP readings is taken as the representative value. Interpretation of BP is dependent on age, gender, height, and population-specific reference standards.

Hypertension, defined as either systolic or diastolic BP more than 95th percentile of the reference standard, can be primary or essential where cause is not known or secondary to cardiac, renal, or endocrine disturbances.

Multiple endocrine systems can lead to hypertension—the renin-angiotensin-aldosterone system (RAAS), mineralocorticoid and mineralocorticoid receptors, catecholamine and sympathetic nervous system, the kinin system, vasopressin, insulin and insulin receptors, endogenous ouabain and cardiotonic steroids, nitric oxide, etc. (Box 1).

Box 1: Endocrine causes of hypertension

- Hyperthyroidism
- Hyperparathyroidism
- Congenital adrenal hyperplasia
  - 11β-hydroxylase defect
  - 17α-hydroxylase defect
- Cushing syndrome
- Pheochromocytoma
- Neuroblastoma and other neural crest tumors
- Primary aldosteronism
- Apparent mineralocorticoid excess
- Dexamethasone suppressible hyperaldosteronism
- Liddle syndrome
- Gordon syndrome
- Mineralocorticoid receptor mutation
- Diabetic nephropathy

CLINICAL APPROACH TO ENDOCRINE HYPERTENSION

Primary hypertension in children and adolescents is incidentally detected as they are silent and chronic. Secondary hypertension that is sustained or is rising rapidly is always symptomatic and mode of presentation depends on age of the child.

Symptoms in infants could vary from irritability, poor feeding, lethargy, vomiting to convulsions, altered sensorium, paresis/paralysis, or congestive cardiac failure. Older children may complain of headache, behavioral changes, epistaxis, dizziness, and visual disturbances. Intense headache, vomiting, ataxia, hyperthermia, altered consciousness, and seizures suggest hypertensive encephalopathy and is a medical emergency.

To rule out cardiac causes, palpation of all peripheral pulses, four limb BP measurements, and auscultation of abdominal bruit is essential. Renal cause of hypertension is either renovascular or glomerular and hence, presence of

TABLE 1: Clinical clues to underlying cause

Endocrine hypertension	Features	Causes
Hyperthyroidism	• Weight loss, goiter, tremors, excessive sweating	• Increased sympathetic activity mediated by high thyroid hormone levels
Hyperparathyroidism	• Muscle weakness, seizures, failure to thrive, polyuria, fever	• Hypercalcemia
Congenital adrenal hyperplasia 11β-hydroxylase defect	• Hypokalemic metabolic alkalosis • In females—virilization, atypical genitalia • In males—precocious puberty • May present in metabolic crisis of salt waste, shock, hypoglycemia	• Excess androgens, low cortisol, • Low aldosterone, high deoxycorticosterone
17α-hydroxylase defect	• In females—sexual infantilism • In males—undervirilization	• Low gonadal steroids, • High 17-deoxy-steroids
Cushing syndrome	• Obesity, poor linear growth, striae, • hyperglycemia, hypertrichosis, abdominal mass	• Hypercortisolism with/without mineralocorticoid excess
Primary aldosteronism	• Edema, muscle weakness, failure to thrive, polyuria, familial hypokalemic metabolic alkalosis	• Hyperaldosteronism
Dexamethasone suppressible hyperaldosteronism	• Autosomal dominant trait	• 11β-hydroxylase gene, aldosterone synthase gene defect
Liddle syndrome	• Autosomal dominant • Low renin, low aldosterone	• Gain of function mutation in epithelial sodium channel
Apparent mineralocorticoid excess	• Low birth weight, failure to thrive, polyuria, nephrogenic diabetes insipidus, nephrocalcinosis, severe hypertension, end-organ damage, renal failure	• 11β-hydroxysteroid dehydrogenase type 2 mutation
Mineralocorticoid receptor activating mutation	• Rare autosomal dominant • Hypokalemic metabolic alkalosis • Low renin, low aldosterone	• Mineralocorticoid receptor activating mutation
Pheochromocytoma	• Features of catecholamine excess, tachycardia, flushing, abdominal mass, excessive sweating, weight loss	• Increased adrenergic hormones
Neuroblastoma and other neural crest tumors	• Similar to pheochromocytoma • Abdominal mass	• Increased sympathetic activity mediated by adrenergic hormones
Diabetic nephropathy	• Poorly controlled diabetes	• Persistent hyperglycemia, glomerular injury due to ultrafiltration

urinary symptoms like oliguria, dysuria, gross hematuria, anasarca, pallor, failure to thrive, rickets must be looked for. Signs of systemic diseases like vasculitis syndrome, collagen vascular disorder, neurocutaneous syndrome should be examined.

Features of stigmata of endocrine disturbances like Cushing syndrome (centripetal fat distribution, pink striae, buffalo hump, etc.), hyperthyroidism (tachycardia, palpitation, flushes, loss of weight, etc.), pheochromocytoma (episodes of palpitation, sweating, flushes, etc.), palpable abdominal mass (Wilms' tumor, pheochromocytoma, adrenal tumor, etc.), features of atypical genitalia [congenital adrenal hyperplasia (CAH) 11β-hydroxylase and 17α-hydroxylase deficiency] are clues to underlying diagnosis (Table 1).

High body mass index, presence of acanthosis nigricans, and normal stature suggest metabolic syndrome and the hypertension is often essential or primary where a cause is not known. A family history for hypertension, stroke, myocardial infarction, and dyslipidemia needs to be elicited in the first-degree relatives.

In comparison to essential hypertension where the typical presentation is an adolescent, who is obese with positive family history and has mildly elevated BP without signs and symptoms of underlying disease, secondary hypertension is seen in younger children, with moderate-to-severe elevation of BP with symptoms and signs pertaining to organ system affection.

Transient hypertension is seen in children with acute illnesses like glomerulonephritis, rapid colloid infusion, drugs (catecholamines), and autonomic disturbances. Although hypertension is transient, these children need to be monitored and treated as other causes.

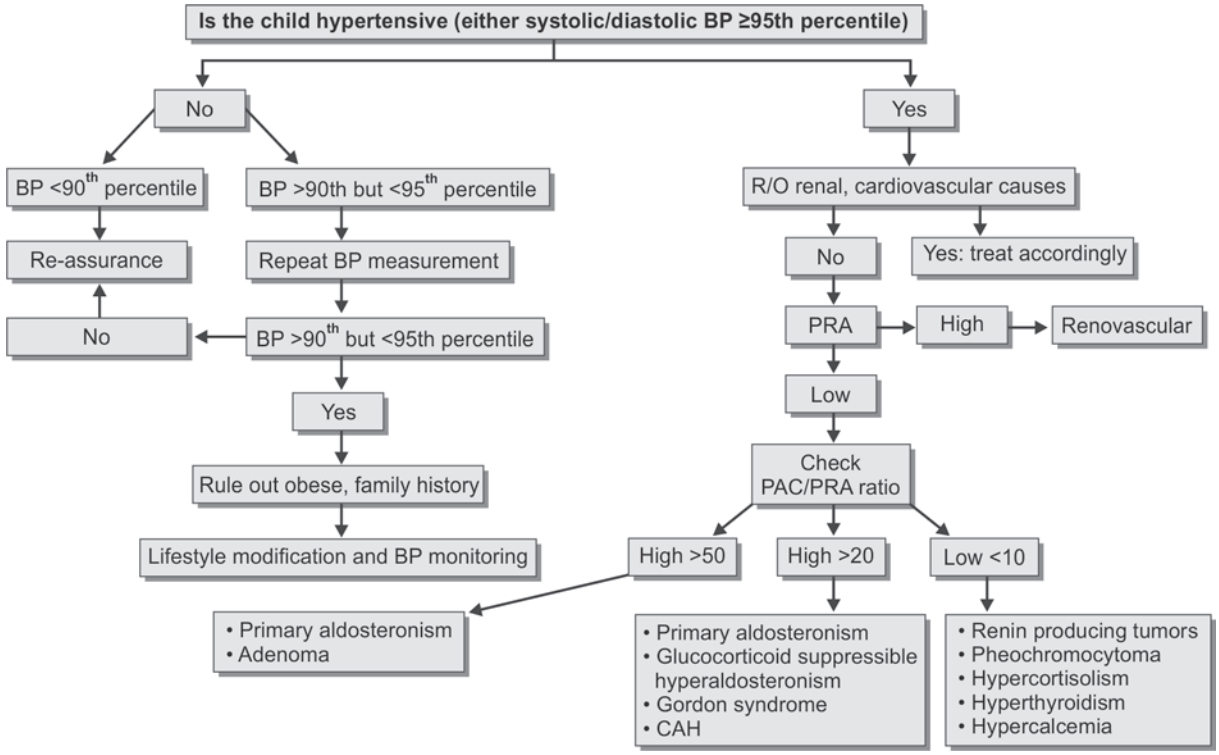
INVESTIGATIVE APPROACH

Investigations are guided by the underlying diagnosis suspected and are not only for ascertaining the etiology but also to find out the degree of end organ damage.

Initial test would include screening for renal and cardiac disorders. Thus, serum creatinine, blood urea nitrogen, serum electrolytes, routine urine analysis, testing for presence of

ALGORITHM 1

Approach to endocrine hypertension



BP, blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; CAH, congenital adrenal hyperplasia.

hematuria, proteinuria, and calciuria would be required in all cases. Renal sonography for sizes of the kidneys, collecting system defects besides renal Doppler and renal scan should be done to rule out renal/renovascular cause of hypertension.

Echocardiography to rule out coarctation of aorta and end-organ changes like hypertrophic cardiomyopathy, diastolic dysfunction, and carotid intimal thickness are advised.

Hypokalemia with metabolic alkalosis is seen in primary or secondary hyperaldosteronism.

Plasma renin activity helps in differentiating the high renin (renal/renovascular hypertension) from low renin (hyperaldosteronism, Gordon syndrome, hypercortisolism) or normal renin (often seen in essential hypertension) forms of hypertension.

Plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio helps in differentiating primary hyperaldosteronism wherein the PAC/PRA ratio is greater than 20 from secondary hyperaldosteronism (renovascular disease, renin producing tumors, coarctation of aorta) where it is less than 10. These ratios are very high in aldosterone producing adrenal adenoma. Both PAC and PRA are low in hypercortisolism and thus the ratio is less than 10. Saline loading test, fludrocortisone suppression, or captopril challenge tests are other confirmatory tests for primary hyperaldosteronism.

Urinary vanillylmandelic acid (sensitivity 63%, specificity 94%), urinary catecholamine (sensitivity 73%, specificity 94%), plasma epinephrine/metanephrine (sensitivity 85%, specificity 80%), urinary total metanephrine (sensitivity 76%, specificity 94%), plasma-free metanephrine (sensitivity 99%, specificity 92%) levels are useful in children suspected to have pheochromocytoma.

Urinary and plasma steroid profile in CAH, hypercortisolism; thyroid profile in suspected hyperthyroidism; serum calcium, parathyroid hormone, and serum 25-hydroxy-vitamin D levels in hypercalcemia; are some of the other tests which provide diagnostic clue.

Radiographic imaging of the adrenals, ^{123}I-metaiodobenzylguanidine (MIBG) scan in suspected pheochromocytoma, positron emission tomography radiotracers like fluorine-18 L-3,4-dihydroxyphenylalanine (18F-DOPA), 18-fluoro-2-deoxyglucose (18F-FDG), etc. help localizing tumors as cause of hypertension.

Detailed ophthalmological evaluation for hypertensive retinopathy and urine for microalbuminuria for hypertensive nephropathy should also be checked to rule out end-organ effects.

TREATMENT

Therapy is provided to children with persistent hypertension and the goal is to decrease BP to less than 95th percentile of the target for age, gender, and height.

In mild cases as also in adolescents with primary hypertension, this could be achieved by nonpharmacological means like dietary modifications, weight reduction, regular exercise, and stress reduction. Sodium intake restricted to less than 1.2 g per day by avoiding added salt in the diet, pickles, baked, canned, and processed foods help decrease BP. Fruits and nuts beneficial in lowering BP should be included in the diet. Regular exercise schedule helps and outdoor activities like swimming, running, sports should be promoted. Weight reduction is an important therapeutic aspect of BP control in obese children.

Children with persistent hypertension require long-term therapy and the drug of choice depends on the underlying pathophysiology.

Angiotensin converting enzyme inhibitors are used in high renin hypertension (renovascular, essential). Angiotensin receptor blockers (ARBs) like losartan are useful in high renin hypertension wherein they block angiotensin II receptors. Aldosterone antagonist (spironolactone) or ARB (eplerenone) is used in hyperaldosterone states. Adrenergic blockers (labetalol, phenoxybenzamine, propranolol) are indicated in increased catecholamine states (pheochromocytoma, neural crest tumors). Diuretics are indicated in high volume output states.

Calcium channel blockers are often used as first line antihypertensives.

In hypertensive crisis, gradual drop in BP over 24–48 hours should be aimed with a drop of not more than 25% every hour as acute drop in BP leads to ischemic damage to brain, myocardium, retina, and kidneys. Controlled drop in BP is best achieved with nitroprusside infusion drip. Sublingual nifedipine can be used where facilities for infusion or monitoring for cyanide toxicity are not available. Labetalol and nicardipine infusions can also be used.

Clinical Pearls

- Hypertension in children is often due to an organic cause
- Measurement of blood pressure should always be done annually in children as a screening parameter
- Blood pressure measurement should be done with appropriate cuff size and interpreted in relation to age gender and height
- Both systolic and diastolic blood pressure should be recorded
- Investigations depend on clinical clues to underlying etiology
- Therapy is tailored to the underlying pathophysiology.

KEY POINTS

- ☞ Endocrine causes of hypertension are rare in children and are often chronic, persistent, and symptomatic
- ☞ Etiological investigations are based on clinical clues.

SUGGESTED READINGS

1. Ali US. Systemic hypertension in children. In: Kumar K, Prabhu S, et al. (Eds). IAP Textbook of Pediatric Cardiology, 1st edition. Jaypee Brothers Medical Publishers; 2009. pp. 143-62.
2. Bernstein D. Systemic hypertension. In: Behrman RE, Kliegman RM, Jenson HB (Eds). Nelson Textbook of Pediatrics, 17th edition. Elsevier Saunders; 2004. pp. 1592-8.
3. Carey RM. Overview of endocrine systems in primary hypertension. Endocrinol Metab Clin North Am. 2011;40(2):265-77.
4. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114 (2 Suppl):555-76.
5. Sahay M, Sahay R. Low renin hypertension. IJEM. 2012;16(5):733-9.
6. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity and the prevalence of hypertension in school aged children. Pediatrics. 2004;113(3):475-82.

SECTION 14: RHEUMATOLOGY

CHAPTER 115

Approach to Oligoarthritis

Vijay Viswanathan

INTRODUCTION

Arthritis in childhood is not that uncommon as it may sound. Depending on the number of joints involved, it could either be oligoarticular (≤4 joints) or polyarticular (≥5 joints). Formerly known as pauciarticular, the oligoarticular variant can be a single joint (monoarthritis) or more than a single but less than 4 joints. It could be acute or chronic. A detailed history with regards to the onset, pattern of involvement, presentation, and duration of arthritis help differentiate between the various possible diagnoses. This, coupled with a meticulous clinical examination and supported by relevant investigations, help in nailing the diagnosis. In this chapter a clinical approach to decipher oligoarticular presentation in a child is discussed.

DEFINITION

Acute monoarthritis: it is inflammation of one joint only, characterized by pain, swelling, redness, and/or restriction of movement with duration of less than 3 weeks.
Chronic monoarthritis: arthritis in the single joint lasting for at least 6 weeks is said to be chronic (Box 1).

Box 1: Causes of monoarthritis in children

Acute

- Septic arthritis
- Reactive
- Hemarthrosis
- Traumatic joint effusion/ mechanical causes
- Bone tumors and acute leukemia
- Juvenile arthritis (systemic onset or enthesitis)/collagen vascular disease

Chronic

- Juvenile arthritis (systemic onset, oligoarticular, and the enthesitis-related arthritis subcategories
- Chronic hemarthrosis
- Malignancies/bone tumors
- Infections such as tuberculosis
- Miscellaneous disorders, e.g., sarcoidosis, pigmented villonodular synovitis

SOME COMMON SCENARIOS OF ACUTE ARTHRITIS

Scenario 1: Reactive/Postinfectious Arthritis

Many viral illnesses may be followed by onset of inflammation at the joints after an incubation period. Most of them are self-limiting and do not leave any long-term deformities. A few specific types of the same with some salient features are shown in box 2.

Box 2: Specific causes of postinfectious/reactive arthritis

Postinfectious/viral

- Immediately/weeks to months
- Pauci/polyarticular
- Lower limb joints knees/ ankles
- Flu virus, parvovirus B19, C
- Coxsackie, chikungunya, arbovirus, HIV, hepatitis A, and HBsAg

Poststreptococcal RA

- Short incubation period
- Large and small joints
- Additive involvement (nonfleeting)
- Poor response to NSAIDs
- Echocardiography/penicillin prophylaxis

Reactive (Reiter syndrome) arthritis

- Arthritis, conjunctivitis, and urethritis
- Time to evolve 2–4 weeks
- Lower limb joints knees/ankles
- Occasionally dactylitis
- *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*, *Chlamydia*, and *Mycoplasma*
- HLA B27

Transient synovitis of hip

- Up to 8 years
- Differentiate from septic arthritis
- Nonweight bearing, leukocytosis, ESR, and CRP
- Always aspirate when in doubt

HIV, human immunodeficiency virus; HbsAG, hepatitis B surface antigen; NSAIDs, nonsteroidal anti-inflammatory drugs; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HLA, human leukocyte antigen; RA, reactive arthritis.

Clinical Pearls

- Most cases of postinfectious/reactive arthritis (RA) are self-limiting
- Anti-inflammatory agents/intra-articular steroids form the main line of therapy
- Poststreptococcal RA necessitates a two dimensional echo-cardiography and occasionally penicillin prophylaxis
- Transient synovitis can recur in 4–17% (first 6 months); differentiation from infection is mandatory.

Scenario 2: Septic Arthritis

Septic arthritis in infancy and childhood is a true clinical emergency. Delay in the diagnosis and treatment of septic arthritis can result in disastrous complications including complete destruction of the articular cartilage and epiphysis, loss of the growth plate, and joint dislocation.

Clinical Pearls

- Fever, malaise, along with erythema, local warmth, and significant pain.
- Pain on passive motion (many times position of pseudoparalysis) highly suggestive of septic arthritis
- Joint aspiration is a must in all doubtful scenarios (occasionally fluid may be sterile)
- Imaging is not the primary means of diagnosing septic arthritis
- Ensure complete therapy for 4–6 weeks.

Scenario 3: Malignancies

Hematological malignancies (leukemia and lymphoma) as well as localized osseous, malignancy (osteosarcoma/ Ewing's sarcoma) can present with musculoskeletal complaints. Symptoms of arthritis, sometimes with a migratory pattern can precede hematological feature of malignancy by months.

Clinical Pearls

- Sick child with nocturnal pains (bone pains)
- Periarticular pain
- Pallor
- Lymphadenopathy
- Organomegaly
- High lymphocytes, elevated erythrocyte sedimentation rate with low platelets
- Whenever in doubt, order a marrow prior to starting steroids.

Scenario 4: Mechanical Causes

Acute pain and limitation of movement may be due to mechanical causes such as Osgood-Schlatter syndrome (osteochondritis), which is a painful condition caused by irritation and sometimes fragmentation at the tibial tuberosity. It is an apophysitis of the immature skeleton subjected to too much physical strain causing pull on the tibial tubercle that sits adjacent to a growth plate. Slipped upper femoral epiphyses occurring in adolescent/preadolescent boys can present with hip pain/knee pain (due to radiation from hip). Perthes disease or avascular necrosis of head of femur is classically seen in toddlers and early childhood. It affects boys more than girls, and presents as a painful limp. In addition, children who have excess ligament laxity (hypermobile) do complain aches and pains and also benign joint effusions.

A detailed history and clinical examination reveal that the problem is mechanical and there is no/mild arthritis on examination.

CHRONIC OLIGOARTICULAR PRESENTATION

History

Inquire about systemic symptoms such as fever, weight loss, and night sweats.

Detailed history of morning stiffness, night pains, and restriction of activities are important. History of a recent sore throat, gastroenteritis, red and painful eyes, and chronic skin disease such as psoriasis or significant trauma should be asked for. A past history of tuberculosis (TB) or contact with an open case of TB is important in India, where monoarticular disease in a child is often considered to be TB unless proved otherwise. It is also important to check for the history of recent travel to an area endemic for Lyme disease, brucellosis, or a history of tick bite.

Examination

Detailed general, systemic, and local examination as previously outlined above including skin examination, formal ophthalmology evaluation by slit lamp for uveitis, and musculoskeletal examination are a must in all children who present with a single swollen joint.

Chronic Oligoarticular Juvenile Idiopathic Arthritis

Oligoarticular juvenile idiopathic arthritis (JIA) can present with less than 4 joints (oligo persistent) or can involve more than 4 joints after 6 months (oligo extended).

Clinical Pearls

- Systemically well
- Present with a painless limp with swollen joint
- Blood tests are usually normal with magnetic resonance imaging revealing effusion and synovitis
- Antinuclear antibody positivity associated with uveitis
- Intra-articular steroids form first line therapy
- Good prognosis except in extended oligovariant
- Rule out mimics like tuberculosis, pigmented villonodular synovitis and associated collagen disorder.

APPROACH TO ACUTE ONSET OLIGOARTICULAR ARTHRITIS

The following approach may assist in finding out the etiology behind the articular involvement. These are generalized guidelines and there may be the odd exception to the rule, however this could serve as a starting approach.

History

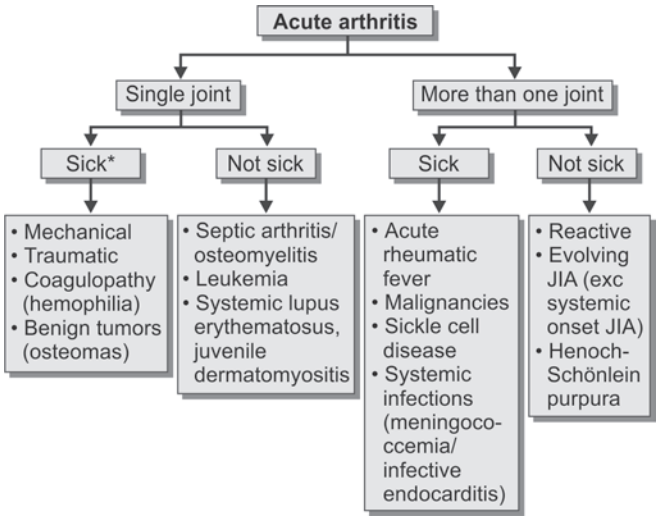
- Number of joints
  - Monoarthritis—reactive, septic/osteomyelitis, malignancies, trauma/mechanical, and other collagen diseases
  - More than one joint-reactive, leukemia, sickle cell disease, systemic (metastatic) infections, e.g., infective endocarditis and meningococcemia
- Nature of onset
  - Acute/in minutes to hours—reactive, septic arthritis, trauma, and coagulopathy/sickle cell disease
  - Hours to days—reactive, systemic infections, hemarthrosis, and leukemia
- Diurnal variation
  - Morning stiffness/pain—inflammatory arthritis
  - Nocturnal pains—malignancies and mechanical (growing pains)
- Trauma—important only when considering coagulopathies
- Pattern of involvement
  - Migratory—acute rheumatic fever and leukemia
  - Additive or simultaneous—reactive/poststreptococcal reactive arthritis (PSRA), collagen vascular disease, systemic infections, and evolving JIA.
- Associated features
  - Fever—infection. Inflammation [other collagen disorders, e.g., systemic lupus erythematosus (SLE)], malignancy, systemic disease and infective endocarditis/meningococcemia
  - Bleeding tendency/fly—hemophilias
  - Septic focus—septic arthritis and osteomyelitis
  - Systemic features—systemic-onset JIA, SLE, juvenile dermatomyositis (JDM), reactive, and infection
  - Eye—conjunctivitis—reactive (Reiters syndrome)
  - Uveitis—evolving JIA
  - Episcleritis/scleritis—collagen vascular disease, e.g., vasculitis.

Physical Examination

- Appearance
  - Sick—malignancy, infection, and systemic disease
  - Well—reactive arthritis and mechanical
- Gait/posture: Antalgic/pain on passive motion/pseudoparalysis—septic arthritis
- Nature of joint swelling
  - Articular—septic arthritis (erythematous and warm joint), acute rheumatic fever, and other arthritis
  - Periarticular/focal tenderness—leukemia and osteomyelitis

ALGORITHM 1

Algorithmic approach to acute arthritis



*Appearance, constitutional.

HSP, Henoch- Schönlein purpura; IE, infective endocarditis; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; JDM, juvenile dermatomyositis.

- Pattern of pain
  - Pain throughout range of movement—septic arthritis and reactive arthritis
  - Pain experienced as the joint is gently forced (i.e., stressed) towards its limitation of range—synovitis (Transient synovitis, evolving JIA)
  - Pain not present throughout the entire range of motion—mechanical and tendinitis.
- Skin—petechiae, purpura, Gottron's papules (JDM), rashes (e.g., Butterfly rash in SLE < vasculitis rashes, etc.).

Laboratory Investigations (As Guided by History and Examination)

- Complete blood count, erythrocyte sedimentation rate, C-reactive protein, viral titers, and blood culture
- Antistreptolysin O titer
- Throat swab
- Coagulation studies
- Tuberculin test
- Joint aspiration (always whenever in doubt to rule out septic arthritis specially hip joint)
- Imaging:
  - X-rays—trauma and malignancy
  - Bone scan—infections
  - Magnetic resonance imaging—synovitis, tumors, and infections
  - Two dimensional echocardiography—PSRA and Kawasaki disease
  - Antinuclear antibody (suspected juvenile oligoarthritis), HLA B27 (suspected enthesitis).

KEY POINTS

- ☞ More than one joint involvement almost always rules out an infective arthritis (more likely to be reactive)
- ☞ Morning stiffness suggests inflammatory etiology, while nocturnal limb pains are always suggestive of a malignancy
- ☞ Always aspirate a joint when in doubt
- ☞ Recognizing patterns through a good history, clinical examination, and less reliance on costly investigations is paramount.

SUGGESTED READINGS

1. Cabral DA, Tucker LB. Malignancies in children who initially present with rheumatic complaints. J Pediatr. 1999;134:53-7.
2. Cassidy JT, Petty RE. Textbook of pediatric rheumatology. 4th ed. Philadelphia: WB Saunders; 2001. pp. 726-79.
3. Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence based clinical prediction algorithm. J Bone Joint Surg Am. 1999;811662-70.
4. Prabhu AS, Balan S. Approach to a child with monoarthritis. Indian J Pediatr. 2010;77(9):997-1004.
5. Roberton DM, South MJ. Arthritis and connective tissue disorders. In: Roberton DM, Robinson MJ. editors. Practical Pediatrics. 5th ed. London: Churchill Livingstone; 1994. p. 457.

CHAPTER 116

Approach to Polyarthritis

Rashna D Hazarika

INTRODUCTION

Joint diseases in children are not so uncommon and can range from infections to injuries to hematological conditions like hemophilia, leukemia, and to the more serious forms of arthritis of varying etiology and prognosis. It often becomes a cause of concern for parents and caretakers especially if the etiology is of a chronic nature. An approach to polyarthritis in children has been discussed in this chapter.

Arthritis is inflammation of the joints and can be a single or a multiple joint involvement. Usually, single joint involvement, like septic arthritis, prompts the parents to seek urgent medical care. Similarly, patients with polyarthritis require detailed evaluation and investigation as the causes are varied and some, like leukemia and lupus, have serious consequences if not treated at the appropriate time. The other important aspect of approaching a child with polyarthritis is "pattern recognition". Polyarticular joint disease has multifactorial etiology. It may present as an acute self-limiting viral illnesses or it can be the beginning of a chronic sinister disease. The underlying etiological process can be anything from infectious or postinfectious, rheumatological, or a manifestation of systemic diseases. It may take days or sometimes weeks for the disease to evolve and thus make it difficult to make a diagnosis at the time of presentation. Some viral infections like parvovirus causes a transient self-limited polyarthritis whereas organisms like *Chlamydia*, *Gonococci*, *Salmonella*, and *Shigella* cause a postinfectious reactive (sterile) arthritis. Arthritis lasting for more than 6 weeks rules out an infective etiology. With these issues in mind, this article will try to give an algorithmic approach to polyarthritis (Algorithm 1).

SOME DEFINITIONS

- Polyarthritis: involvement of more than one joint is known as polyarthritis
- Acute polyarthritis: joint involvement of less than 6 weeks
- Chronic polyarthritis: joint involvement for more than 6 weeks.

ETIOLOGY

The etiology of polyarthritis is varied and outlined in table 1.

IMPORTANT POINTS IN HISTORY

Looking at the diverse etiologies of polyarthritis, it may seem difficult to know where to start looking for a diagnostic label. However, attention to a number of important clinical clues both in the history and examination can help to narrow down the possibilities. We look at each of these issues in detail.

Age

Juvenile idiopathic arthritis (JIA), juvenile psoriatic arthritis, Kawasaki disease (KD), and septic arthritis are most frequent in early childhood (1–4 years of age). Polyarticular JIA, Juvenile dermatomyositis, Henoch–Schönlein purpura, and Polyarteritis nodosa have their peak frequencies by mid-childhood (7–11 years). Juvenile ankylosing spondylitis (JAS) and systemic lupus erythematosus (SLE) show a marked increase in late childhood. Rheumatoid factor positive arthritis mimicking adult rheumatoid arthritis usually occurs after the age of 10 years. Diseases like gout, calcium pyrophosphate deposition disease, polymyalgia rheumatica, and primary osteoarthritis almost never occur in childhood.

Sex

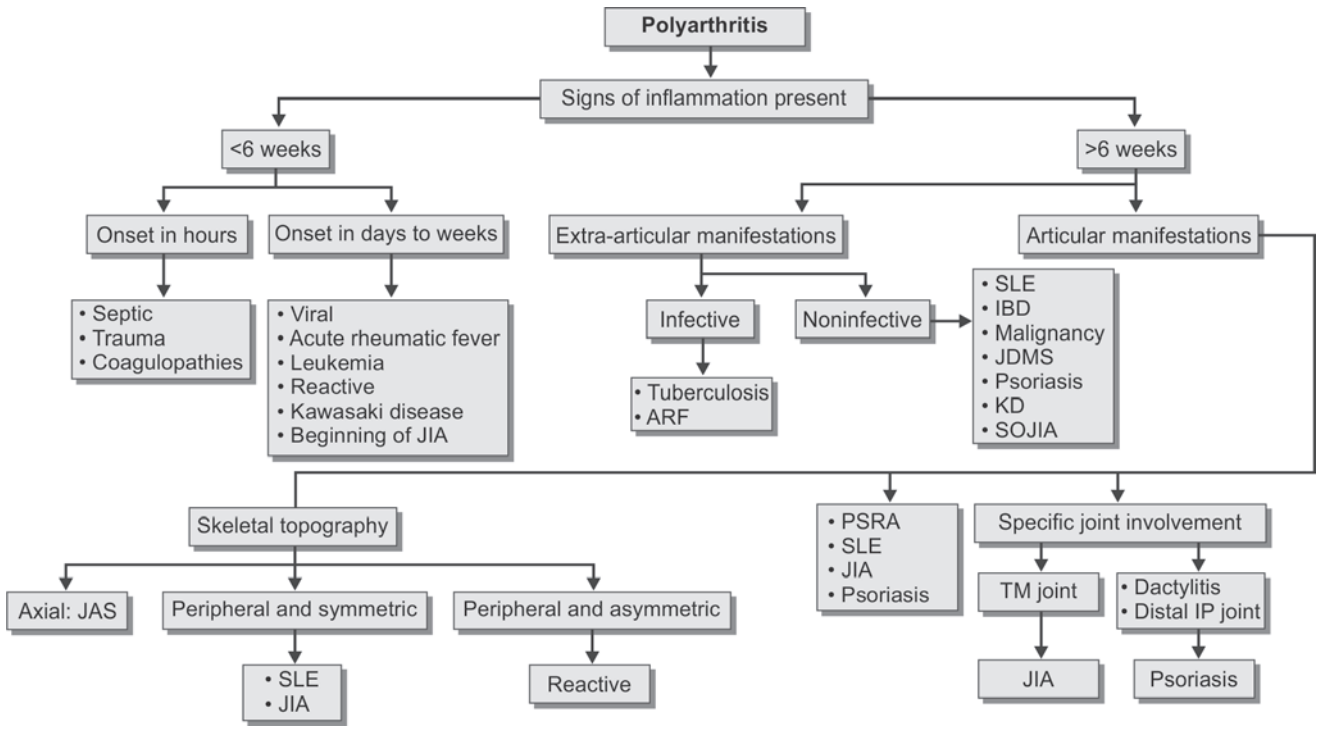
Polyarticular JIA and SLE have a predilection for girls whereas JAS and KD for boys. However, many of these diseases can occur in both the sexes and one should keep an open mind when evaluating a patient with polyarthritis.

Onset and Duration

Usually, septic arthritis, trauma, and coagulopathies present within hours. Viral arthritis, acute rheumatic fever, vasculitides, leukemia, reactive arthritis, and beginning of JIA can evolve over days to weeks. Polyarticular JIA, tubercular arthritis, sarcoidosis,

ALGORITHM 1

Algorithmic approach to polyarthritis



KD, Kawasaki disease; ARF, acute rheumatic fever; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; JDMS, juvenile dermatomyositis; SOJIA, systemic onset juvenile idiopathic arthritis; JAS, juvenile ankylosing spondylitis; PSRA, poststreptococcal reactive arthritis; TM, temporomandibular; IP, interphalangeal.

TABLE 1: Etiology of polyarthritis

Viral	Parvovirus B 19, mumps, rubella, varicella, hepatitis B, coxsackie virus, cytomegalovirus, EBV, HIV, enteroviruses, and adenoviruses
Bacterial	Neisseria meningitidis, gonococci, bacterial endocarditis, staphylococci, streptococci, and *Haemophilus*
Other infectious agents	Mycobacteria, fungal infections, leptospirosis
Reactive arthritis	*Chlamydia*, *Yersinia*, *Mycoplasma*, *Campylobacter*, *Salmonella*, *Shigella*, tuberculosis (Poncet's arthritis), HIV
Rheumatological	Juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, Behcet's disease
Vasculitides	Kawasaki disease, Henoch–Schönlein purpura, Polyarteritis nodosa
Spondyloar-thropathy	Juvenile ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis
Miscellaneous	Drug reactions, leukemia, sickle cell crisis, neuroblastoma, metabolic conditions (Fabry's, Gaucher's), mechanical problems (Ehlers Danlos syndrome and benign joint hypermobility syndrome), skeletal dysplasias, inflammatory bowel disease

EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

and fungal arthritis go through an indolent process and present in weeks to months. However, many of these conditions may be in the evolution phase in the initial weeks and it may not be appropriate to give a diagnostic label at this stage.

Pattern

Usually, in inflammatory arthritis, there will be complaints of early morning stiffness, stiffness after a period of activity (gelling).

Past History

History of recent diarrhea, acute conjunctivitis, urethritis, and fever with or without rash may give a clue to reactive arthritis. A past history of heel pain, back pain, or transient redness of eyes can indicate the beginning of JAS. Past history of repeated swelling in the same joint after a trivial trauma may indicate a previously undiagnosed bleeding disorder.

Family History

Diseases such as JIA, inflammatory bowel disease (IBD), and psoriasis may have a familial predilection.

EXAMINATION

The examination of the affected joints as well as picking up the extra-articular manifestations form an important step toward

arriving at a diagnosis. A systemic approach in examination has to focus on identifying the following.

Articular Involvement

Synovium, synovial fluid, articular cartilage, intra-articular ligaments, joint capsule, and juxta-articular bone form a part of the articular structures. Presence of pain, joint line tenderness and limitation of both active and passive movements, instability, locking of the joint, crepitus, and joint deformity signify articular involvement. In addition, swelling may be there due to synovial thickening, joint effusion, or joint enlargement. In nonarticular involvement, findings are away from the joint and pain may occur only on active movement.

Inflammatory Versus Noninflammatory

Signs of local inflammation are erythema, tenderness, and redness of the joint. Systemic inflammatory signs include fever, weight loss, and fatigue. An effusion and pain at the end of range of movement indicates active arthritis.

Pattern of Joint Involvement

Important clues to the diagnosis can be picked up if one tries to identify some of the patterns known with specific diseases such as:

- Evolution of the joint pain:
  - Migratory joint involvement is seen in acute rheumatic fever as well as gonococcal arthritis. In acute rheumatic fever, the joint can swell up in hours whereas in gonococcal arthritis this happens over days
  - Additive joint involvement where new joints are involved when the previously affected ones are still painful occur in poststreptococcal reactive arthritis, SLE, JIA, and psoriasis
  - Intermittent arthritis where the symptoms can appear and disappear is typical of reactive arthritis
- Topography: involvement of the axial or peripheral skeleton is an important clue to diagnosis. Axial skeleton includes the spine, sacroiliac joints, sternoclavicular joints, and the manubriosternal joints. Juvenile ankylosing spondylitis has involvement of the sacroiliac and the lower spine. Others, like JIA and SLE, have peripheral skeletal involvement though rarely they can have a combined involvement
- Symmetry: usually symmetrical joint involvement is seen in JIA and SLE and asymmetric joint involvement is seen in reactive arthritis
- Specific joint involvement: some diseases involve specific joints like dactylitis and distal interphalangeal joint involvement indicates psoriatic arthritis. Similarly, temporomandibular joint involvement indicates JIA. Most reactive arthritis would have a lower limb joint involvement
- Presence of joint deformity: joint deformity usually follows long standing undiagnosed or untreated arthritis and is usually seen with JIA or hemophilia. Arthritis associated with SLE and IBD are usually nondeforming.

Extra-articular Manifestations

Diseases like SLE, IBD, malignancies, and systemic onset JIA have dominant extra-articular manifestations (Table 2).

TABLE 2: Extra-articular features in a patient with polyarthritis

Site	Manifestations	Diseases
Eye	• Nonpurulent conjunctivitis • Anterior uveitis • Posterior uveitis	• KD • JIA • Psoriasis
Mouth	• Fissures in lips, strawberry tongue • Oral ulcers • Red gums at tooth line	• KD • SLE, Behcet's disease • JDMS
Head and neck	• Alopecia/hair loss • Malar rash • Heliotrope rash • Psoriasis	• SLE • SLE • JDMS • Psoriatic arthritis
Hands	• Raynaud's phenomenon • Nail pitting, onycholysis • Nail fold infarct • Periungual desquamation • Digital infarct • Gottron's papules • Subcutaneous calcinosis	• SLE, JDMS, scleroderma • Psoriasis • Connective tissue disease • KD • PAN • JDMS • JDMS
Trunk and arms	• Erythema marginatum • Subcutaneous nodules • Urticaria	• ARF • ARF, RF+ve JIA • CTD
Muscles	• Wasted muscles • Tender muscles, proximal muscles weakness	• JIA • JDMS
Hemato-logical	• Lymphadenopathy • Petechiae • Pallor	• TB, SLE, malignancy, KD • Malignancy, SLE • Malignancy, SLE, SOJIA
Gastro-intestinal	• Dysphagia • Abdominal pain • Diarrhea • Malabsorption • Hepatic involvement • Organomegaly	• JDMS, sclerodema • SLE, PAN • IBD, reactive arthritis • Scleroderma • SLE • SLE, malignancy
Respiratory	• Upper airway symptoms • Pleuritis, pleural effusion	• Wegener's granulomatosis • SLE, SOJIA

Continued

Continued

Site	Manifestations	Diseases
Cardiovascular	• Pericarditis • Myocarditis • Valvular disease	• SLE, SOJIA, ARF • ARF, SOJIA, polymyositis • ARF, SLE, JAS, hypermobility
Genitourinary	• Urethritis • Genital ulcers • Proteinuria • Renal failure, hematuria	• Reactive arthritis, Reiter's syndrome • Behcet's syndrome • SLE, amylodosis, NSAIDS • SLE, NSAIDS, amyloidosis, systemic vasculitides
Central nervous system	• Chorea • Convulsions, coma, psychosis, headache • Neuropathies	• ARF, SLE • SLE • PAN

KD, Kawasaki disease; TB, tuberculosis; ARF, acute rheumatic fever; JIA, Juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; JDMS, juvenile dermatomyositis; SOJIA, systemic onset JIA; JAS, juvenile ankylosing spondylosis; PAN, polyarteritis nodosa; CTD,Connective tissue disease; NSAIDS, nonsteroidal anti-inflammatory drugs.

Pattern Recognition

A good history and clinical examination can help the astute and observant clinician recognize some typical patterns of joint disease. Some examples are:

- Polyarthritis in a young girl may suggest SLE or polyarticular JIA
- Scattered small distal interphalangeal joint involvement indicates psoriatic arthritis
- Hip and lower back involvement may point toward JAS
- Inflammatory tarsal and enthesopathy may be a distinguishing feature between JAS and JIA in the absence of axial disease.

An algorithmic approach to polyarthritis is shown in algorithm 1.

LABORATORY TESTS

More than 95% of the cases of polyarthritis can be diagnosed based on a good history and examination. However, specific tests like cell count and morphology can give clues to a malignant process like leukemia, thrombocytopenia in SLE, thrombocytosis in KD, raised acute phase reactants, like ESR and CRP, indicate an active inflammatory process, antineutrophil antibodies in SLE, rheumatoid factor positivity in polyarticular JIA, human leukocyte antigen B 27 in JAS and Antineutrophil cytoplasmic antibody for systemic vasculitides. Other investigations, like ASO and echocardiography, are useful in acute rheumatic fever and synovial fluid analysis to differentiate between an infective and an inflammatory process.

TREATMENT

Treatment of polyarthritis depends on the specific diagnosis. Pending the diagnosis, one must focus on providing symptomatic relief by using nonsteroidal anti-inflammatory agents, rest to the affected part as well as physiotherapy if possible. A brief outline of the management is shown in table 3. However, many diseases may require extensive and long-term management for achieving remission and prevention of morbidity.

PROGNOSIS

Prognosis depends on the diagnostic label, time to diagnosis, presence of complications, and how aggressive the management has been. For example, reactive arthritis would have an excellent prognosis with supportive management, intravenous immunoglobulin in Kawasaki disease would lead to a possible cure and prevention of complications if treated at the appropriate time. Early diagnosis and aggressive management of arthritis prevent joint damage and other complications. Acute rheumatic fever responds well to treatment and initiation of penicillin prophylaxis prevents future recurrences and the development of rheumatic valvular damage. Steroids in lupus is life saving and drugs like mycophenolate mofetil are offering good outcome in renal

TABLE 3: Outline of treatment of polyarthritis

Etiology	Specific treatment	Supportive treatment
Viral arthritis	NSAIDS	Self-limiting illness—counseling and reassurance
Bacterial arthritis	Specific antibiotics. NSAIDS/steroids if needed	Long-term penicillin prophylaxis for patients with rheumatic fever
Reactive arthritis	NSAIDS	Specific treatment for bacterial etiology if any such as gonococcal infection
Rheumatological arthritis	NSAIDS/steroids depending on specific etiology	Physiotherapy, counseling, and occupational therapy
Systemic vasculitides	Intravenous immunoglobulin for Kawasaki disease, NSAIDS or steroids in Henoch–Schönlein purpura and other vasculitides	Appropriate and prompt treatment in Kawasaki disease with intravenous immunoglobulin prevents long-term cardiac morbidity and steroids in lupus may be life saving

NSAIDS, nonsteroidal anti-inflammatory drugs.

lupus. However, the main factor influencing the prognosis is how early one has been able to identify the possible etiology of polyarthritis and initiate the treatment.

Clinical Pearls

- Pattern recognition helps to arrive at a diagnostic label
- Extra-articular manifestations form an important clue to diagnosis
- Early morning stiffness characteristic of inflammatory arthritis
- Diagnosis mostly clinical. Laboratory tests only helps to rule out sinister conditions such as leukemia, and also useful for follow-up.

KEY POINTS

- ☞ Polyarthritis has multifactorial etiology
- ☞ Pattern recognition is very important
- ☞ Rheumatoid factor positive arthritis mimicking adult onset rheumatoid arthritis usually occurs after 10 years of age
- ☞ Though polyarthritis can occur in both the sexes, it is important to remember that juvenile idiopathic arthritis and systemic lupus erythematosus are more common in girls whereas juvenile ankylosing spondylitis and Kawasaki disease are more common in boys
- ☞ Inflammatory arthritis is characterized by early morning stiffness
- ☞ Prominent extra-articular manifestations must be looked for and aid in arriving at a diagnosis
- ☞ Diagnosis is mostly clinical. Tests help to rule out a malignancy or idiopathic thrombocytopenic purpura
- ☞ Treatment depends on the etiology, number of joint involved, and other associated manifestations.

SUGGESTED READINGS

1. Hull RG. Management guidelines for arthritis in children. Rheumatology. 2001;40:1308.
2. Khubchnadani RP, D'Souza S. Initial evaluation of a child with arthritis—an algorithmic approach. Indian J Pediatr. 2002;69(10):875-80.
3. Singh S, Mehra S. Appriach to polyarthritis. Indian J Pediatr. 2010;77:1005-10.
4. Sawhney S, Dass R. editors. Approach to Arthritis in Childhood. 2009.

CHAPTER 117

Fever with Arthritis: An Algorithmic Approach

Sathish Kumar

INTRODUCTION

Musculoskeletal and joint diseases appear to have increased in the last decade. Confusion over terminology and a lack of awareness of these conditions have probably contributed to their under recognition. In pediatric practice, physicians are often faced with a child presenting with musculoskeletal complaints. The differential diagnosis of fever with arthritis is broad and includes a variety of causes. This chapter, is focused on algorithmic approach to a child who presents with fever and arthritis.

All joint pains are not arthritis. Arthritis is defined as a swollen joint or a joint having at least two of the following conditions: tenderness, limited range of motion, pain on movement, or warmth overlying the joint.

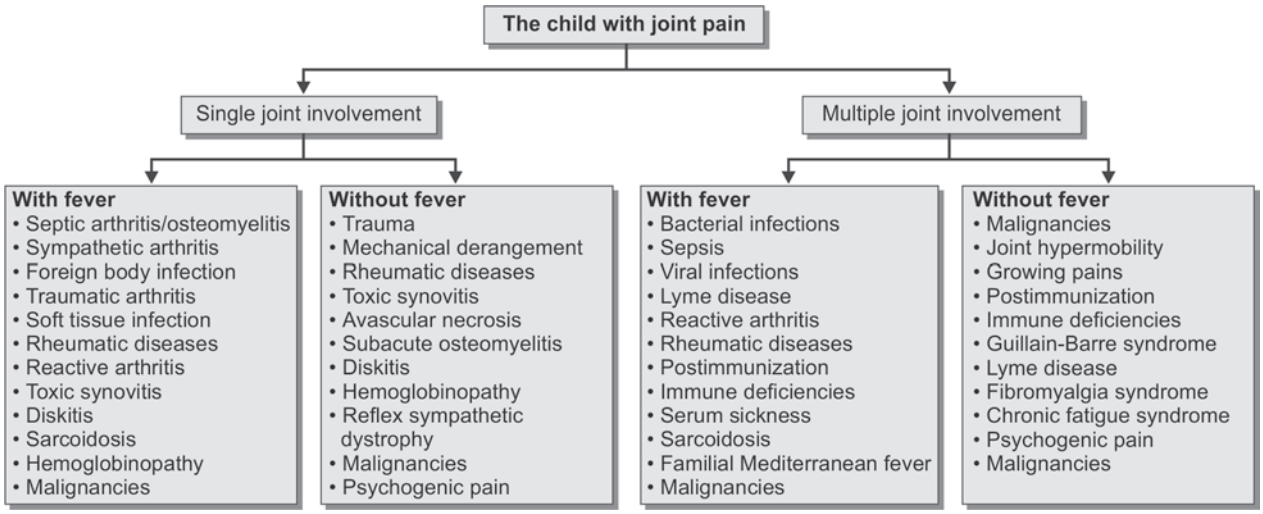
The first step in initial screening is to establish whether a single joint or multiple joints are involved. The second important step is to determine whether or not there is associated fever (Algorithm 1). For practical purposes, this initial screening should lead to the following four possible groups of diagnoses:

1. Single joint involvement with associated fever
2. Single joint involvement without fever
3. Multiple joint involvement with associated fever
4. Multiple joint involvement without fever.

ALGORITHMIC APPROACH TO MONOARTHRITIS (SINGLE JOINT)

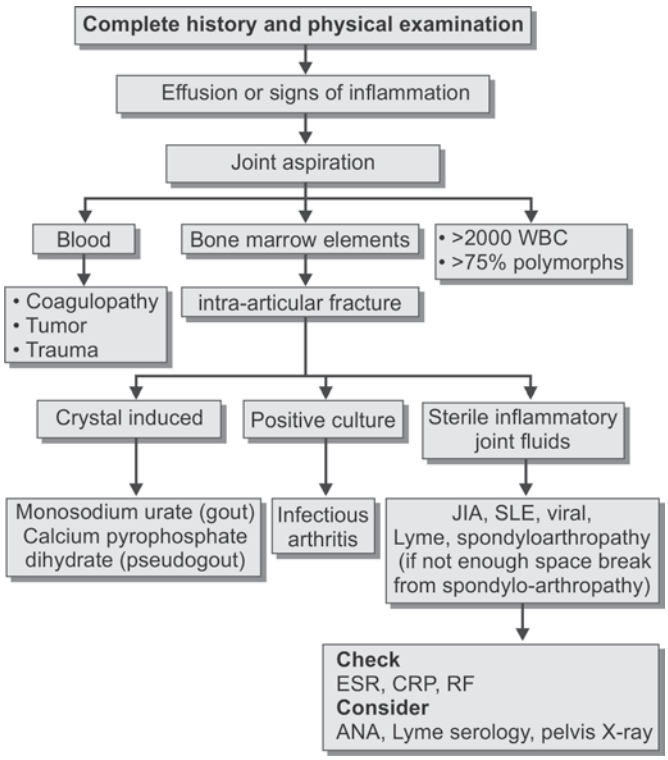
A carefully conducted history taking and physical examination are the initial and most important steps in narrowing the differential diagnosis and guiding the diagnostic evaluation (Algorithm 2).

ALGORITHM 1



ALGORITHM 2

Approach to fever with monoarhritis



WBC, white blood cell; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; ANA, antinuclear antibody.

History Taking

Important aspects to be considered in the history taking are as follows:

- Characteristics of the pain and/or stiffness (site, number of joints, severity, frequency, duration, pattern, and association of warmth or discoloration). Morning stiffness is a characteristic feature of inflammatory arthritis. Night pain should alert the clinician to a malignancy or an osteoid osteoma
- Review of systems focused on the presence of fever or other constitutional symptoms (e.g., weight loss, anorexia, night sweats, or nocturnal pain)
- Precipitating factors: traumas, infections (streptococcal, enteric), travel to Lyme disease or tuberculosis (TB) endemic areas or other risk factors for TB (exposure to a person with TB; close contact with a person with a positive TB skin test result)
- Presence of extra-articular features (diarrhea, urethral discharge, ocular symptoms, and rash)
- Personal or family history of a bleeding diathesis or human leukocyte antigen (HLA) B27-associated diseases like inflammatory bowel disease (IBD), acute anterior uveitis, psoriasis, ankylosing spondylitis.

Physical Examination

The presence of fever should alert the clinician to the potential for more severe conditions requiring urgent treatment (e.g., septic arthritis). On general examination, clues to underlying diagnosis include rash (psoriasis, viral exanthems), iritis (IBD or enthesitis-related arthritis), and hepatosplenomegaly/lymphadenopathy suggestive of malignancy.

The focused examination of the affected joint should include inspection of the skin for warmth, redness, swelling, and soft tissue involvement, using the contralateral side for comparison. Palpation of the surrounding bone is important because the presence of pinpoint bony tenderness is suggestive of fracture, osteomyelitis, or malignancy. An exquisite pain in the joint on range of motion or a joint that is severely restricted in its range of motion suggests an etiology other than inflammatory arthritis (e.g., septic joint).

The differential diagnosis of monoarthritis includes entities in the broad categories of infection, postinfection, inflammation, and malignancy and trauma related to a systemic illness (Box 1).

Preliminary investigations that are to be considered for the evaluation of monoarthritis are presented in box 2. Laboratory investigations of acute or chronic monoarthritis are performed to confirm the clinician's impression regarding the suspected diagnosis or to exclude conditions.

Laboratory Investigations

Complete blood count (CBC) and differential white blood cell count, inflammatory markers, and liver and renal functions should be considered in any child with monoarthritis.

If the presentation is acute (<72 hours), a joint aspiration must be performed if the clinician is concerned about a septic joint, with the fluid sent for blood cell count, Gram stain, and culture. In addition, culture of the throat, blood, stool, and/or urine should be considered to identify a potential organism in the case of reactive arthritis. An acute presentation is also observed with hematologic and malignant diseases (e.g., hemophilia and leukemia), highlighting the importance of CBC and coagulation studies. Antistreptolysin O (ASO) and

Box 1: Differential diagnosis of monoarthritis

Infection-related
- Septic arthritis
- Osteomyelitis
- Transient synovitis
- Reactive arthritis
- Lyme disease
- Tuberculosis

Trauma
- Fracture: accidental and nonaccidental
- internal derangement: ligament rupture
- Foreign body: synovitis

Malignancy
- Leukemia
- Neuroblastoma

Inflammation
- Juvenile idiopathic arthritis
- Inflammatory bowel disease
- Familial Mediterranean fever

Hemarthrosis
- Hemophilia
- Pigmented villonodular synovitis
- Synovial hemangioma

Box 2: Preliminary investigations to be considered for the evaluation of monoarthritis

Basic screening	Further investigations
• Complete blood count and differential white blood cell count	• Cultures of throat, blood, joint fluid, stool, and/or urine
• Erythrocyte sedimentation rate	• Partial thromboplastin time
• C-reactive protein	• Antinuclear antibody titer
• Renal function and liver enzyme	• Serologic testing for Lyme disease
• Serum lactate dehydrogenase	• Antistreptolysin O titer
• Radiographs	• Urinalysis
	• Tuberculin skin test
	• Further imaging (ultrasonography, magnetic resonance imaging)
	• Bone marrow aspiration
	• Slit lamp examination of the eyes

antideoxyribonuclease B (anti-DNaseB) titers are useful to identify a recent streptococcal infection.

In chronic monoarthritis, Lyme serology (when history is suggestive of an exposure) and antinuclear antibody (ANA) and rheumatoid factor (RF) titers should be considered. Human leukocyte antigen B27 testing is most relevant in chronic arthritis when the child is suspected of having a specific category of juvenile idiopathic arthritis (JIA) (enthesitis-related arthritis), which is generally seen in boys older than 8 years and often associated with enthesitis, lumbosacral back pain, and a family history of HLA-B27-associated diseases (e.g., IBD, ankylosing spondylitis).

The presence of ANA or RF is neither necessary nor sufficient to make a diagnosis of JIA. Antinuclear antibody should not be used as a screening test for rheumatic illness in a primary care setting, because it may be positive in up to 5–10% of healthy children.

Antinuclear antibody is used as a diagnostic test for children with probable systemic lupus erythematosus or mixed connective tissue disease and other overlap-like illnesses. In the context of JIA, a positive ANA titer is associated with a significantly increased risk of developing chronic anterior uveitis.

Rheumatoid factor has been associated with aging (>60 years), infections (bacterial endocarditis, hepatitis B or C, parasitic disease, viral infection), pulmonary disease (sarcoidosis, interstitial pulmonary fibrosis), malignancy, and primary biliary cirrhosis and thus is not a specific test for the diagnosis of rheumatic disease.

Only 5–10% of patients with JIA have a positive RF, highlighting the lack of sensitivity for the diagnosis of JIA.

A joint aspiration must be performed when a septic joint (bacterial) is suspected but is also recommended for the diagnosis of TB arthritis. The presence of hemarthrosis suggests coagulation disorder, trauma, or rare causes, including synovial hemangioma or pigmented villonodular synovitis. The more common and/or serious causes of monoarthritis are addressed here.

Septic arthritis: this condition classically presents with a severely painful, swollen, warm, and red joint in a febrile child. The join must be aspirated for Gram stain, cultures and examination of the synovial fluid, and cell count. In the absence of Gram stain or culture, a cell count of 40,000/mm^3 is regarded as evidence of bacterial infection.

Osteomyelitis: with reactive arthritis or sympathetic arthritis, this is arthritis with effusion in a nearby joint as a reaction to osteomyelitis. A technetium or gallium joint bone scan often reveals an osteomyelitis in the adjacent bone.

Presence of foreign body in the joint: a thorn, shard of glass, or other foreign body may cause a secondary infection or sterile synovitis. Computerized tomographic scan is superior to a radiograph in demonstrating a nonopaque foreign body.

Traumatic arthritis: traumatic serosanguineous effusion can cause fever secondary to blood within the joint. There is almost always a history of trauma. Aspiration usually reveals sterile surgery will reveal the nature of this condition. In addition, clotting abnormalities must be ruled out.

Rheumatic diseases: oligoarticular onset of juvenile idiopathic arthritis may present with single joint disease. Usually, one of the large joints is affected, and the patient is either afebrile or has a low grade fever. Very rarely, children with systemic onset JIA may also present initially with monoarticular disease, usually in the knee or hip. In that case, look for other manifestations of the disease such as rheumatoid rash, hepatosplenomegaly, lymphadenopathy, pericarditis and, in rare instances, iritis. A diagnosis of JIA is made based on history taking and physical examination and after exclusion of other causes.

It is unusual for children with systemic lupus erythematosus to present with single joint involvement. Occasionally, rheumatic fever, Kawasaki disease, juvenile dermatomyositis, and certain viral infections may begin with arthritis affecting one joint.

Postinfectious reactive arthritis: this includes postviral or postbacterial diseases such as post-streptococcal reactive arthritis and post-salmonella, Shigella, and Yersinia reactive arthritis. These postviral or postbacterial conditions have a benign, self-limited course that may require symptomatic and supportive therapy.

Toxic synovitis: if the hip joint is affected, toxic synovitis must be taken into account. It is also called transient synovitis and, occurs in children aged 8 ± 10. Most of the patients are boys, and there is often a history of respiratory infection. Within a few weeks, a limp and pain referred to the knee develop along with a low grade fever. The erythrocyte sedimentation rate may be mildly elevated. The disease usually subsides after 1 ± 2 weeks and does not commonly recur. However, Legg-Calve-Perthes disease is occasionally a sequelae.

Hemoglobinopathy: in a child, sickle cell anemia must be ruled out by hemoglobin electrophoresis. In the very young child, it causes a dactylitis that may mimic true arthritis; in older children it causes microinfarcts that give rise to periostitis and periarthritis which are responsible for the pain crises in this disease.

Malignancies: leukemia is the most common malignancy in childhood. However, it rarely presents with single joint involvement. Tumors, such as synovial cell sarcoma or

bone tumors like osteosarcoma and Ewing's sarcoma, can rarely present as single joint involvement with fever. In any malignancy, bone pain is usually prominent, and other features, such as weight loss and fatigue, are commonly present.

ALGORITHMIC APPROACH TO POLYARTHRITIS (MULTIPLE JOINTS)

Differential diagnosis of polyarthritis essentially includes infectious, inflammatory, and malignant causes (Box 3).

The review of systems and physical examination (Algorithm 3) is critical to establishing a diagnosis because

Box 3: Differential diagnosis of polyarthritis

Infection-related
- *Neisseria gonorrhea* infection
- Viral infections (e.g., parvovirus B19, rubella virus/vaccine)
- Infective endocarditis
- Acute rheumatic fever
- Post-streptococcal reactive arthritis
- Reactive arthritis

Inflammatory
- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Juvenile dermatomyositis
- Systemic vasculitides (Henoch-Schonlein purpura, Kawasaki disease)
- Hereditary autoinflammatory syndromes
- Sarcoidosis
- IBD-related arthritis

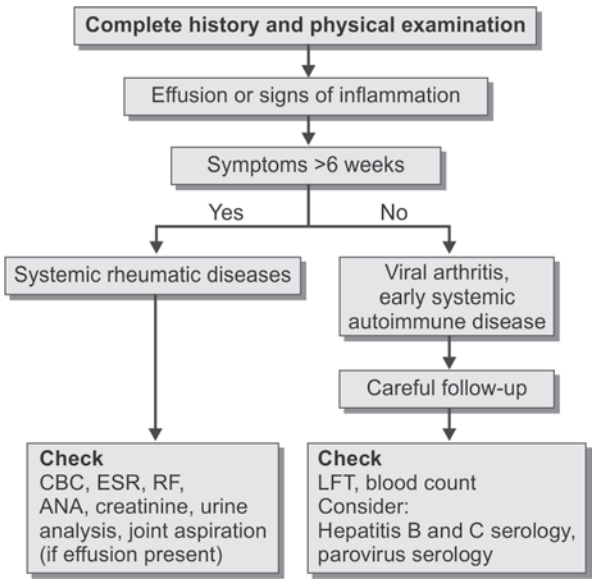
Malignancy
- Leukemia
- Neuroblastoma

Mechanical
- Hypermobility
- Skeletal dysplasia

Other systemic illness
- Immunodeficiency-associated arthritis
- Serum sickness

ALGORITHM 3

Approach to fever with polyarthritis



ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ANA, antinuclear antibody.

infection as indicated, ASO and anti-DNAase B titers, cardiac evaluation (electrocardiography and echocardiography), chest radiography, ANA titer, other autoantibodies (anti-Ro,

TABLE 1: Review of systems in the differential diagnosis of polyarthritis

System involved	Review of system or physical finding	Diagnosis
Ophthalmologic	Uveitis	JIA
	Conjunctival injection without exudate	KD
Dermatologic	Malar rash, alopecia	SLE
	Heliotrope rash, Gottron papules	JDM
	Polymorphous rash, perianal desquamation, edema, and erythema of hands	KD
	Evanescent salmon-colored rash	SOJIA
	Palpable purpura	HSP, SLE
	Nail pitting or onycholysis	JIA (psoriatic)
	Oral ulcers	SLE
Cardiovascular	New heart murmur	ARF, IE
	Pericarditis	SOJIA, SLE, ARF
	Raynaud phenomenon	SLE, MCTD, scleroderma
Respiratory tract	Pleuritis	SOJIA, SLE
	Acute or chronic sinusitis, pulmonary nodules, or hemorrhage	GPA
	Interstitial lung disease	SLE or scleroderma
Gastrointestinal/ genitourinary tract	Weight loss or poor growth	IBD, malignancy, SLE
	Diarrhea/hematochezia, colicky abdominal pain	IBD, HSP
	History of gastroenteritis	Reactive arthritis
	History of urethritis or cervicitis	Reactive arthritis, gonococcal arthritis
Neurologic	Seizures, psychosis, mood disorder, decline in school performance	SLE
	Stroke	SLE, vasculitis
	Proximal muscle weakness	JDM, MCTD

JIA, Juvenile idiopathic arthritis; KD, Kawasaki disease; SLE, systemic lupus erythematosus; JDM, juvenile dermatomyositis; SOJIA, Systemic onset Juvenile idiopathic arthritis; HSP, Henoch–Schonlein purpura; ARF,acute rheumatic fever; IE, Infective endocarditis; MCTD, mixed connective tissue disease; GPA, granulomatosis with polyangiitis; IBD, Inflammatory bowel disease.

there are clues in the characteristics of the arthritis, fever, rash, and other system involvements that often provide the correct diagnosis (Table 1).

When polyarthritis is the presenting complaint, in addition to the investigations outlined in box 2, additional investigations may include serum C3 and C4 complement levels, serum levels of quantitative immunoglobulins, urinalysis, serologic testing for viral pathogens, swabs for gonococcal

anti-La, anti-Smith, anti-ribonucleoprotein, anti-Scl 70), and antineutrophil cytoplasmic antibody.

CONCLUSION

Differential diagnosis for monoarthritis and polyarthritis is broad. An organized approach within the framework presented, including carefully attending to clues in the history taking and physical examination allows for correct diagnosis in most cases. Laboratory evaluation is performed to support the clinician's impression. Serious and/or potentially life-threatening infections, malignant or orthopedic causes need to be identified, and the patient is referred for surgical or medical management.

Clinical Pearls

- Presence of antinuclear antibody or rheumatoid factor is neither necessary nor sufficient to make a diagnosis of juvenile idiopathic arthritis
- Antinuclear antibody should not be used as a screening test for rheumatic illness in a primary care setting, because it may be positive in 5–10% of healthy children
- High antistreptolysin O titer with arthralgia does not warrant Penicillin prophylaxis.

KEY POINTS

- ☞ A detailed history and physical examination are critical in the initial assessment, with attention paid to the nature of the pain, presence of limp, weight-bearing status, morning stiffness, systemic symptoms (fever, rash, weight loss, fatigue), history of past medical illnesses, travel or positive family history (arthritis, bleeding disorders, sickle cell anemia, inflammatory bowel disease, psoriasis)
- ☞ The important aspects of physical examination include assessing the joints (swelling, erythema, warmth, tenderness, deformity, range of motion), adjacent structures (bones, tendons, muscles, skin), and gait and leg length discrepancy
- ☞ The extent of investigations is determined from the information gained through the history and physical examination
- ☞ Basic screening laboratory tests and radiographs of the affected site should be obtained. Additional investigations can be performed to arrive at a clinical diagnosis
- ☞ Fever, redness, moderate-to-severe pain, pinpoint pain or tenderness, and weight loss are clues to more serious causes of limb pain that require additional investigations and referrals to specialists (rheumatologists, orthopedic surgeons, neurologists, hematologist/oncologists).

SUGGESTED READINGS

1. Abbassian A. The limping child: a clinical approach to diagnosis. Br J Hosp Med (Lond). 2007;68(5):246-50.
2. Berard R. Approach to the child with joint inflammation. Pediatr Clin North Am. 2012;59(2):245-62.
3. Gedalia A. Joint pain in children: an algorithmic approach. Isr Med Assoc J. 2002;4(10):837-42.
4. Leung AK, Lemay JF. The limping child. J Pediatr Health Care. 2004;18(5): 219-23.
5. Tse SM, Laxer RM. Approach to acute limb pain in childhood. Pediatr Rev. 2006;27(5):170-9.

CHAPTER 118

Childhood Vasculitis

Indira Banerjee, Rakesh Mondal

INTRODUCTION

Vasculitis is characterized by inflammation of blood vessel walls with resultant tissue ischemia and necrosis. The first case was described by Adolf Kussmaul and Rudolf Maier more than 150 years ago, when they described a patient with what is today known as polyarteritis nodosa (PAN). Since then, many more in these categories have been described. Most pediatric vasculitis disorders need individual specific classification criterias for their identification.

EPIDEMIOLOGY

Estimated overall annual incidence of new cases of pediatric vasculitis is 53.3 per 100,000 children under 17 years of age. The two most common vasculitides were Henoch-Schönlein purpura (HSP) and Kawasaki disease, with estimated annual incidences of 20.4 and 5.5 per 100,000 in children less than 17 years of age, respectively. Reported geographical variations in vasculitis may reflect an environmental influence, like infections, drugs, allergy, vaccination, and desensitization procedures.

PATHOGENESIS

The exact pathogenesis of pediatric vasculitis is not known. The proposed mechanisms are vascular injury caused by inflammation of vascular wall (vasculitis). The triggers for injury are genetic, environmental, infective, and immune factors.

Irrespective of the initial insult, inflicted injury to the vessel wall resulted in healing of vascular wall by fibrosis. It causes narrowing of vascular lumen and ischemic injury to target organ. Abnormal healing of the vascular wall leads to aneurysm formation with disorganized blood flow which can lead to ischemic target organ damage with or without thrombus formation (Fig. 1).

CLASSIFICATION

International Consensus Conference in Vienna (June 2005) under the Pediatric Rheumatology European Society resulted in a new proposal for childhood vasculitis classification summarized in box 1. These were validated and given the final form at the 2008 Ankara Consensus Conference with support from the European League Against Rheumatism (EULAR) and

Box 1: Classification of childhood vasculitis

- Predominantly large vessel vasculitis:
  - Takayasu's arteritis
- Predominantly medium-sized vessel vasculitis:
  - Childhood PAN
  - Cutaneous polyarteritis
  - Kawasaki disease
- Predominantly medium-sized vessel vasculitis:
  - Granulomatous:
    - Granulomatous polyangiitis (previous nomenclature Wegner's granulomatosis)
    - Churg-Strauss syndrome (eosinophilic polyangiitis)
  - Nongranulomatous
    - Microscopic polyangiitis
    - Henoch-Schönlein purpura (immunoglobulin A vasculitis)
    - Isolated cutaneous leukocytoclastic vasculitis
    - Hypocomplementemic urticarial vasculitis
- Other vasculitides:
  - Behçet's syndrome
  - Vasculitis secondary to infection (including hepatitis B-associated PAN), malignancies and drugs (including hypersensitivity vasculitis)
  - Vasculitis associated with connective tissue diseases
  - Isolated vasculitis of the central nervous system
  - Cogan's syndrome
  - Unclassified

PAN, polyarteritis nodosa.

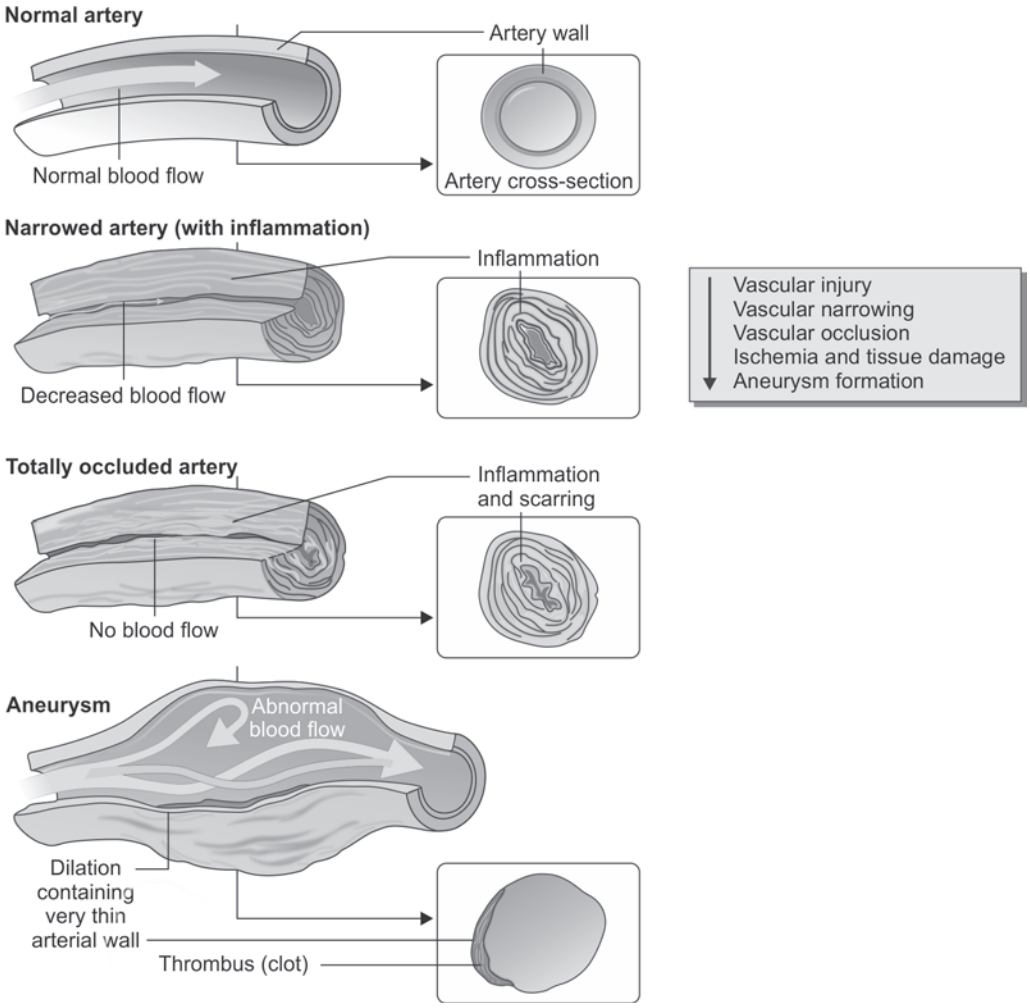


Fig. 1: Schematic diagram showing vascular injury causing different changes including aneurysm formation

the Pediatric Rheumatology International Trials Organization. There has been trend for use of vasculitic disorders names that reflect increased pathophysiologic understanding of these conditions. Revision in the commonly used terms has been proposed by the 2012 International Chapel Hill Consensus Conference (CHCC) on nomenclature of vasculitides. Among the notable changes suggested by the 2012 CHCC were use of the term eosinophilic granulomatosis with polyangiitis (EGPA), in place of Churg-Strauss syndrome, and adoption of the term antineutrophil cytoplasmic antibody (ANCA) associated vasculitis for the three disorders likely microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), and EGPA.

ALGORITHMIC APPROACH TO CHILDHOOD VASCULITIS

Diagnosis and treatment of childhood vasculitis is explained in detail below (Algorithm 1).

Suspect Childhood Vasculitis

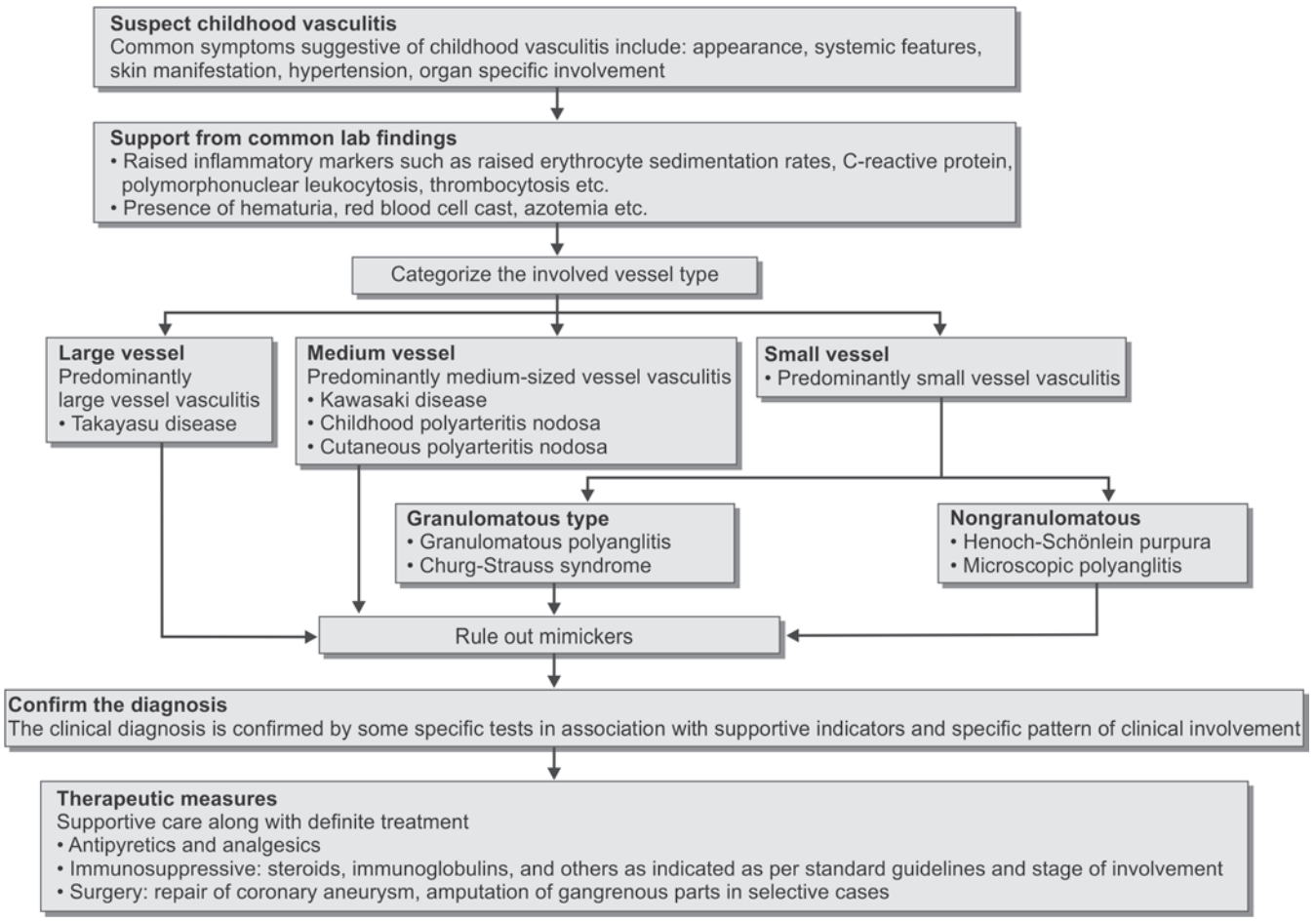
Common symptoms suggestive of childhood vasculitis include:

- Appearance: miserable look, more in pain or irritable, and no toxic look
- Systemic features: fever, weight loss, fatigue, and arthralgias
- Skin manifestation: range from palpable purpura to urticaria, livedo reticularis, nodules, and ulcers, even gangrenes
- Hypertension

  Organ specific involvement: this depends on the size of the vessel involved, degree of collateral circulation, and the organ involved:
  - Nephrology: hematuria and proteinuria
  - Joints: arthritis and joint effusions
  - Muscles: myalgia and myositis
  - Serous cavities: serositis
  - Cardiac: hypertension, myocarditis, and cardiomyopathy
  - Pulmonary: infiltrates, infract and or hemorrhage
  - Neurologic: mono- or polyneuritis.

ALGORITHM 1

Approach to childhood vasculitis



Clinical Pearl

- Severe constitutional symptoms, skin rash, and hypertension are important clues for suspicion of vasculitides in children.

Support from Common Laboratory Findings

- Raised inflammatory markers such as raised erythrocyte sedimentation rates, C-reactive protein, polymorphoneuclear leukocytosis, thrombocytosis, etc.
- Presence of hematuria, red blood cell cast, azotemia, etc.

Clinical Pearl

- Raised inflammatory parameters, e.g., raised C-reactive protein, erythrocyte sedimentation rate, polymorphoneuclear leukocytosis, and thrombocytosis adds as diagnostic clues.

Categorize the Involved Vessel Type

Typical clinical findings according to vessel involvement are given in table 1.[5]

TABLE 1: Clinical findings according to vessel involvement

Large vessel	Medium vessel	Small vessel
• Limb claudication • Asymmetric blood pressure • Absent pulses • Bruits • Aortic dilation	• Cutaneous nodules • Ulcers • Livedo reticularis • Digital gangrene • Mononeuritis multiplex • Microaneurysms	• Purpura • Vesiculobullous nodules • Urticaria • Glomerulonephritis • Alveolar hemorrhage • Cutaneous granulomas • Splinter hemorrhages • Uveitis/Episcleritis/Scleritis

Predominantly Large Vessel Vasculitis

Takayasu disease

Angiographic abnormalities [conventional, computed tomography (CT), and magnetic resonance imaging] of the aorta or

its main branches (mandatory criterion), plus at least one of the following four features:
- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Bruits over aorta and/or its major branches
- Hypertension (related to childhood normative data)
- Blood pressure difference >10 mmHg

Predominantly Medium-sized Vessel Vasculitis

Kawasaki disease

Fever for 5 days or longer and least four of the following five signs:
- Nonpurulent conjunctivitis
- Rash (polymorphous erythematous)
- Hyperemic lips and/or mucous membranes
- Changes to the extremities (peripheral edema, peripheral erythema, and periungual desquamation)
- Cervical adenopathy (usually unilateral)

Complication: coronary artery aneurysm

Childhood polyarteritis nodosa

Histological evidence of necrotizing vasculitis in medium or small-sized arteries or angiographic abnormalities (aneurysm or occlusion) as a mandatory criterion, plus two of the following seven:
- Muscle tenderness or myalgia
- Skin involvement (livedo reticularis, tender subcutaneous nodules, and other vasculitic lesions)
- Systemic hypertension
- Mononeuropathy or polyneuropathy
- Abnormal urine analysis and/or impaired renal function
- Testicular pain or tenderness
- Signs or symptoms suggesting vasculitis of any other major organ system (gastrointestinal, cardiac, pulmonary, or central nervous system)

Cutaneous polyarteritis nodosa

Cutaneous PAN is limited to skin with possible manifestations in the musculoskeletal system. It is characterized by the:
- Presence of painful subcutaneous nodules
- Nonpurpuric lesions with or without livedo reticularis
- With no systemic involvement (except for myalgia, arthralgia, and nonerosive arthritis).

Predominantly Small Vessel Vasculitis

Granulomatous type

Granulomatous polyangiitis

In January 2011, the Board of Directors of the American College of Rheumatology, the American Society of Nephrology, and the EULAR recommended that the name Wegener's granulomatosis be changed to granulomatosis with polyangiitis (Wegener's), abbreviated as GPA.

The proposed classification criteria for GPA were that three of the following six criteria should be presented:
- Abnormal urinalysis
- Granulomatous inflammation on biopsy
- Naso-sinus inflammation
- Subglottic, tracheal, or endobronchial stenosis
- Abnormal chest X-ray or CT and
- Proteinase 3 ANCA or cytoplasmic ANCA staining.

Churg-Strauss syndrome

The proposed classification criteria for presence of Churg-Strauss syndrome is any four or more of the six criteria:
- Asthma
- Eosinophilia >10%
- Neuropathy: mono- or polyneuropathy
- Pulmonary infiltrates, non-fixed
- Paranasal sinus abnormality
- Extravascular eosinophils.

Nongranulomatous type

Henoch-Schönlein purpura

Purpura with lower limb predominance and the presence of at least one of the following four features:
- Arthralgia or arthritis
- Diffuse abdominal pain
- Any biopsy showing predominant immunoglobulin A deposition
- Renal involvement (any proteinuria and/or hematuria).

Complication: Mainly HSP nephritis.

Microscopic polyangiitis

Microscopic polyangiitis (MPA) is characterized by necrotizing vasculitis with few or no immune deposits affecting small vessels.

Clinical features of MPA include disease involving the kidneys, lungs, joints, skin, gastrointestinal tract, and peripheral nerves. The cardinal features of MPA include glomerulonephritis, pulmonary hemorrhage, fever, and mononeuritis multiplex. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs, but no granulomatous lesions of the respiratory tract is seen.

Rule Out Mimickers

Mimickers for vasculitis include following:
- Infections such as pneumococcal, mycobacterial, rickettsial
- Connective tissue disorders
- Bacterial endocarditis
- Atrial myxoma
- Vasoconstrictive drugs such as ergot
- Malignancy such as lymphomas
- Disorders associated with antiphospholipid antibody syndrome.

Confirm the Diagnosis

The clinical diagnosis is confirmed by some specific tests in association with supportive indicators and specific pattern of clinical involvement such as:
- Tissue biopsy (PAN)
- X-rays of the sinuses and chest
- Angiographic studies of the vessels (PAN, Takayasu arteritis)
- Nerve conduction studies

- Assessment of autoantibodies such as antinuclear antibody (ANA), ANCA.
- ANA would be positive in lupus associated vasculitis
- Cytoplasmic ANCA (c-ANCA) in Wegener's granulomatosis
- Perinuclear ANCA in microscopic polyangiitis
- Rheumatoid factor positivity is seen in hepatitis B associated cryoglobulinemia.

Therapeutic Measures

Supportive care along with definite treatment:

- Antipyretics and analgesics
- Immunosuppressive: steroids, immunoglobulins, and others as indicated as per standard guidelines and stage of involvement
- Surgery: repair of coronary aneurysm, amputation of gangrenous parts in selective cases.

Medical

- Anti-inflammatory and analgesics: naproxen, sulfasalazine
- Steroids: reduce pain and inflammation of severe joint disease, skin lesions, eye disease, and central nervous system. Routine follow-up is needed to detect features of steroid toxicity
- Other immune suppressants: methotrexate (main stay of disease-modifying antirheumatic drug in the treatment of juvenile idiopathic arthritis), azathioprine, cyclophosphamides
- Biologics:
  - Monoclonal tumor necrosis factor-α antibody (Infliximab: a chimeric monoclonal antibody)
  - Adalimumab (A humanized monoclonal antibody)
  - Anakinra (anti-interleukin (IL)-1)
  - Toclizumab (humanized monoclonal antibody, targeting both membrane bound and soluble IL-6 receptors)
  - Abatacept: (fusion protein that blocks the CD80 or CD86 interaction with CD28 with inhibition of T cell)
  - Rituximab (chimeric monoclonal antibody against CD20, targeting B cells)
- Other: aspirin, clopidogrel and intravenous immunoglobulin (IVIG) (Kawasaki disease).

Surgical

- Amputation of nonsalvageable gangrenous part
- Repair of aneurysm.

INDIAN SCENARIO

Large studies with uniform comprehensive data are not available from Asia. Indian data that included adult population is not a true representation of pediatric vasculitides from all over the country.

A pediatric study was done from Eastern India over a period of 7 years (2004 to 2010), on prospectively followed up children (under 12 years) with vasculitis from a tertiary care hospital from Kolkata. The study revealed 10.2% children (n = 158) had vasculitis among all rheumatological cases (n = 1544). HSP (56.9%) and Kawasaki disease (24%) were major groups. The study revealed that primary vasculitides were diagnosed in 135 patients (male:female ratio was 1.9:1 and the mean age of onset was 5.5 years). Among the 38 cases of Kawasaki disease, 20 had coronary artery involvement, 5 had persistent aneurysms, 29 received IVIG, non required angioplasty. Other vasculitides included PAN (n = 4), Wegener's granulomatosis (n = 2), and Takayasu disease (n = 1). Secondary vasculitis accounted for 23 cases.

CONCLUSION

Pediatric vasculitis is a challenging disease for diagnosis as well as treatment. It should be considered whenever there is unexplained multisystem disease with evidence of vascular involvement. Fever, extreme irritability, hypertension, hematuria, and skin lesions are some of the important clues for diagnosis. Other organs, such as the eye, peripheral nervous system and the kidneys, must be examined to pick up asymptomatic involvement. Prompt and aggressive treatment can prevent complications and decrease the morbidity and mortality in pediatric populations.

KEY POINTS

Common childhood vasculitis

- ☞ Henoch-Schönlein purpura (HSP) is the most common vasculitis in children
- ☞ The main clinical features of HSP include purpura, arthritis, abdominal pain, gastrointestinal bleeding, and nephritis. Palpable purpura is the presenting sign in 100% of the patients
- ☞ Glucocorticoids can lessen tissue edema, arthritis, and abdominal pain. It decreases the rate of intussusception. However, glucocorticoid therapy does not prevent recurrence of abdominal symptoms, skin involvement, or renal disease and does not shorten the duration or lessen the likelihood of relapse. Glucocorticoids combined with a cytotoxic agent might be beneficial in patients with active glomerulonephritis and progressive renal insufficiency
- ☞ Nonpurulent conjunctivitis and hyperemic lips and/or mucous membranes with antibiotic-unresponsive fever for more than 5 days—suspect Kawasaki disease
- ☞ Coronary artery lesions are responsible for most of the disease-related morbidity and mortality in Kawasaki disease. Aneurysms appear 1–4 weeks after the onset of fever and develop in 15–25% of untreated children
- ☞ Standard treatment of Kawasaki disease in the acute phase is with intravenous gamma globulin (2 g/kg single dose in a 10–12 h infusion) and aspirin (50–80 mg/kg daily divided into four doses)
- ☞ Polyarteritis nodosa (PAN) is characterized by necrotizing inflammatory changes in medium and/or small-sized arteries
- ☞ Unlike clinical diagnosis of HSP and Kawasaki disease, diagnosis of PAN needs histologic evidence of necrotizing vasculitis in medium or small-sized arteries or angiographic abnormalities (aneurysm or occlusion) as a mandatory criterion. So, difficult to diagnose in resource poor country

- ☞ The mainstay of therapy for PAN includes steroids and various immunosuppressive medications, depending on disease severity
- ☞ Cutaneous PAN is usually limited to skin with possible manifestations in the musculoskeletal system
- ☞ ANCA-associated vasculitis (AAV) includes microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), and eosinophilic granulomatosis with polyangiitis
- ☞ Two types of ANCA have been identified in patients with vasculitis
  1. ANCA directed against the neutrophil serine protease proteinase 3 (PR3), which cause a cytoplasmic immunofluorescence pattern (cytoplasmic ANCA) on ethanol fixed neutrophils and
  2. ANCA directed against the neutrophil enzyme myeloperoxidase (MPO), which result in a perinuclear immunofluorescence pattern (perinuclear ANCA)
- ☞ Granulomatous polyangiitis is primarily associated with PR3-ANCA, while microscopic polyangiitis is primarily associated with MPO-ANCA
- ☞ Takayasu arteritis is a disease that affects the aorta, its main branches, and the pulmonary arteries in which granulomatous vasculitis results in stenosis, occlusion, or aneurysms of affected vessels
- ☞ Takayasu arteritis can present as pulseless disease, asymmetric hypertension with encephalopathy
- ☞ Asthma, atopy, and eosinophilia with vasculitis syndrome—suspect Churg-Strauss syndrome
- ☞ Recurrent apthous oral ulcer with painful genital ulcers with ocular features—suspect Bechet's syndrome
- ☞ Infection induced vasculitis is a common mimicker of vasculitis for pediatric population.

SUGGESTED READINGS

1. Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. Lancet. 2006;368:404-18.
2. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet. 2002;360:1197-202.
3. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1-11.
4. Joshi VR, Mittal G. Vasculitis—Indian perspective. JAPI. 2006;54:12-4.
5. Kelley's TB of Rheumatology, 8th edition. WB Saunders & Co. 2008.
6. Khasnis A, Langford CA. Update on vasculitis. J Allergy Clin Immunol. 2009;123:1226-36.
7. Kussmaul A, Maier R. Ueber eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (Periarteritis nodosa). Deutsches Arch F Klin Med.1865; 66:484-518.
8. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum. 2007;56:1000-9.
9. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010;69:798-806.
10. Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, et al. EULAR/PRES endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis. 2006;65:936-41.
11. Peru H, Soylemezoglu O, Bakkaloglu SA, Elmas S, Bozkaya D, Elmaci AM, et al. Henoch-Schonlein purpura in childhood: clinical analysis of 254 cases over a 3-year period. Clin Rheumatol. 2008;27:1087-92.
12. Sarkar S, Mondal R, Nandi M, Ghosh A. Trends of childhood vasculitides in eastern India. Indian Pediatr. 2011;48:814.
13. Saulsbury FT. Henoch-Schonlein purpura in children. Report of 100 patients and review of the literature. Medicine (Baltimore). 1999;78:395-409.
14. Tse SM, Silverman ED, McCrindle BW, Yeung RS. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease. J Pediatr. 2002;140:450-5.

CHAPTER 119

Kawasaki Disease

Anju Gupta

INTRODUCTION

Kawasaki disease (KD) is an acute systemic medium vessel vasculitis with strong predilection to childhood. Since its first description in early 1960s by Dr Tomisaku Kawasaki, this disease continues to remain enigmatic. What makes this disease so are factors like our inability to identify an etiologic agent, absence of a specific diagnostic test in acute phase, and our inability to predict cardiac complications. Moreover, clinical features often appear transiently and the examining physician may not be able to see all the characteristic clinical features at a time. Now, this disease has been described worldwide with a distinct predilection for Japanese descent.

EPIDEMIOLOGY

Japan has a maximum incidence of KD with rates of 240/100,000 children less than 5 years. Korea and Taiwan have reported the next high incidences. Whereas, the incidence in the United States (20 per 100,000 children of less than 5 years) is static over the years, Japan has been reporting increasing incidence rates over the years. A distinct seasonal predilection is seen in extratropical Northern hemisphere with maximum cases seen in January to March with a nadir from August to October. However, a similar seasonal predilection is not consistently described in tropics.

ETIOLOGY

Etiology of KD remains elusive and likely involves an environmental agent in presence of certain genetic factors. A ubiquitous environmental agent has been implicated because of distinct seasonality, occurrence of epidemics, occurrence of rash-like in toxin mediated diseases, and efficacy of intravenous immunoglobulins (IVIg). Genetic factors also have been implicated because of strong racial predilection seen in Japanese descent.

PATHOGENESIS

Kawasaki disease is characterized by intensive T cell stimulation with activation of inflammatory cytokines and leukocyte recruitment. Activation of T cell may be responsible for Bacillus Calmette–Guerin (BCG) site activation seen so frequently in this disease. This leads to upregulation of proteolytic activity causing elastin degradation and vessel wall damage, which is responsible for characteristic coronary lesions seen in this disease.

CLINICAL FEATURES

Characteristic clinical features of KD include fever, polymorphous exanthem, bilateral conjunctival congestion, changes in extremities, changes in lips and oral cavity, and cervical adenopathy. Fever is typically high grade (>39°C) with an abrupt onset and responds transiently to antipyretics. Usually, fever persists for more than 5 days (median 11 days) and can persist for more than 3 weeks, if not treated. There is usually a diffuse erythematous maculopapular rash which usually appears within first 5 days of illness. Conjunctivitis is typically bilateral, nonexudative, and spares limbus (Fig. 1). Changes in extremities include diffuse nonpitting edema on the dorsum of hands and feet and characteristic periungual desquamation starting in late second or third week of illness (Figs 2 and 3). Perianal desquamation is also characteristic and usually precedes periungual desquamation (Fig. 4). Changes in lips and oral cavity include strawberry tongue (Fig. 5) and cracking of lips. Cervical adenopathy is usually single, unilateral, and nontender and involves anterior cervical chain.

Besides these clinical features described in American Heart Association criteria (Box 1), lots of other clinical features may be present and may help or confuse treating physician further. Irritability is usually extreme in infants to the extent that clinician may think of pyogenic meningitis.

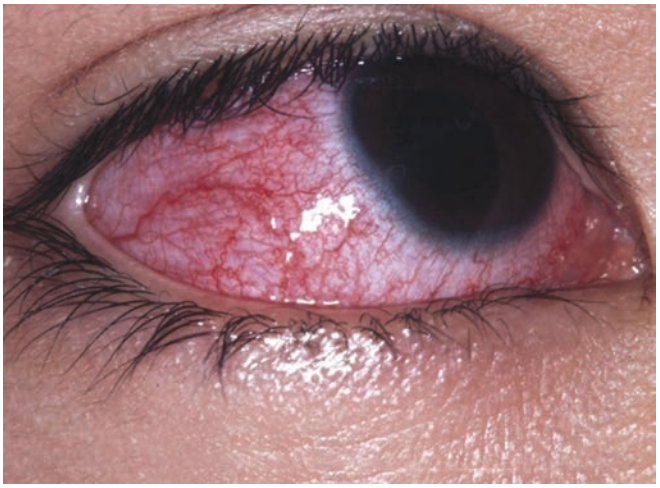


Fig. 1: Nonexudative conjunctivitis sparing limbus

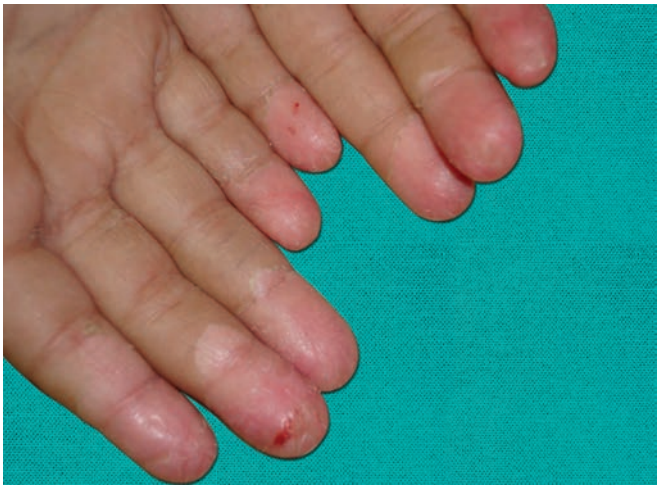


Fig. 2: Periungual desquamation in upper limb

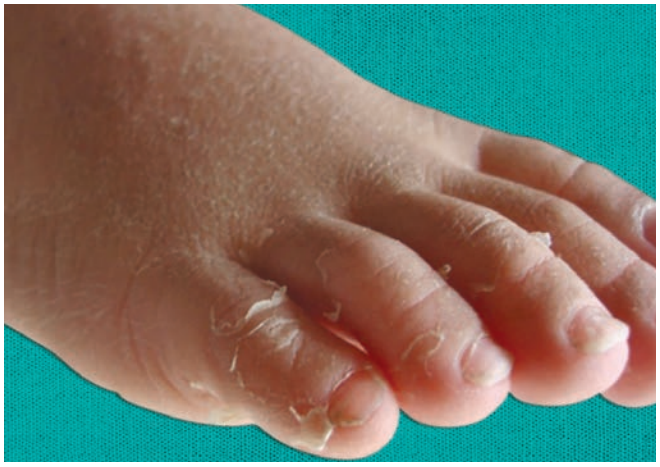


Fig. 3: Periungual desquamation in lower limb, which usually follows similar findings in upper limbs

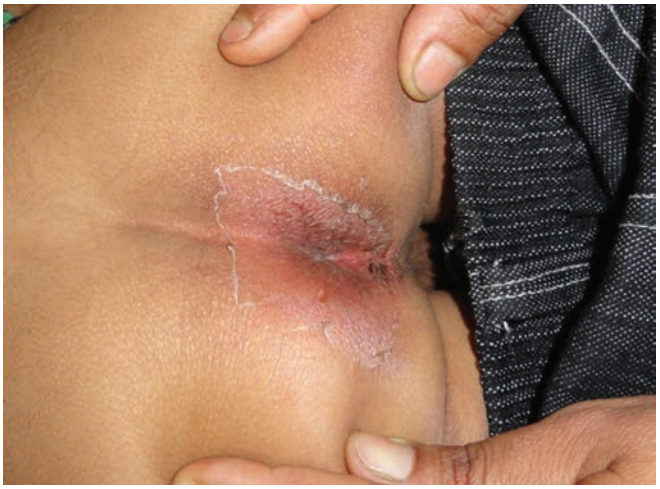


Fig. 4: Perianal desquamation

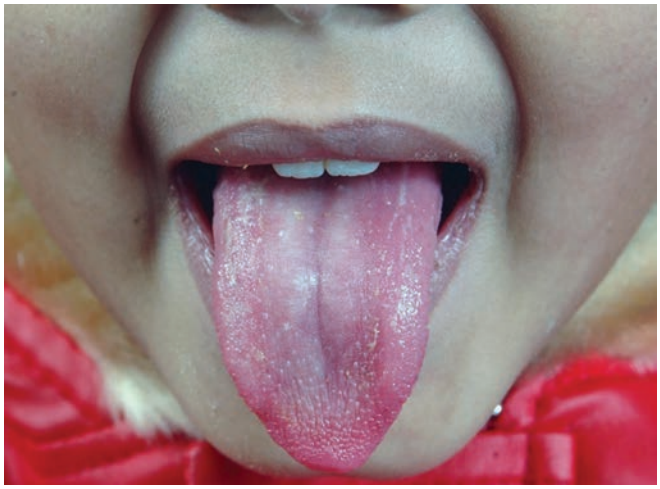


Fig. 5: Strawberry tongue

Box 1: Diagnostic criteria for Kawasaki disease

Fever (>39°C) for at least 5 days plus at least four of the following five diagnostic features

- Polymorphous exanthem
- Bilateral bulbar conjunctival injection without exudate
- Changes in lips and oral cavity: erythema, fissured cracked lips, strawberry tongue, or diffuse injection of oral and pharyngeal mucosae
- Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
- Changes in extremities:
  - Acute: erythema of palms and soles, edema of hands and feet
  - Subacute: periungual peeling of fingers and toes (in the second and third week) plus exclusion of other diseases with similar clinical features

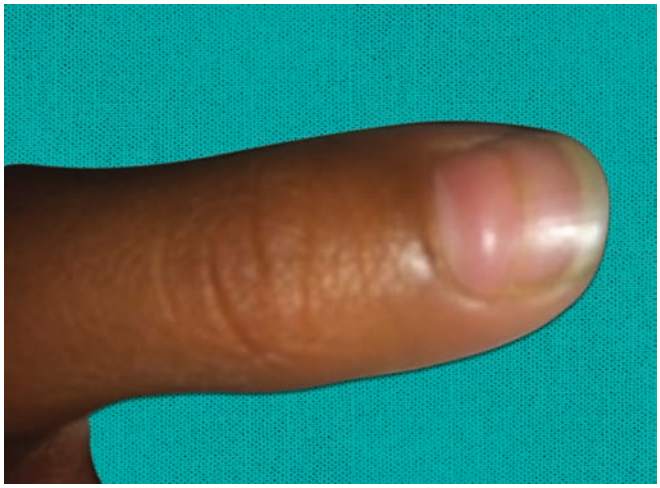


Fig. 6: Prominent Beau's lines

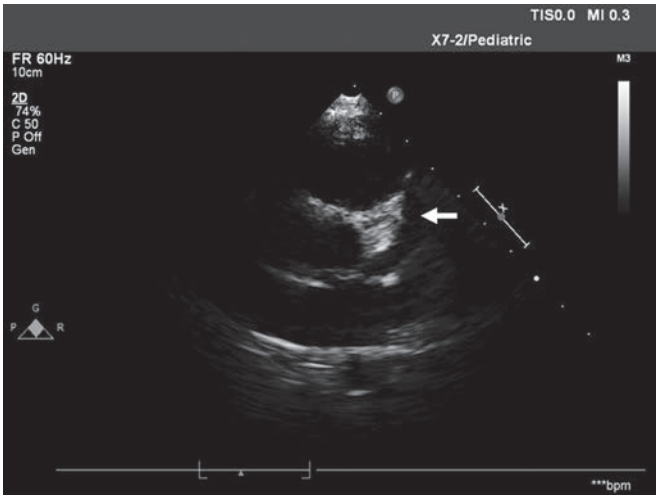


Fig. 7: Coronary aneurysms on echocardiography

Aseptic meningitis is common in KD and responds briskly to intravenous immunoglobulins (IVIG). We have seen significant joint manifestations in children with KD. These may include arthralgia and arthritis which could involve both large and small joints. Significant right hypochondriac pain can occur due to hydrops of gallbladder. Hepatic dysfunction with conjugated jaundice and transaminitis can lead to a diagnosis of viral hepatitis. Reactivation of BCG site with erythema and induration can be a helpful sign. Rarely, respiratory complications in the form of pulmonary nodules, interstitial infiltrates, pleural effusions, and pneumothorax can occur. Cranial nerve palsies, anterior uveitis, myocarditis, valvular regurgitation, and peripheral gangrene are other rarely described manifestations. Beau's lines are frequently seen in convalescent phase (Fig. 6).

INVESTIGATIONS

None of the investigations are diagnostic in acute phase of KD. Thrombocytosis which is described as characteristic feature of KD is not seen before the end of second week and hence, is not useful in making a decision regarding treatment. Acute phase is associated with various markers of inflammation which include neutrophilia, high erythrocyte sedimentation rate (ESR), high C-reactive protein (CRP), anemia, hypoalbuminemia, sterile pyuria (due to uretheritis), and transaminitis. Cerebrospinal fluid analysis may reveal pleocytosis. In children with arthritis, there may be synovial fluid pleocytosis. Thrombocytopenia has been described in a small minority of patients at onset and has been attributed to increased adherence of platelets to activated endothelium or to disseminated intravascular coagulation.

Echocardiography is an important tool and is usually done at baseline and then after 6–8 weeks of illness (Fig. 7). Another echocardiography may be needed in second week of illness in children who do not show response to IVIG. Coronary dilatation is described as Z scores of more than or equal to 2.5 for internal diameters for both left anterior descending and right coronary arteries. However, coronary dilatation is usually not seen in first week of illness. There could be other suggestive findings in echocardiography like perivascular brightness, lack of tapering of vessels, low ejection fraction, mitral regurgitation, and pericardial effusion. These findings may be useful in diagnosis especially in those infants where all the clinical features are not present (incomplete KD). A repeat echocardiography at 6–8 weeks of illness is useful in picking up coronary abnormalities and guiding further treatment.

DIFFERENTIAL DIAGNOSIS

Since the clinical features are relatively nonspecific, there are many differential diagnoses of KD (Box 2). These include viral infections (measles, adenovirus, enterovirus, Epstein-Barr virus), Stevens-Johnson syndrome, toxin mediated syndromes, scarlet fever, leptospirosis, and hypersensitivity reactions to drugs. Exudative pharyngitis, exudative conjunctivitis, discrete intraoral lesions, bullous or vesicular rash, and diffuse lymphadenopathy suggest another diagnosis. Scarlet fever usually is not associated with conjunctivitis and shows a brisk response to antibiotics. Visceral involvement and hypotension are frequent in toxin mediated syndromes.

Box 2: Differential diagnosis

- Viral infections (measles, adenovirus, enterovirus, Epstein-Barr virus)
- Stevens-Johnson syndrome
- Toxin mediated syndromes
- Scarlet fever
- Leptospirosis

Clinical Pearls

Think of another diagnosis in presence of:

- Exudative pharyngitis
- Exudative conjunctivitis
- Discrete intraoral lesions
- Bullous or vesicular rash
- Diffuse lymphadenopathy.

TREATMENT

Standard treatment of KD involves administration of IVIg and aspirin. It is better to wait for a day or two if one is seeing the child for the first time on day 4 or 5 of illness and clinical features are not clear-cut. This duration helps in evolution of disease signs as well as in evaluation of response to empirical antibiotics.

Intravenous immunoglobulins: IVIg is usually given at a dose of 2 g/kg as a single dose infusion. Single dose infusion has been found to be more effective than divided dose infusions. Most patients show a brisk response to IVIg with defervescence and general well-being. Inflammatory parameters also show gradual improvement. Erythrocyte sedimentation rate is not useful in evaluating response as high ESR continues to be seen after administration of IVIg.

However, 10–15% patients show IVIg resistance which is described as persistence or recrudescence of fever after 36 hours of completion of IVIg infusion. This is important to identify as this is the most important clinical feature associated with high risk of coronary abnormalities (Box 3). One or two fever spikes during or immediately after IVIg infusion are common and should not be labeled as IVIg resistance.

Intravenous immunoglobulin therapy has been shown to reduce the risk of coronary abnormalities from 25 to 3–5%, if given within first 10 days of illness. Beyond the first 10 days, the benefit is not so great; however, most clinicians would give IVIg even beyond 10 days if the child is febrile and continues to have high inflammatory parameters. It has also been seen that the children who receive IVIg within first 5 days of illness are more likely to need additional therapy. Whether this is due to more inflammation per se and hence, more severe disease is not very clear.

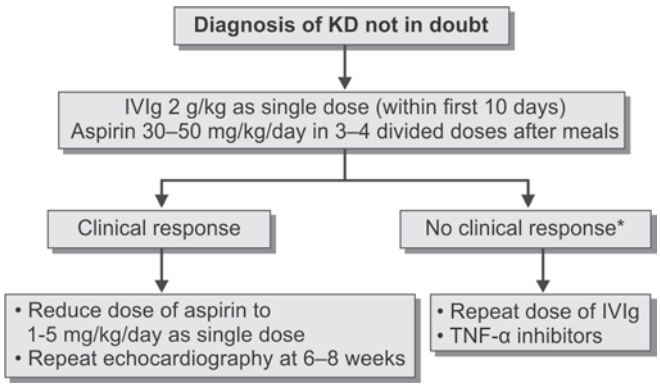
Aspirin: aspirin is routinely used as first line therapy along with IVIG. Use of aspirin has not been shown either to reduce the coronary risk or the time to defervescence. Usually anti-inflammatory doses in the range of 80–100 mg/kg/day are used till subsidence of inflammation. However, because of significant gastrointestinal toxicity, lower doses in the range of 30–50 mg/kg/day are being used frequently nowadays. Once the child is afebrile and inflammatory parameters (CRP) show declining trend, dose of aspirin can be reduced to antiplatelet doses (1–5 mg/kg/day). Aspirin is discontinued if the follow-up echocardiography at 6–8 weeks is normal. In all other children, aspirin may be needed for longer duration.

Box 3: Risk factors for coronary abnormalities

- Young age of less than 6 months
- Age more than 9 years
- Male sex
- Asian or Pacific Islander race
- Hispanic ethnicity
- Markers of severe inflammation (high neutrophils, low platelets, low sodium, high C-reactive protein, and transaminitis)
- Intravenous immunoglobulin resistance

ALGORITHM 1

Management of Kawasaki disease



IVIG, intravenous immunoglobulins; TNF-α, tumor necrosis factor-α.

*Means reappearance or continuation of fever after 36 h of completion of IVIg infusion.

About 85% children show response to IVIg and aspirin (Algorithm 1). Rest of the children may need additional therapy. There is no consensus on the second line treatment in KD; some centers use an additional dose of IVIg whereas others use tumor necrosis factor-α inhibitors. Of late, there has been resurgence in usage of corticosteroids in IVIg resistant KD despite initial reports showing contradictory results.

PROGNOSIS

In the pre-IVIg era, about 25% children would go on to develop coronary abnormalities. Use of IVIg has reduced this risk to 3–5%. Coronary abnormalities can persist as ectasia or aneurysms which can be saccular, fusiform, or segmental. These aneurysms carry a significant risk of rupture, thrombosis and stenosis, and predispose the individual to ischemic events. Hence, all patients who develop coronary abnormalities should continue to be on lifelong follow-up programs. These children also need long-term aspirin in antiplatelet doses. Those with giant aneurysms (>8 mm or Z scores >4) have higher risk of complications. Addition of warfarin or heparin to aspirin in such patients has been shown to reduce risk of thrombosis and lead to better event-free survival. Peripheral artery involvement can occur in KD, however, is uncommon in the absence of coronary artery involvement.

CONCLUSION

Kawasaki disease is an acute systemic vasculitis which can mimic a myriad of childhood illnesses. Importance of timely recognition and management is important as it reduces the risk of coronary complications to a significant extent. No single diagnostic test is useful in the acute phase. Intravenous immunoglobulins along with aspirin are the standard of care, and most patients respond briskly to this treatment.

KEY POINTS

- ☞ Diagnosis of Kawasaki disease in acute phase is based on clinical findings and supportive investigations. No single investigation helps in clinching the diagnosis in this phase
- ☞ Coronary involvement is the most sinister long-term complication and seen more frequently in infancy
- ☞ Intravenous immunoglobulin therapy is the standard of care and has been shown to significantly reduce the risk of coronary complications
- ☞ Despite timely intravenous immunoglobulin therapy within 10 days, 3–5% children would develop coronary involvement. Whereas, diffuse coronary dilatation and ectasia is more likely to show regression by remodeling, the same is not frequently seen in giant aneurysms. These aneurysms carry a high likelihood of thrombosis, stenosis, calcification, and rupture.

SUGGESTED READINGS

1. Cheung M, Burgner D. Kawasaki disease: the importance of prompt recognition and early referral. Aus Fam Physician. 2013;42:473-6.
2. Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. Arch Dis Child. 2014;99(1):74-83.
3. Dajani AS, Bisno AL, Chung KJ, Durack DT, Gerber MA, Kaplan EL, et al. Committee on rheumatic fever, endocarditis, and Kawasaki disease of the American Heart Associations Council on Cardiovascular Disease in the Young Diagnostic Guidelines for Kawasaki disease. Am J Dis Child. 1990;144:1218-9.
4. Rowley AH, Shulman ST. Kawasaki syndrome. Pediatr Clin North Am. 1999;46:313-29.
5. Son MBF, Newburger JW. Kawasaki disease. Pediatrics in Review. 2013;34; 151-62.
6. Yim D, Curtis N, Cheung M, Burgner D. An update on Kawasaki disease II: clinical features, diagnosis, treatment and outcomes. J Paediatrics and Child Health. 2013;49:614-23.
7. Zhang T, Yanagawa H, Oki I, Nakamura Y, Yashiro M, Ojima T, et al. Factors related to cardiac sequelae of Kawasaki disease. Eur J Pediatr. 1999;158:694-7.

CHAPTER 120

Henoch-Schönlein Purpura

Anand P Rao

INTRODUCTION

Henoch-Schönlein purpura (HSP) is the most common childhood vasculitis with an annual incidence of 20.4 per 100,000 population less than 17 years. It is characterized by leukocytoclastic vasculitis histopathologically. It commonly affects children between 5 and 15 years of age. About 50% cases are reported in less than 5 years and 75% cases in less than 10 years of age. It occurs most frequently between the ages of 3 and 15 years and is slightly more common in boys than in girls (1.5:1).

It commonly affects the small vessels of the skin, joints, gastrointestinal tract, and kidneys. It is generally a self-limited condition, but rarely can be associated with complicated chronic course.

ETIOPATHOGENESIS

Henoch-Schönlein purpura is thought to be an immunoglobulin A (IgA) mediated dysregulated immune process with probable involvement of alternate complement pathway caused by as yet unknown etiological agent.

CLINICAL MANIFESTATIONS

Constitutional: it may be associated with low grade fever and malaise.

Cutaneous: predominant lower limb purpura with involvement of buttocks, upper limbs, face, and very rarely, the trunk is the classical feature of this condition. The rashes can range from petechiae to ecchymosis to hemorrhagic bullae. Edema of the dorsal surfaces of feet, hands, scrotum, scalp, and face may sometimes be seen. Presence of palpable purpura is a sine qua non for the diagnosis of HSP (Fig. 1).

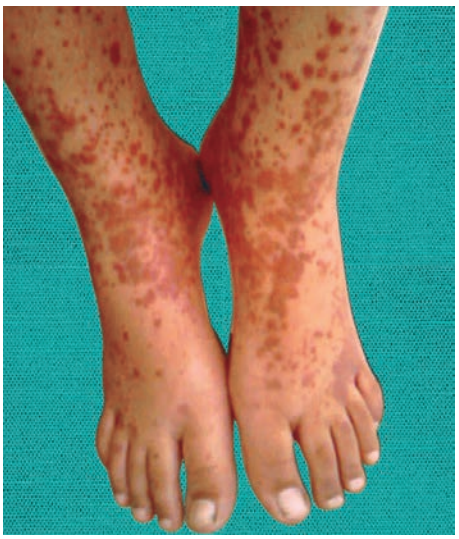


Fig. 1: Predominant lower purpura in an adolescent girl

Gastrointestinal manifestations: it is seen in about 70% of patients. It can precede the purpura in about 14–46% of the patients but mostly happens in the first week of the onset of the disease. Vasculitis of the bowel wall can lead to intussusception, gangrene, and perforation of the bowel wall.

Clinical Pearl

- Please keep in mind Henoch-Schönlein purpura in any child who presents with acute abdominal pain and look for rashes over the lower limbs before involving the surgeon.

Genitourinary involvement: it more often than not determines the outcome of the disease. The manifestations can range from microscopic hematuria and mild proteinuria to nephrotic syndrome, acute nephritic syndrome, hypertension, or renal failure. The renal manifestations have been reported to be seen in about 40% of patients and about 1–3% of the patient's progress to an end-stage renal disease (ESRD). Acute pain in

the scrotum can sometimes bring the child to medical attention and might indicate testicular ischemia.

Clinical Pearl

- The nephritis in Henoch-Schönlein purpura can be silent. It is important to look for it by checking the blood pressure, urine routine, and microscopy weekly for at least 3 months from onset of disease. Serum creatinine should be checked at baseline.

Arthritis: large joints like knee, ankle, wrist, and elbow seem to be involved in this condition. It may precede the rashes occasionally. It tends to be transient and may last from a few days to a few weeks. Arthritis rarely goes on for months.

The diagnosis of HSP is based on the classification criteria proposed by EULAR/PRINTO/PRES.

Purpura (mandatory criterion): purpura (commonly palpable and in crops) or petechiae, with lower limb predominance. At least one of the following criteria is required for the diagnosis of HSP:

- Abdominal pain: diffuse abdominal colicky pain with acute onset assessed by history and physical examination. It may include intussusception and gastrointestinal bleeding
- Histopathology: typically leukocytoclastic vasculitis with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits
- Arthritis or arthralgia: arthritis of acute onset defined as joint swelling or joint pain with limitation of motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation of motion
- Renal involvement: proteinuria more than 0.3 g/24 hours or more than 20 mg/mmol of urine albumin/creatinine ratio on a spot morning sample. Hematuria or red blood cell casts: more than 5 red blood cells/high power field or red blood cells.

The following factors that are thought to be associated with severe renal disease:

- Age more than 7 years of age
- Severe gastrointestinal disease as manifested by severe abdominal pain or bloody stools
- Persistent or recurrent skin disease.

The cumulative proportion of patients with HSP developing HSP nephritis by 1 month is 85%, by 2 months is 90%, and by 6 months is 97%, respectively. It has been suggested that all patients should have urine routine microscopy examination once a week for 3 months and for 6 months in those with evidence of nephritis or recurrent purpura.

INVESTIGATIONS

- Complete blood count might reveal mild leukocytosis and thrombocytosis
- Mild elevation of erythrocyte sedimentation rate is expected
- Urine routine microscopy might reveal hematuria/proteinuria
- Serum creatinine might be increased in cases of nephritis
- Skin biopsy is indicated in incomplete or atypical HSP. It reveals leukocytoclastic vasculitis involving dermal capillaries and postcapillary venules with IgA deposition
- Imaging like ultrasonography might be required in patients with severe abdominal pain to rule out intussusception.

Clinical Pearl

- Serum immunoglobulin A levels are not useful for the diagnosis of Henoch-Schönlein purpura (HSP) as they are elevated only in 50% of patients with HSP.

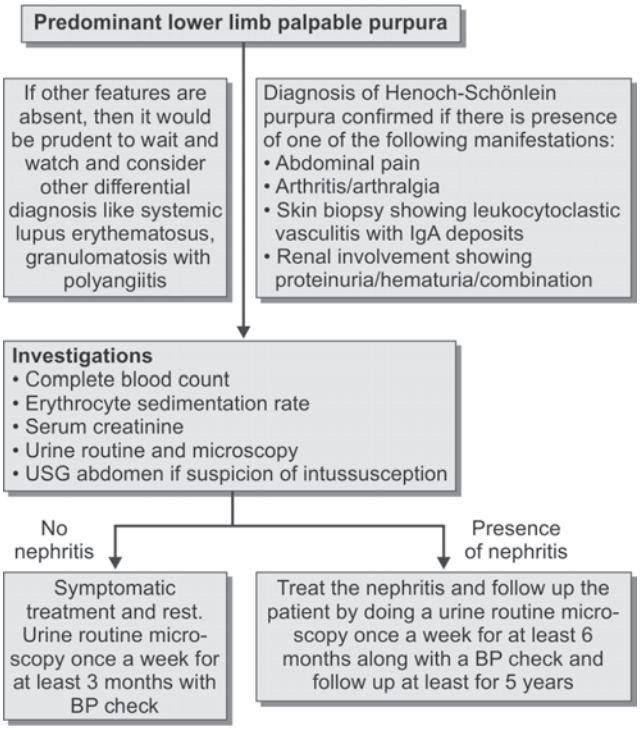
TREATMENT

- Rest
- Hydration
- Paracetamol/nonsteroidal anti-inflammatory drugs for analgesia
- Steroids indicated in the following conditions:
  - Orchitis
  - Severe gastrointestinal disease and hemorrhage
  - Henoch-Schönlein purpura nephritis (prophylactic steroid therapy has no role in preventing onset of nephritis).

The steroid regimen recommended for severe extrarenal manifestations and renal manifestations of HSP is 1 mg/kg for 2 weeks followed by gradual taper over the subsequent 2 weeks time. The diagnosis and management of HSP has been outlined in algorithm 1.

ALGORITHM 1

Diagnosis and management of Henoch-Schönlein purpura



IgA, immunoglobulin A; USG, ultrasonography; BP, blood pressure.

COURSE

Two-thirds of patients get better by 4 weeks. But, one-third of patients can have recurrences, commonly manifesting as rash and abdominal pain and tends to be milder than the previous one. Prognostic features which portend poor outcome are:

- Severe gastrointestinal manifestations
- Frequent skin rashes
- Severe renal manifestation at onset.

Less than 5% of patients progress to ESRD. Those with clinical nephritis should be closely followed up for at least 5 years.

KEY POINTS

- ☞ Henoch-Schönlein purpura is a usually benign small vessel vasculitis involving skin, joint, and kidneys
- ☞ The presence of severe gastrointestinal and renal involvement would indicate worse prognosis
- ☞ Skin biopsy is indicated when the diagnosis is in doubt
- ☞ Steroids are recommended when there is evidence of gastrointestinal or genitourinary involvement
- ☞ Weekly urine dipstick for the first 3 months useful to pick up patients with indolent nephritis.

SUGGESTED READINGS

1. Jauhola O, Ronkainen J, Koskimies O, Ala-Houhala M, Arikoski P, H ltt T, et al. Clinical course of extrarenal symptoms in HenochSch nlein purpura: a 6-month prospective study. Arch Dis Child. 2010;95:871-6.
2. Jauhola O, Ronkainen J, Koskimies O, Ala-Houhala M, Arikoski P, H ltt T, et al. Renal manifestations of Henoch-Sch nlein purpura in a 6-month prospective study of 223 children. Arch Dis Child. 2010;95:877-82.
3. Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schonlein purpura with normal or minimal urinary findings: a systematic review. Arch Dis Child. 2005;90:916-20.
4. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch Sch nlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara; 2008. Part II: Final classification criteria.
5. Saulsbury FT. Henoch-Schonlein purpura in children. Report of 100 patients and review of the literature. Medicine (Baltimore). 1999;78:395-409.

CHAPTER 121

Systemic Lupus Erythematosus

Suma Balan

INTRODUCTION

Acquired connective tissue disorders in children are a group of conditions among which the most common is systemic lupus erythematosus (SLE). This is a disease of immune dysregulation where the immune system appears to be activated with the formation of autoantibodies to a wide variety of antinuclear antigens and the formation of immune complexes which can affect any organ, thus, creating a multisystem illness which can damage any organ in the body if left untreated long term.

EPIDEMIOLOGY

Worldwide SLE has an incidence between 20–150/100,000. Most prevalence studies come from developed world literature where comparing the incidence between various ethnic minorities shows a significantly higher incidence in Asian/Afro-Caribbean and Oriental population compared to the white/Caucasian population. The incidence in children has been quoted between 4–250/100,000 depending upon race and location.

Approximately 20% of SLE commences in childhood, before 18 years of age. The most common age of onset is during teenage coinciding with puberty; however, it can occur at any age. It is very uncommon to present below 5 years of age. In prepubertal children, the boy:girl ratio is almost equal (4:3), but postpubertal children show a significant girl to boy dominance of 4:1.

There are no clear described prevalence figures for SLE in the Indian population.

DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Like tuberculosis (TB) and syphilis, SLE is considered as one of the great mimics in medicine owing to its widely variable presentation, multisystem involvement, and the diagnosis, especially in the absence of the classic malar rash can be very confusing. A series of clinical and laboratory criteria have been set out with mainly toward standardization for research purposes, but generally the presence in four criteria even over a longitudinal manner contribute toward making a diagnosis. They have greater than 95% sensitivity and specificity toward the diagnosis; however, it is equally essential that obsessive use of the criteria alone is not essential toward making the diagnosis (Table 1).

TABLE 1: Updated Revised criteria for classification of SLE

Criterion	Definition
Malar rash	Flat or raised erythema over the malar eminences, spares the nasolabial folds
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
Photo-sensitivity	Skin rash following sunlight exposure, by history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis—convincing history of pleuritic pain or rub on auscultation or evidence of pleural effusion or Pericarditis—documented by electrocardiogram, echocardiogram, or rub
Renal disorder	Persistent proteinuria greater than 0.5 g/day or Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neuro-logical disorder	Seizures in the absence of offending drugs or metabolic derangements or Psychosis in the absence of offending drugs or metabolic derangements

Continued

Continued

Criterion	Definition
Hemato-logical disorder	Hemolytic anemia with reticulocytosis or Leukopenia <4,000/mm^3 on two or more occasions, or Lymphopenia <1,500/mm^3 on two or more occasions, or Thrombocytopenia <100,000/mm^3
Immuno-logical disorder	Antibody to native deoxyribonucleic acid, or Antibody to Sm protein, or Antiphospholipid antibodies—either anticardiolipin antibodies, presence of the lupus anticoagulant, or false positive serological test for syphilis
Antinuclear antibody	Presence of antinuclear antibody by immunofluorescence or an equivalent assay

CLINICAL PRESENTATION

Systemic lupus erythematosus can present as a chronic slowly progressing low grade illness with troublesome skin, joint and constitutional symptoms, as a subacute illness with internal organ involvement or even as an acute florid illness with catastrophic presentations like renal failure, strokes, major thrombosis, etc.

As it is capable of involving every organ, the clinical features are myriad and difficult to outline all possible presentations. There are several children who are initially diagnosed as Henoch-Schonlein purpura or idiopathic thrombocytopenic purpura who turn out to have SLE. Again, children with existing autoimmune disease as in autoimmune hypothyroidism or autoimmune hemolytic anemia might over the course of time develop a second autoimmune illness like SLE.

WORKUP

Once SLE is suspected, the following multisystem assessment should be carried out.

- Skin: a biopsy can often be confirmatory especially if a second sample is also sent for immunofluorescence
- Eyes: retinopathy and vasculitis of the retina can be frequently associated and a professional ophthalmological examination must be undertaken in all children
- Blood: check for hematological manifestations. Baseline clotting tests with prolongation of activated partial thromboplastin time (APTT) are strongly suggestive of the presence of antiphospholipid antibodies. A differential diagnosis for a child presenting with constitutional symptoms and pancytopenia/bicytopenia is SLE and the presence of lymphopenia on the white blood cell count is a clue as opposed to neutropenia in childhood hematological malignancies
- Renal: check serum albumin and a routine urine examination in all children—the presence of active urinary sediment is indicative of nephritis. If edema, hypertension, oliguria, etc. are present, be alert to a proliferative nephritis and work-up has to be prioritized toward a biopsy to aid early treatment
- Musculoskeletal system: often more symptoms and signs and rarely erosive arthritis. Muscle enzymes may be elevated
- Central nervous system: observe mood and sleep patterns and be alert to cognitive changes or seizures. Baseline scans, electroencephalogram are not warranted unless clinical concern exists
- Pulmonary: observe clinical changes
- A chest X-ray will reveal the presence of pleural effusion/pneumonitis, etc. One needs to be cautious to distinguish between active disease and secondary infection that can present with similar signs. A serum C-reactive protein is rarely elevated in active SLE and is often a good marker to distinguish active disease and intercurrent sepsis. Tuberculosis can present with similar features and prior to commencement of immunosuppressive therapy, it is recommended to check a Mantoux and other tests as required—lymph node biopsy if significant

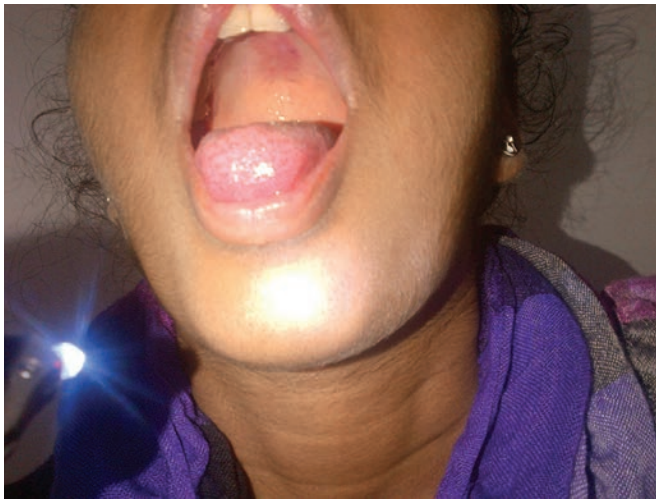


Fig. 1: Oral ulcer on hard palate in systemic lupus erythematosus

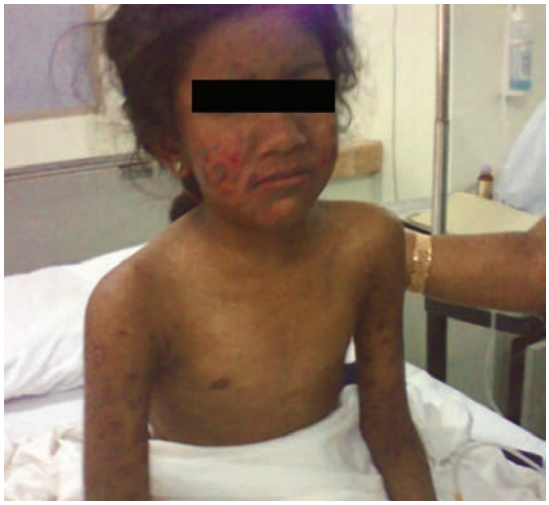


Fig. 2: Extensive rash malar and on extremities in a child with systemic lupus erythematosus

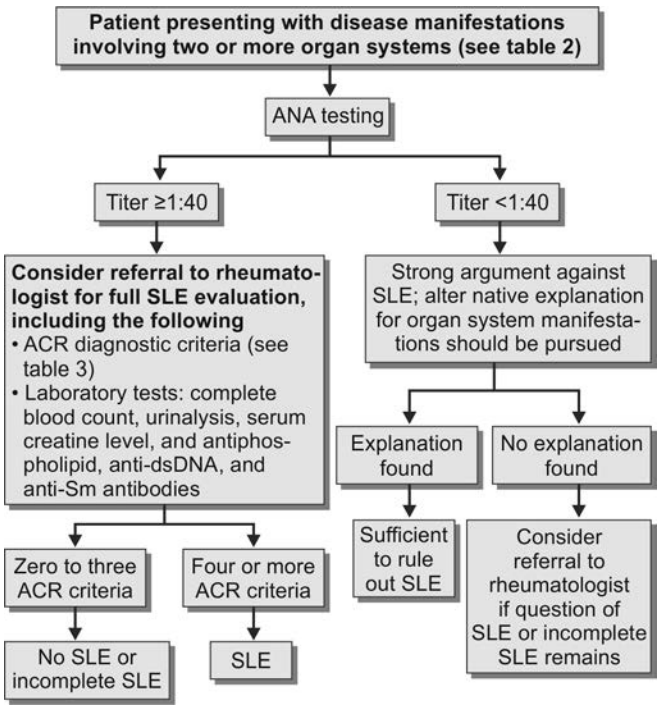
TABLE 2: The varied clinical manifestations of SLE

System	Clinical feature
Constitutional	• Fever—low grade/high grade • Weight loss • Malaise
Cutaneous	• Rashes—malar/discoid/vasculitis • Photosensitivity • Oral ulcers (oral, nasal) • Alopecia
Musculoskeletal	• Polyarthralgia/arthritis (nonerosive) • Tenosynovitis • Myopathy • Avascular necrosis
Vascular	• Lupus crisis • Raynaud's • Livedo reticularis
Cardiac	• Pericarditis • Myocarditis • Endocarditis • Coronary arteritis
Pulmonary	• Pleuritis/effusion • Pneumonitis • Pulmonary hemorrhage
GI manifestations	• Esophagus—dysphagia/reflux • Stomach—gastritis, pernicious anemia (rare) • Small bowel—mesenteric vasculitis • Intestinal pseudo—obstruction (enteric nervous system dysfunction) • Malabsorption—antigliadin antibodies • Peritonitis/ascites • Large bowel—enteritis • Vasculitic ulcers of rectum • Liver—deranged LFTs • Autoimmune hepatitis • Hepatic vein thrombosis • Biliary tract—sclerosing cholangitis • Acalculous cholecystitis • Autoimmune cholangiopathy • Pancreatitis—rare, but can be fulminant
Immunological—increased susceptibility to infection	• Functional asplenia • Multiple defects—macrophage/neutrophil/T cell/B cell/complement
Renal	• Nephritis classified as per WHO/ISKDC classification • Renal vein thrombosis
Neuropsychiatric	• Aseptic meningitis • Headache • Seizures • Cerebrovascular disease • Movement disorder • Acute confusional state • Anxiety disorder • Mood disorder • Psychosis • Guillain—Barre syndrome • Acute transverse myelitis • Mono/poly/cranial neuropathy • Plexopathy
Hematological	• Anemia—hemolytic/macrocytic • Leukopenia—often lymphopenia • Occasionally neutropenia • Thrombocytopenia • Antiphospholipid antibodies

LFTs, liver function tests; WHO, World Health Organization; ISKDC, International Study of Kidney Disease of Children.

ALGORITHM 1

How to interpret ANA positivity



SLE, systemic lupus erythematosus; ANA, antinuclear antibody; ACR, American College of Radiology; dsDNA, double stranded deoxyribonucleic acid.

lymphadenopathy, etc. to rule out the presence of latent or active TB

- In the presence of significant pneumonitis or pulmonary vasculitis, a high resolution computed tomography scan of the chest may be required to delineate the detailed changes present. Children can present with acute respiratory deterioration, hypoxia, and diffuse alveolar hemorrhage must be suspected if ground glass picture of lungs noted. Hemoptysis may not be present externally and the child can develop acute pallor in this setting. Equally, a pulmonary embolism can also cause acute respiratory deterioration and hypoxia
- Central nervous system: pericardial effusion at presentation is not uncommon. Myocarditis due to SLE carries a grave prognosis if not recognized early and treated with aggressive immunosuppression. Endocarditis with large valve deposits (traditionally known as Libman-Sacks endocarditis) is rare. The author has seen two children with coronary arterial dilatations and aneurysms akin to the picture in Kawasaki who presented with cardiac failure at presentation
- Abdomen: SLE can present with a picture of hepatitis, hepatosplenomegaly and ascites, abdominal lymphadenopathy, etc. Acute abdominal pain in SLE needs attention as can be rarely due to pancreatitis, mesenteric vasculitis, or mesenteric thrombosis or even renal vein thrombosis and these conditions need to be addressed very urgently.

Clinical Pearl

- Along with making the diagnosis, describing the extent of involvement is also important

INVESTIGATIONS

- Complete blood count: anemia—usually direct Coombs test/cold agglutinin positive
- White blood cell: leukopenia with lymphopenia
- A child with SLE presenting with fever and a neutrophilic count must be assessed for the presence of secondary infection
- Platelet counts (often reduced) rarely below 50,000/mm^3
- When significant pancytopenia is present with high fever, always consider the possibility of macrophage activation syndrome due to uncontrolled inflammation from active disease and look for the necessary parameters in biochemical testing and bone marrow examination may be helpful
- Inflammatory markers: erythrocyte sedimentation rate often elevated significantly in disease activity. C-reactive protein is rarely elevated in active lupus disease—unless in presence of active pleural and pericardial effusions or synovitis with effusions. C-reactive protein can be considered a good marker for detecting secondary bacterial infection in a child with SLE, a condition that needs to be addressed urgently
- Baseline renal function tests: liver function tests must be done in every patient. A low serum albumin can be part of active inflammation as well as indicate proliferative nephritis or hepatic disease
- A detailed urine routine examination with examination of the urinary sediment has to be done for every patient. The presence of proteinuria/active sediment should lead to quantification of proteinuria by 24 hours urinary protein estimation or a random spot urinary protein/creatinine ratio.

Immunological Testing

Antinuclear Antibody Test

The antinuclear antibody (ANA) screening is advised by immunofluorescence rather than the more commonly or cheaper mode of enzyme-linked immunosorbent assay (ELISA) testing. Immunofluorescence yields a titer and has both qualitative and quantitative enumeration with less false positivity and greater reliability than the ELISA test. It is important to know that presence of ANA positivity does not imply SLE—the ANA can be falsely positive in normal individuals, common infective, and other inflammatory conditions as well as other autoimmune diseases. The clinical strength of a suspicion of SLE or the pretest probability of a patient to have lupus makes the positive ANA more diagnostic. However, a negative ANA (by immunofluorescence) with today's techniques is more than enough to rule out a diagnosis of lupus in the vast majority of patients. No single titer is diagnostic though titers of 1:1,280 or greater are less associated with false positives.

Clinical Pearls

- All that is antinuclear antibody positive is not systemic lupus erythematosus
- The pretest probability (clinical suspicion) increases the diagnostic yield of the immunological testing
- Antinuclear antibody screen is for diagnosis and does not need repeating.

If ANA is positive, the serum complements have to be estimated as hypocomplementemia is a feature of disease activity. The anti-double stranded deoxyribonucleic acid (anti-dsDNA) is the most common antibody associated with SLE and can be estimated qualitatively by immunofluorescence and quantitatively by ELISA. A quantitative estimation is recommended since these levels and those of serum complements are used for disease monitoring. The ANA profile estimates the presence of other extractable antinuclear antibodies like the ribonucleoproteins (anti-RNP), the Sm and the Ro (anti-SSA), and La (anti-SSB) and antihistone levels. Many of these antibodies remain positive and are used more for diagnosis rather than monitoring, so they need not be repeated. Various antibodies are related to system manifestations in SLE e.g., anti-dSDNA and Sm for nephritis and anti-RNP for neuropsychiatric disease.

All patients suspected/diagnosed to have SLE should have their antiphospholipid antibody testing done. The presence of a prolonged APTT/Prothrombin time gives a clue to the presence of these antibodies. The serum levels of anticardiolipin-immunoglobulin (Ig) G and IgM, the lupus anticoagulant and the anti-β-lipoprotein 1 (IgG and IgM) are the ones tested.

Tissue Diagnosis

Skin biopsy can be done to make the diagnosis—the histopathological appearances are characteristic as well as immunofluorescence showing "full-house" deposition of IgG/IgM/IgA/C3/C1q.

Lymph node biopsy may pick up Kikuchi-like changes or a paracortical hyperplasia. Depending on the clinical presentation, the presentation of a significant lymphadenopathy in the background of a pyrexia of unknown origin presentation may necessitate a lymph node biopsy to rule out differentials like TB or lymphoma.

Renal Biopsy

A renal biopsy with histologic, immunofluorescent, and electron micrographic analysis (where available) is necessary to classify the histologic type of renal disease. In our country, electron microscopy is very expensive with very limited availability, hence, not routinely requested.

Renal biopsy is rarely done to make a diagnosis of SLE or lupus nephritis which is often already decided by this time;

however, it is to ascertain the class of nephritis which can then guide the level of treatment.

The International Society of Nephrology and the Renal Pathology Society have revised the original World Health Organization classification of renal biopsy findings in SLE into six different classes.

- Class 1 is generally considered minimal change and needs no treatment
- Class 2 is mesangioproliferative and needs no additional treatment to steroids for a few months as would likely be used for background systemic disease
- Class 3 (focal proliferative) and 4 (diffuse proliferative) are proliferative and the most common presentations. This class of patients commonly present with proteinuria/nephritis, hematuria, hypertension, and some azotemia. Patients may change from one class to another either before or during treatment. These classes of patients are meant to be treated aggressively to recruit back as many nephrons to normal activity and degree of reversibility makes timely and appropriately aggressive therapy very important in these patients
- Class 5 is called membranous nephropathy and often presents as a nephrotic syndrome with the ongoing issues of anasarca. It can also be associated with proliferation which indicates aggressive management compared to pure membranous change which is controlled by antiedma measures and lower levels of immunosuppression
- Class 6 or advanced glomerular sclerosis when >90% of glomeruli are sclerosed, dictates poor renal prognosis and need for renal replacement therapy and a transplant.

TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

The treatment of SLE can be divided into:

1. General measures
2. Specific measures.

General Measures

- Use of sunscreen of sun protection factor 30+ to exposed body areas when going out in sun
- Ensuring activity and exercise and preventative measures toward good cardiovascular health
- Maintenance of weight and body mass index in healthy zone
- Intake of nutritious healthy varied diet unless specific restriction advised
- Medication compliance
- Regular follow-up as advised
- Hydroxychloroquine is now recommended to be continued indefinitely for all children with SLE to improve cardiovascular health and stabilization of antiphospholipid antibodies.

Specific Measures

The pharmacological management depends on level of disease activity and severity of internal organ involvement.

Mild lupus: largely characterized by musculoskeletal symptoms, and signs, mild systemic symptoms and mild hematological manifestations. A combination of low dose steroids and hydroxychloroquine (up to 6 mg/kg/day) may be all that is required.

Moderate lupus: some systemic symptoms, moderate degree of hematological, and some internal organ affectation. Moderate dose of steroids 0.5–1 g/kg/day weaned slowly over 3–6 months with hydroxychloroquine and often second line agents like methotrexate/azathioprine may be needed.

Severe lupus: with severe internal organ involvement, lupus nephritis, neuropsychiatric manifestations, macrophage activation syndrome, etc. are seen. High dose pulsed intravenous steroids (30 mg/kg methylprednisolone to a maximum dose of 1 g/day for 3 days) followed by high dose oral steroids—1–2 mg/kg/day initially in divided doses moving to single dose over 2 weeks and then a very slow wean is essential in the management of these patients. After appropriate assessment, there is a need for early consideration of a secondary agent in the form of mycofenolate mofetil or intravenous cyclophosphamide (intravenous pulse/month for 6 months). In nonrenal systemic severe lupus like neuropsychiatric/lung etc., cyclophosphamide has better results than mycophenolate mofetil.

Catastrophic lupus; e.g., pancreatitis, diffuse alveolar hemorrhage, severe neuropsychiatric manifestation, gangrene, etc.—high dose steroids intravenous cyclophosphamide have to be commenced early. Intravenous immunoglobulin 2 g/kg over 1 day, 2 days in divided doses or divided over 5 days has also been very helpful in serious emergencies with SLE.

Overall, the management is targeted toward seriousness of disease manifestations and balanced between controling active disease, preventing organ damage due to disease and damage, and morbidity due to treatment itself. All medications used in SLE have significant potential toxicity and administration and care should be under the supervision of a rheumatologist. Currently, the management of SLE solely with long duration of systemic steroids alone is discouraged due to problems with long-term steroid usage. Rituximab, an anti-CD20, monoclonal antibody is gaining preference in the management of refractory or resistant manifestations of SLE and may become part of the primary protocol for the management of proliferative lupus nephritis in the future.

Counseling

Counseling the family and the patient about the diagnosis of SLE is very important. The family and patient need to understand that it is a chronic lifelong disease. However, there can be periods of activity and inactivity and inactive periods can often last very long durations. Hydroxychloroquine is now recommended for indefinite use (and 6–12 monthly eye assessments with Humphrey Field Analyzer assessments are very important). Along with the medication, the need for regular follow-up and disease monitoring is very important. Pregnancy and fertility are specific areas that need very careful counseling and a rheumatologist has to remain part of the loop

from the advice of planning pregnancy through the pregnancy and delivery. Medications have to be explained with awareness of potential side effects. The relationship between the rheumatologist and the patient and family is very important to the patients overall improvement and well-being.

KEY POINTS

- ☞ Between 15–20% of systemic lupus erythematosus commences in childhood
- ☞ High clinical suspicion in a child with a multisystem illness
- ☞ Investigations only when there are clinical pointers because false positive antinuclear antibody screen can cause much concern
- ☞ A detailed multisystem assessment at diagnosis needs to be done
- ☞ Treatment is tailored according to disease manifestations
- ☞ Appropriate disease related counseling is essential
- ☞ Long-term follow-up and management is necessary for these patients

SUGGESTED READINGS

1. Habibi S, Saleem MA, Ramanan AV. Juvenile systemic lupus erythematosus: review of clinical features and management. Indian Pediatrics. 2011;48(11): 879-87.
2. Morgan TA, Watson L, McCann LJ, Beresford MW. Children and adolescents with SLE: not just little adults. Lupus. 2013;22(12):1309-19.
3. Pediatric lupus nephritis: more options, more chances? Lupus. 2013;22(6): 545-53.
4. Pediatric Systemic Lupus Erythematosus: More Than a Positive Antinuclear Antibody Weiss. Pediatrics in Review. 2012;33:62-74.

CHAPTER 122

Approach to Juvenile Dermatomyositis

Deepti Suri, Sagar Bhattad

INTRODUCTION

Juvenile dermatomyositis (JDM) is an uncommon inflammatory myositis, characterized by a proximal muscle weakness, a heliotrope rash, and Gottron papules over the knuckles and elbows. It can involve several other organ systems like the gastrointestinal tract, lungs, and heart. Lipodystrophy with insulin resistant diabetes is also a well-known association with this condition.

The primary lesion in JDM is a small vessel vasculopathy of varying severity. Unlike adults, in whom polymyositis (PM), inclusion body myositis, and cancer associated myositis are common causes of inflammatory myopathy; JDM is the most common inflammatory myopathy in children. In the pre-steroid era, one-third children died, one-third recovered, and one-third of those who survived had significant residual problems of contractures and muscle atrophy. Over the last few decades, survival and outcome has improved considerably with aggressive immunosuppressive therapies. Mortality rate in children in the West is reported to be less than 3%. However, JDM is still associated with significant morbidity and mortality in our setting.

DEFINITION

Traditionally, the diagnosis of JDM is based on Bohan and Peters criteria or Rider Taggoff criteria. The diagnosis is essentially clinical and with the advent of muscle magnetic resonance imaging (MRI), very few rheumatologist obtain electromyographs, or muscle biopsies unless the diagnosis is in doubt.

EPIDEMOLOGY

Incidence of JDM is reported to be 3.2 children/million/year and girls are more commonly affected than the boys. Onset is between 4–10 years, with average age at onset being 7 years. However, 25% of children have onset before 4 years of age.

CLINICAL MANIFESTATIONS

Classical JDM, as the name suggests, involves skin along with proximal muscle weakness. Characteristic cutaneous abnormalities are seen in 75% of patients. These include erythematous violaceous heliotrope rash seen over the upper eyelids, Gottron papules symmetrical shiny, erythematous, scaly papules noted over extensor surfaces of small joints, and wrist and elbows (Fig. 1). Nailfold capillaroscopy reveals periungual erythema and capillary loop abnormalities which are pathognomonic and correlates with the disease severity.

Classical JDM presents with insidious progression of malaise, easy fatigue, muscle weakness, fever, and rash that may predate diagnosis by 3–6 months. Muscle weakness at onset is predominantly proximal and children most commonly present with involvement of musculature of hip girdle. Involvement of anterior neck flexors leads to inability to hold head upright and is an important finding pointing toward the diagnosis of JDM. Pharyngeal, hypopharyngeal and palatal muscles are frequently affected, resulting in difficulty in swallowing, nasal regurgitation of feeds, and nasal twang to the voice. Weak gag reflex increases the risks of aspiration pneumonias. Although,

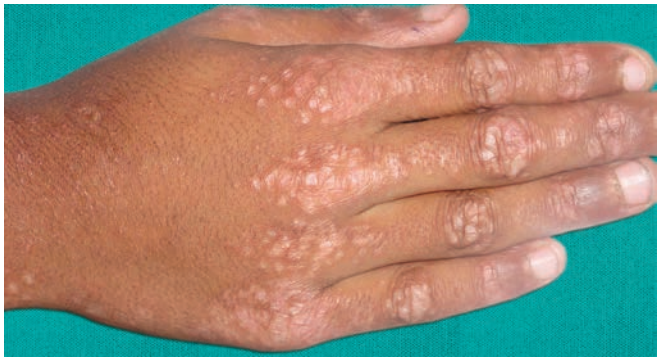


Fig. 1: Juvenile dermatomyositis. Erythematous, scaly papules noted over extensor surfaces of small joints, and wrist and elbows

muscle weakness may be impressive, the deep tendon reflexes are usually preserved.

Clinical Pearl

- Weakness of anterior flexor muscles of the neck is important early indicator of inflammatory myositis.

Diagnosis is rather clinical and certain in presence of pathognomonic dermatological findings and proximal muscle weakness. However, some children present with atypical features like subcutaneous tissue edema and can be confused with nephritic syndrome and other causes of anasarca. Some children demonstrate exquisite muscle tenderness and refusal to walk or bear weight. Close looks for the dermatological features help differentiate it from viral myositis. Transient nondeforming arthritis may also occasionally occur. However, presence of significant and persistent arthritis in a child with JDM should suggest the possibility of an overlap syndrome such as mixed connective tissue disorder.

Juvenile dermatomyositis sine myositis or amyopathic dermatomyositis: it is characterized by only the skin manifestations and paucity of muscle involvement and is relatively rare in childhood. Whether these children develop clinical overt myositis at follow-up is unclear, although some studies report up to 26% of children do, when followed for about 4 or more years. In contrast to adult amyopathic dermatomyositis, interstitial lung disease or internal malignancy has not been reported from pediatric cases, and thus this subgroup carries good prognosis in children. Magnetic resonance imaging is said to be a sensitive modality for detection of muscle abnormalities in patients with amyopathic dermatomyositis.

Juvenile dermatomyositis with associated rheumatic diseases: a subset of children with JDM may have features of other rheumatic diseases as well. If children present with features of any two of the following diseases—juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic scleroderma, and JDM—one should consider mixed connective tissue disease. Manifestations develop sequentially, but not in any predictable order, although majority would have the rash of SLE or JDM at the onset. Anti U1Anti-U1 small nuclear ribonucleoproteins antibodies are characteristically elevated.

COMPLICATIONS

Vasculopathy results in many systemic complications in JDM. Gastrointestinal vasculitis and mesenteric ischemia can lead to acute gastrointestinal hemorrhages, intestinal perforation, and even mortality. Abdominal pain, therefore, must never be neglected in patients with JDM as this could be the earliest clue to gastrointestinal vasculitis.

Clinical Pearl

- Abdominal pain in patients with juvenile dermatomyositis may be the earliest clue to intestinal vasculopathy.

Pulmonary involvement can occur in the form of interstitial lung disease, bronchiolitis obliterans organizing pneumonias, and rarely pneumothorax and other air leak syndromes.

During the convalescence phase late complications like calcinosis and lipodystrophy are recognized. They have been linked to poor management of the disease at the initial presentation and also corroborate well with the severity of the first presentation. Calcinosis occurs in 10–40% of JDM patients and are extremely disfiguring. Calcinosis affecting subcutaneous tissues may result in cellulitis and painful superficial ulceration of overlying skin. Flexion contractures may occur when these occur across joints.

Lipodystrophy is usually associated with series of metabolic derangements like insulin resistance, glucose intolerance and hypertriglyceridemia, and lipid abnormalities. Hirsutism and prominent dilated peripheral veins are also seen in some patients.

Clinical Pearl

- Calcinosis is a late complication seen in patient with poor initial immunosuppressive therapy.

INVESTIGATIONS

Indicators of inflammation (thrombocytosis, elevated erythrocyte sedimentation rate, and C-reactive protein) correlate with the degree of inflammation and help to differentiate inflammatory myopathies from noninflammatory disorders like muscular dystrophy.

Muscle Enzymes

Serum levels of muscle enzymes are important for diagnosis and for monitoring patients of JDM on therapy. Aspartate aminotransferase, creatinine kinase (CK), lactate dehydrogenase (LDH), and aldolase should be measures at baseline. Aspartate aminotransferase or CK may be elevated 20–40 times normal. However, it is to be noted that occasionally, CK levels may be normal, particularly with a longer duration of untreated disease. Lactate dehydrogenase appears to correlate best with measures of disease activity. Serum levels of all muscle enzymes usually decrease 3–4 weeks before improvement in muscle strength and rise 5–6 weeks before clinical relapse. As a general rule, CK levels return to normal first (usually several weeks after instituting therapy); and aldolase and LDH levels return to normal the last.

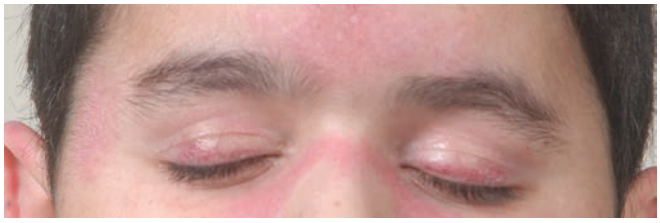


Fig. 2: Erythematous violaceous heliotrope rash seen over the upper eyelids

Autoantibodies

Antinuclear antibodies may be positive in 10–85%. Myositis specific antibodies like anti-Jo-1 are uncommon in pediatric population and occur only in about 10% of children with JDM. Anti-PM/Scl is associated with overlap syndrome.

Magnetic Resonance Imaging

Magnetic resonance imaging has dramatically replaced the need for muscle biopsy for the diagnosis of JDM. The T2-weighted magnetic resonance image with fat suppression demonstrates muscle edema and inflammatory changes by a hyperintense signal. magnetic resonance also helps in guiding the extent of disease and also helps in selecting a site for muscle biopsy.

Electromyography

Electromyography findings that suggest inflammatory myopathy include a combination of changes of myopathy and denervation.

Muscle Biopsy

Muscle biopsy is largely performed when the diagnosis is in doubt, if there are no skin findings and sometimes to evaluate the disease activity. It may occasionally help in making alternative diagnosis in children who fail trial of immunosuppression.

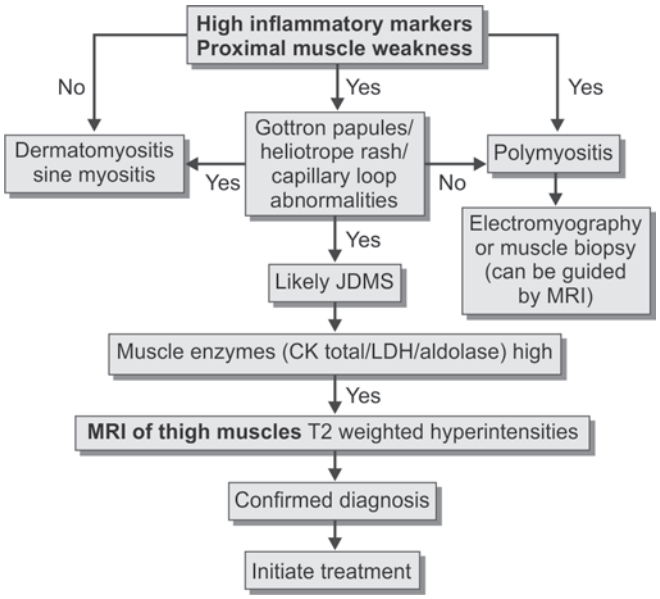
Biopsy usually is performed from quadriceps or deltoid, although the best specimen may be chosen based on electomyography or MRI. Muscle biopsy reveals perifascicular atrophy and variations in fiber size, as an outcome to ongoing degeneration and regeneration. Areas of focal necrosis would be noted and inflammatory exudates are often presented.

TREATMENT

Morbidity and mortality have greatly reduced over the decades as a result of effective immunosuppressive therapies. Use of high dose corticosteroids early in the disease course has dramatically improved prognosis. Treatment regimen consists of high dose oral corticosteroids (up to 2 mg/kg/day prednisone) with a slow tapering regimen, often over a minimum of 2 years. Intravenous pulse methyl prednisolone (30 mg/kg/dose) for 3–5 doses are administered at the onset of therapy in some children with severe inflammation and marked weakness. Majority of the children are also initiated on alternative immunosuppressive drugs, like methotrexate (15 mg/m^2 subcutaneous weekly) along with folic acid as steroid sparing agents. Children who fail to respond to these, second line agents including intravenous immunoglobulins, cyclophosphamide, mycophenolate mofetil, tacrolimus, and rituximab can be tried. Supportive care with graded physiotherapy and skin care are of utmost importance.

ALGORITHM 1

Basic diagnostic algorithm for diagnosis of juvenile dermatomyositis



CK, creatinine kinase; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging.

KEY POINTS

- ☞ Juvenile dermatomyositis (JDM) is the most common inflammatory myopathy of childhood
- ☞ Serum muscle enzymes correlate with disease activity, although normal creatinine kinase level does not exclude JDM
- ☞ Magnetic resonance imaging is a good modality to demonstrate muscle inflammation and is investigation of choice
- ☞ Muscle biopsy/electromyography is less commonly used and has a role in cases with diagnostic difficulties
- ☞ Corticosteroids and methotrexate form the cornerstone of therapy for the majority of patients with JDM.

SUGGESTED READINGS

1. Ravelli A, Trail L, Ferrari C, Ruperto N, Pistorio A, Pilkington C, et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multicenter study of 490 patients. Arthritis Care Res. 2010;62:63-72.
2. Stringer E, Bohnsack J, Bowyer SL, Griffin TA, Huber AM, Lang B, et al. Treatment approaches to juvenile dermatomyositis (JDM) across North America: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) JDM Treatment Survey. J Rheumatol. 2010;37;1953-61.

CHAPTER 123

Acute Osteoarticular Infections

Jasodhara Chaudhuri, Tapas K Sabui

INTRODUCTION

Acute osteoarticular infections (AOI) are prominent areas of bacterial infection in infancy and childhood with variable clinical features that are often nonspecific. They may cause significant mortality and morbidity. Major clinical entities that are seen in children are septic arthritis, classic long bone osteomyelitis, skeletal tuberculosis, disitis, and osteochondritis complicating puncture wounds to the foot. Early diagnosis and treatment of musculoskeletal infection are critical to prevent sequelae. In children, these mean impaired growth with restricting lifelong deformity. However, children show a high potential for healing and remodeling and less comorbidity than adults. Childhood bone infection generally has good outcome provided appropriate treatment with antibiotics and surgical intervention are offered in timely manner.

The patterns of bone infection in children are changing in terms of both clinical syndrome (fewer acute presentation) and of microbiology (e.g., increased bacterial resistance among community acquired *Staphylococcus aureus*). A greater understanding of pathogenesis and the varied manifestations of osteomyelitis and septic arthritis is thus required. There is also a need of clear guidelines with respect to treatment strategy, particularly the role of surgery and choice of antibiotic agents.

Clinical Pearls

- Acute osteoarticular infections are prominent areas of bacterial infection in infancy and childhood
- Joint space infection in children usually arises as a complication of bacteremia
- Virus, fungal, and tuberculous infections are rare.

SEPTIC ARTHRITIS AND OSTEOMYELITIS

Joint space infection in children usually arises as a complication of bacteremia. Virus, fungal, and tuberculous infections are rare. Bacterial infection elsewhere in the body may also give rise to reactive arthritis.

Acute hematogenous osteomyelitis is most common in childhood with a peak incidence in neonates. The reported incidence has been falling around the world but remains high in developing nations.

Osteomyelitis often is categorized into three different types:

- Acute hematogenous osteomyelitis
- Osteomyelitis secondary to contiguous spread of infection after trauma, puncture wounds, surgery, or joint replacement
- Osteomyelitis secondary to vascular insufficiency.

Acute hematogenous osteomyelitis is seen most often in children. Osteomyelitis caused by contiguous spread of infection is less common in children, and infection secondary to vascular insufficiency is rare in children.

Clinical Pearls

- Osteomyelitis is most common in neonates
- Osteomyelitis is most common at metaphysis of long bones
- The history of trauma is common.

PATHOGENESIS

Pyogenic arthritis usually occurs as a result of infection of the vascular synovium by means of hematogenous dissemination of bacteria followed by an acute inflammatory response, resulting in migration of polymorphonuclear white blood cells (WBCs), production of proteolytic enzymes, and cytokine secretion by chondrocytes. Degradation of articular cartilage begins 8 hours after onset of infection. In children younger than 18 months of age, pyogenic arthritis can result from extension of a metaphyseal bone infection through transphyseal blood vessels. The growth plate, the epiphysis, and eventually the joint space may be infected.

On the other hand, osteomyelitis occurs mostly by hematogenous colonization of the bones by bacteria. The metaphysis of long bones is the most common site. Theories supporting this fact include decreased blood flow in sinusoidal vessels in this area along with relative lack of phagocytic cells. Although many children give a history of minor trauma, it is

very rare to see osteomyelitis complicating a closed fracture treated by nonoperative means. Other notable features of epidemiology including the male preponderance and peak incidence remain to be explained. The pathological response to osteomyelitis is one of acute inflammation in the intramedullary cavity of the metaphysis of the long bone. After 48 hours, pus accumulates subperiosteally and then portions of the cortex may die as a result of the loss of blood supply forming a sequestrum and the abscess may rupture. Occasionally, osteomyelitis can involve the epiphysis of a long bone and then is usually subacute although acute epiphyseal osteomyelitis has been reported.

EPIDEMIOLOGY

Most cases of AOI occur in children 3 years old or younger. Boys are more frequently affected. The lower extremities (hips, knees) are most commonly affected.

Clinical Pearls

- Acute osteoarticular infections is most common under 3 years of life
- The most common agent is *Staphylococcus aureus*

MICROBIOLOGY

The most common agent is *Staphylococcus aureus*, followed by respiratory pathogens *Streptococcus pyogenes, Streptococcus pneumoniae* (pneumococcus), and *Haemophilus influenza* type b (Hib). *Kingella kingae* is a common cause of osteomyelitis and septic arthritis in some areas and requires special culture techniques or real-time polymerase chain reaction for diagnosis.

CLINICAL MANIFESTATIONS

The classical presentation of AOI is a locally swollen, warm limb, or joint combined with high fever with no or minor prior history of trauma. Pyrexia of unknown origin may be initial mode of presentation.

Generally, children with septic arthritis are clinically more ill than those with osteomyelitis, which has a more insidious onset. Plenty of useful information may be obtained from the disease history and mere observation of the patient. Limping, pseudoparalysis, refusal to use particular limb, and focal tenderness are the common mode of presentation. Whenever a previously well child presents with monoarthritis of acute origin, the possibility of septic arthritis should be considered. Pelvic osteomyelitis is well known to mimic a number of other diseases including appendicitis, lumbar disk prolapse, and septic arthritis of the hip.

Clinical Pearls

- The classical presentation of acute osteoarticular infections (AOI) is a locally swollen, warm limb, or joint combined with high fever
- Children with septic arthritis are clinically more ill than those with osteomyelitis
- Whenever a previously well child presents with monoarthritis of acute origin, think of AOI.

DIFFERENTIAL DIAGNOSIS

The most common cause of hip pain in childhood is transient synovitis. Transient synovitis is predominantly seen in children 5–10 years old. Pain is usually unilateral. Pain ranges from mild to severe enough to wake the child up. Physical examination generally reveals a nonill appearing child with decreased range of motion of the hip joint. Other common causes of joint pain and swelling include reactive arthritis, rheumatic fever, juvenile rheumatoid arthritis, trauma, and malignancy. Malignancy often turns out to be the most important differential diagnosis for osteomyelitis. Legg-Calve-Perthes disease is an idiopathic avascular necrosis of the capital femoral epiphysis and may cause mild pain and limp in boys.

DIAGNOSIS

A sample for bacteriology may be obtained by needle aspiration of soft tissue in neonates, subperiosteal aspiration in infants, or drilling of bone in older children. (Blood and joint fluid) should be obtained for aerobic and anaerobic cultures.

Blood tests, namely hemogram and acute phase reactants, are used to assess the extent of inflammation. Blood leukocyte count (WBC) is nonspecific and elevated only in 20% of cases. Out of all acute phase reactants, C-reactive protein (CRP) here is extremely helpful in diagnosis and monitoring of AOI. Traditional radiographs have minimum or no value in diagnosis of it as the changes appear late. Ultrasound is extremely helpful for detection of joint effusion. However, magnetic resonance imaging and computed tomography are the investigations of choice for early diagnosis. Bone scans in acute hematogenous osteomyelitis have a sensitivity of 84–100% and a specificity of 40–96%. The sensitivity of bone scans is least in the first 48 hours due to the transitional period between decreased and increased activity. Scintigraphy is most helpful in detecting multiple foci of disease and in the assessment of the young child, where localization is difficult. Although cultures frequently fail to disclose the causative agent, every attempt should be made for isolation of causative agent from the site of infection. The only indication of joint aspiration in pediatric age group nowadays is septic arthritis, even though the chance of getting positive culture is only 30%. Aspirated fluid should be inoculated directly into blood culture bottles. Gram stain and cell count should also be performed on joint fluid. A WBC count of 50,000/mm^3 or greater with a predominance of polymorphonuclear cells is consistent with bacterial infection.

Clinical Pearls

- Every attempt should be made to find out the etiological agent from infected tissue
- C-reactive protein here is extremely helpful in diagnosis and monitoring of acute osteoarticular infections
- Traditional radiographs have minimum or no value in diagnosis
- Magnetic resonance imaging and computed tomography is the investigation of choice for the early diagnosis.

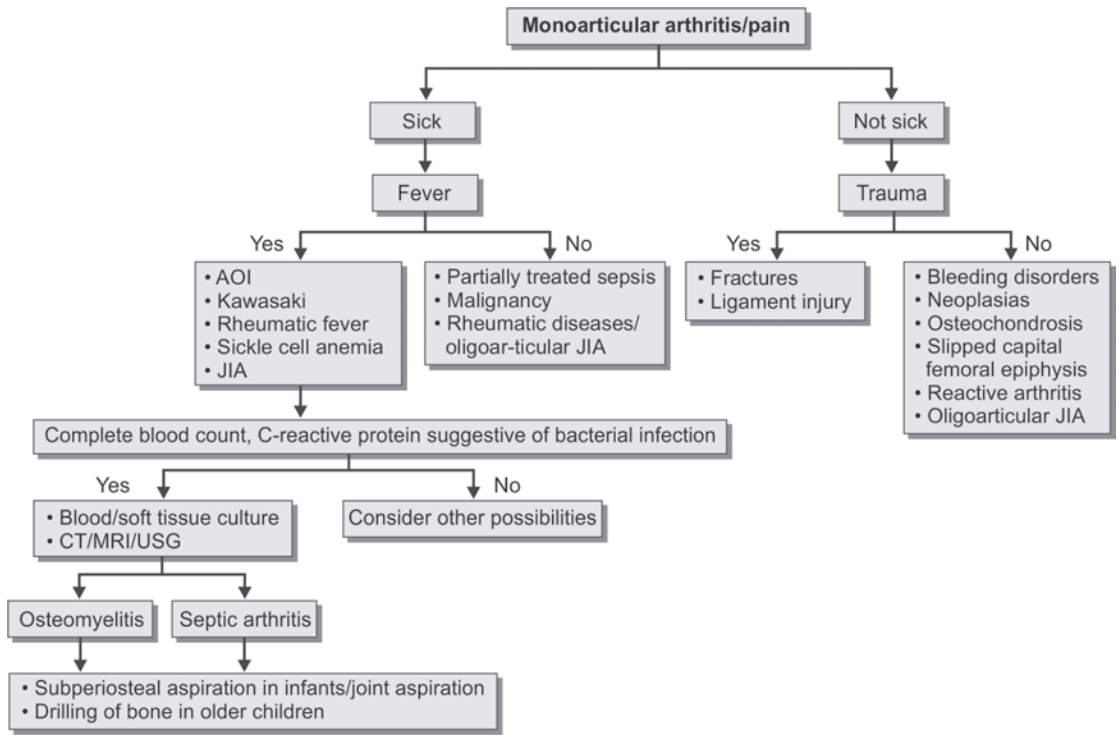
TREATMENT

A local antibiogram would be of paramount importance in these situations. As *Staphylococcus aureus* is a major player in AOIs, its local sensitivity pattern influences the choice of the initial antibiotic. The empiric antibiotic treatment of AOI in primary methicillin sensitive and methicillin resistant *Staphylococcus aureus* (MRSA) is first or second generation cephalosporins (150 mg/kg/day four times a day)/cloxacillin (200 mg/kg/day four times a day) and vancomycin (40 mg/kg/day four times a day)/trimethoprim/sulfamethoxazole (TMP-SMX) (TMP16 mg/kg/day twice a day), respectively. Linezolid (30 mg/kg/day three times a day) is the drug of choice in areas where the organism is resistant to vancomycin/TMP-SMX. A Hib unvaccinated child from Hib endemic area should receive concomitant ampicillin or amoxicillin (200 mg/kg/day divided in four equal doses) until the agent is identified. Currently, there is no consensus about the route or duration for antibiotic treatment of acute osteomyelitis in children. Until recently, the standard therapy was a long intravenous therapy and a long duration of 4–6 weeks. However, the short antibiotic courses tested in recent trials on osteomyelitis and septic arthritis. The entire course of antibiotic was approximately 3 weeks for uncomplicated osteomyelitis and 10–14 days for septic arthritis. A high dose of well absorbed first/second generation cephalosporins or clindamycin in equal doses four times a day was used. These antibiotics penetrate bone and soft tissue well in intravenous and oral administration. In absence of definite laboratory or clinical parameters that would determine the decision to switch to oral therapy, there is no clear guideline of when to switch from intravenous to oral therapy. The drugs were given in recent trials intravenously for first 2–4 days except in newborns and thereafter it was given orally, provided the first signs of recovery including disappearance of fever, taking oral fluids were observed, and the level of CRP began to descend. However, this protocol is not applicable in the case for the management of complex infections including those with multifocal disease, significant bone destruction, resistant or unusual pathogens, sepsis or in immunosuppressed children, and in neonates. The intravenous therapy to be continued for 14–21 days in complex situations and switched over to oral medication provided the baby is afebrile, pain-free for at least 24 hours, and CRP descended by two-thirds of highest value. The total antibiotic therapy here will be 6 weeks both in septic arthritis and osteomyelitis. The role of surgery in the treatment of septic arthritis is in fact poorly defined except in relation to the hip, where prompt surgical drainage is absolutely necessary. Aspiration, irrigation, and intravenous antibiotic therapy is the preferred first line of treatment of septic arthritis except in hip joint. No consensus prevails in the timing, procedures, extent, or even the overall need for surgical intervention in osteomyelitis. Surgical drainage is mandatory in osteomyelitis if pus is obtained from the subperiosteal space or metaphysic in nature. The abscess should be decompressed, evacuated, and washed-out under general anesthesia. A suction drain should be left in place for 48 hours.

Though further studies are needed in this field, a placebo controlled randomized controlled trial examined the use of 4 days of intravenous dexamethasone (0.2 mg/kg/dose intravenously 8 hourly) and it significantly reduced the duration of acute phase and morbidity.

ALGORITHM 1

Algorithmic approach to monoarticular joint pain and arthritis



AOI, acute osteoarticular infections; JIA, juvenile idiopathic arthritis; CT, computed tomography; MRI, magnetic resonance imaging; USG, ultrasound.

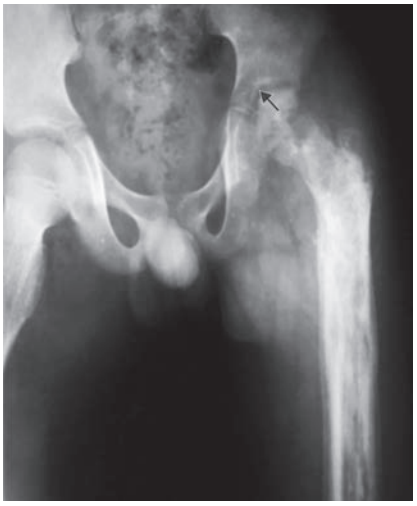


Fig. 1: X-ray of hip joint in a case of septic arthritis. The arrow sign shows the affected hip joint showing decreased and eroded joint space. Periosteal reaction in adjoining femur

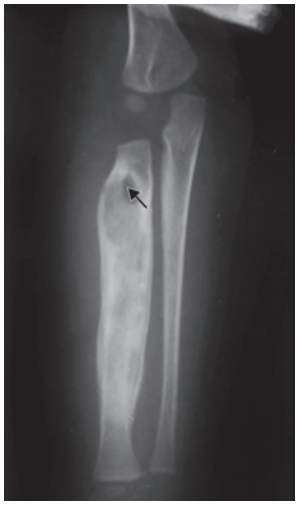


Fig. 2: X-ray showing osteomyelitis. The arrow sybmol shows the visible osteolytic changes of osteomyelitis and sequestrum

PROGNOSIS

Complications of AOI include abnormal bone growth, limp, unstable articulation of the affected joint, and decreased range of motion. Complications are reported in approximately 10–25% of all cases. Risk factors for squeal include delay in time to diagnosis of more than 4 or 5 days, onset of disease in infancy, infection with *Staphylococcus aureus* or Gram-negative bacteria, and infection of adjacent bone.

Clinical Pearls

- A local antibiogram would be of paramount help
- The Empiric antibiotic treatment depends on nature of etiological agent
- No consensus about the route or duration for antibiotic treatment of acute osteomyelitis in children
- Complications are reported in approximately 10–25% of all cases.

CONCLUSION

The number of bone and joint infections resulting from vaccine preventable pathogens like *Haemophilus influenza* and *Streptococcus pneumoniae* are on the decline. *Staphylococcus aureus* is the most common pathogen causing septic arthritis and osteomyelitis in children all over the world. The incidence of community acquired MRSA is increasing and is a cause of concern for pediatricians. Early diagnosis and prompt and appropriate treatment consisting of antibiotic therapy and surgical intervention when required is the mainstay of treatment and is extremely rewarding in majority of the occasions.

KEY POINTS

- ☞ Acute osteoarticular infections (AOI) are common in infancy and childhood under 3 years of age
- ☞ Joint space infection in children usually arises as a complication of bacteremia and the most common agent is *Staphylococcus aureus*
- ☞ High fever, painful warm swollen limb or joint are the most common mode of presentation
- ☞ Children with septic arthritis are clinically more ill than those with osteomyelitis
- ☞ Whenever a previously well child presents with monoarthritis of acute origin, think of AOI
- ☞ Magnetic resonance imaging and computed tomography is the investigation of choice for the early diagnosis
- ☞ Identification of etiological agent and local antibiogram are of paramount help
- ☞ There is no consensus about the route or duration for antibiotic treatment of acute osteomyelitis in children
- ☞ Treatment is rewarding.

SUGGESTED READINGS

1. Faust SN, Clark J, Pallett A, Clarke NM. Managing bone and joint infection in children. Arch Dis Child. 2012;97:545-53.
2. Grammatico-Guillon L. Paediatric bone and joint infections are more common in boys and toddlers: a national epidemiology study. Acta Paediatrica. 2012; 11:1-6.
3. Grimprel E, Lorrot M, Haas H, Pinquier D, Parez N, Ferroni A, et al. Bone and joint infections: treatment proposals from the Group of Pediatricians Specialised in Infectious Diseases (GPIP) French Pediatrics Society. Arch Pediatr. 2008;15:S74-80.
4. Gutierrez K. Bone and joint infections in children. Pediatr Clin North Am. 2005;52:779-94.
5. Peltola H, Pääkkönen M, Kallio P, Kallio MJ; Osteomyelitis-Septic Arthritis Study Group. Short-versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. Pediatr Infect Dis J. 2010;29:1123-8.
6. Susan S. Review article: paediatric bone and joint infection. J Orthop Surg. 2001;9:83-90.

CHAPTER 124

Eye Involvement: Beyond Infections

Manjari Agarwal

INTRODUCTION

Eyes are a window to systemic disease and can help a clinician reach an elusive diagnosis, by simply doing a proper detailed ophthalmological examination. Eyes are involved in a multitude of rheumatological illnesses and every incidence of eye problem is not due to infection. For the sake of this review, infectious etiologies would not be discussed. This review aims at stressing upon the eye involvement in various rheumatological/immunoinflammatory diseases. For ease of explanation, involvement of each layer of the eye is discussed separately (Fig. 1).

CONJUNCTIVITIS

Redness of eyes with photophobia is seen in about 85% children with Kawasaki disease. Bilateral, nonexudative, and bulbar conjunctivitis is the hallmark of the disease. Perilimbal sparing of the conjunctiva is usually seen. Uveitis may or may not be present in Kawasaki disease. Presence of purulent conjunctivitis usually rules out Kawasaki disease.

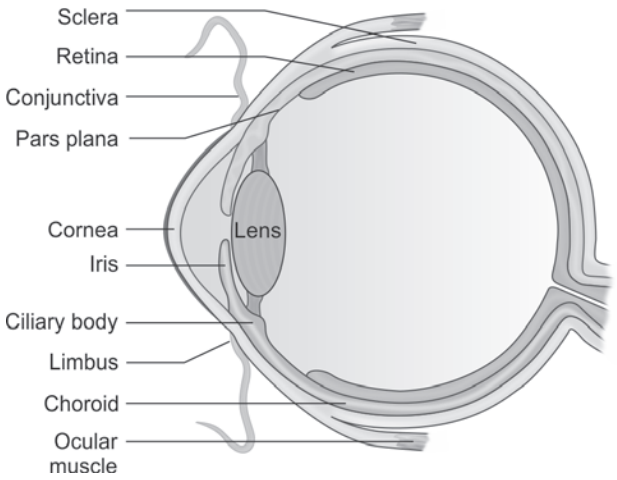


Fig. 1: Schematic representation of eye

SCLERITIS

Sclera is the outer protective layer of the eye, begins at the limbus and is continuous with the cornea and ends at the optic canal in continuity with the dura.

Episcleritis is usually more painful and is often self-limiting.

Scleritis usually affects the adult population between 30 and 50 years of age. The most commen association of scleritis in this age group is with Granulomatous polyangiitis and rheumatoid arthritis (Table 1).

DIAGNOSIS

Detailed history, and physical examination is a must. Investigations pertaining to the system involved must be carried

TABLE 1: Etiology of scleritis

Infections	Autoimmune diseases	Others
Viruses (varicella zoster, herpes simplex, hepatitis C)	Rheumatoid arthritis	Trauma
Bacteria	Granulomatous polyangiitis	Drug induced pamidronate
Mycobacteria	Inflammatory bowel disease	35–45
Fungi	Systemic lupus erythematosus	–
Amebae	Sarcoidosis	–
Parasites	• Takayasu's arteritis • Cogan's syndrome • Spondyloarthropathies • Polyarteritis nodosa • Vasculitis	

out. Specific serologic testing should include antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, and anticyclic citrullinated peptide antibodies.

Other investigations like Mantoux test can be done after history and physical examination.

TREATMENT

Treatment of scleritis can be divided on the type of scleritis and has been detailed in table 2.

INTERSTITIAL KERATITIS

Interstitial keratitis is characterized by a nonsuppurative inflammation, with vascularization of the cornea. It is commonly seen with Cogan syndrome. It usually presents with pain, lacrimation, photophobia, and conjunctival injection. This usually responds to topical corticosteroid therapy.

Clinical Pearls

- Eyes can be involved in a myriad of immunoinflammatory conditions
- Redness of eyes with photophobia, with or without diminution of vision might be a red flag and should be appropriately evaluated.

RETINAL VASCULITIS

Retinal vascular inflammatory diseases are termed retinal vasculitis even in the absence of true vasculitis. It can be defined as inflammation of the retinal vessels accompanied by intraocular inflammation and retinal vessel occlusion. Retinal vasculitis may involve retinal arteries, veins, or capillaries.

A common cause of retinal vasculitis leading to significant ocular morbidity is Behçet's disease. Both retinal veins as well as arteries can be involved in Behçet's disease and may lead to arterial occlusion.

Systemic vasculitides can also cause retinal vasculitis although these are uncommon.

Systemic lupus erythematosus can also cause retinal vasculitis even in the absence of antiphospholipid antibodies. The retinal vessels can be involved causing cotton-wool spots or microinfarcts of the nerve fiber layer of retina.

Therapy

Systemic glucocorticoids usually pulse methylprednisolone (10–30 mg/kg/day) for 3–5 days followed by oral glucocorticoids are needed. Steroid sparing agents like methotrexate and mycophenolate mofetil might be required for maintenance therapy.

TABLE 2: Therapy of scleritis

Type of scleritis	Systemic therapy
Nodular anterior scleritis	NSAIDs
Necrotizing anterior scleritis	• Systemic glucocorticoids • Systemic immnuosuppression: ○ First line agents: – Cyclophosphamide – Methotrexate – Azathioprine – Mycophenolate mofetil ○ Second line agents: – Cyclosporine – Tacrolimus ○ Third line/experimental – Infliximab – Rituximab
Posterior scleritis	• Systemic glucocorticoids • Systemic immunosuppression

ORBITAL DISEASE

Primary inflammation of the orbital tissue, e.g., orbital pseudotumor or orbital myositis due to inflammation of the extraocular muscles is usually seen. Secondary involvement occurs most commonly due to contiguous spread of inflammation from the sinuses seen typically in ANCA associated vasculitis.

Therapy

Control of underlying disease with systemic corticosteroids or immunosuppressive drug therapy, decreases associated symptoms, as well as improves visual acuity.

UVEITIS

It is the most common ocular involvement of immunoinflammatory diseases in childhood. Usually uveitis in children is asymptomatic and hence can lead to significant ocular morbidity.

Standardization of Uveitis Nomenclature working group has defined the types of uveitis along with descriptors for each type of uveitis (Tables 3–5).

TABLE 3: Standardization of Uveitis Nomenclature Working Group classification of uveitis

Type	Primary site of inflammation	Lesions
Anterior uveitis	Anterior chamber	• Iritis • Iridocyclitis • Anterior cyclitis
Intermediate uveitis	Vitreous	• Pars planitis • Posterior cyclitis • Hyalitis
Posterior uveitis	Retina/choroid	• Chorioretinitis • Neuroretinitis • Retinochoroiditis • Focal, multifocal, diffuse choroiditis • Retinitis

TABLE 4: Standardization of Uveitis Nomenclature working goup descriptors of uveitis

Category	Description	Comment
Onset	Sudden insidious	–
Duration	Limited persistent	≤3 months >3 months
Course	Acute	Episodes of sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment >3 months in duration
	Chronic	Persistent uveitis with relapses in <3 months after discontinuing therapy

TABLE 5: Guidelines for the ophthalmological screening of children with juvenile idiopathic arthritis

JIA onset type	ANA	Onset <7 years of age	Onset >7 years of age
Oligoarticular	Positive	Every 3–4 months	Every 4–6 months
Oligoarticular	Negative	Every 4–6 months	Every 4–6 months
Polyarthritis	Positive	Every 3–4 months	Every 4–6 months
Polyarthritis	Negative	Every 4–6 months	Every 4–6 months
Systemic onset	Negative/ positive	Every 12 months	Every 12 months

JIA, juvenile idiopathic arthritis; ANA, antinuclear antibodies.

Acute anterior uveitis is characteristic of human leukocyte antigen B27 (HLA-B27)–associated diseases such as enthesitis-related arthritis. Patient presents with a red, painful, and photophobic eye. The anterior chamber is best visualized by the help of a slit lamp. The presence of cells in the anterior chamber indicates disease activity. At times, the cells might aggregate in the lower part of the anterior chamber due to gravity and produce a hypopyon. If left untreated, there is a tendency to form adhesions between the posterior part of iris and lens; these are termed as posterior synechiae.

Clinical Pearl

- Acute anterior uveitis might often be the first presentation of disorders like juvenile spondyloarthropathy and inflammatory bowel disease.

Similar adhesions between peripheral iris and posterior cornea are called anterior synechiae. Chronic uveitis is the most common ocular complication of oligoarticular juvenile idiopathic arthritis (JIA). It is initially asymptomatic and is picked up on routine screening. It is predominantly insidious in onset, anterior, nongranulomatous inflammation affecting the iris and ciliary body.

Few children, especially older than 7–8 years of age can complain of pain, redness, headache, photophobia, or blurring of vision.

Slit lamp examination is mandatory to diagnose uveitis. Presence of inflammatory cells and increased protein concentration (flare) in the aqueous humor of the anterior chamber are the classic hallmark.

Keratic precipitates (deposition of inflammatory cells on the inner surface of the cornea) may be detected at onset or may develop later.

Band keratopathy occurs due to deposition of calcium in the corneal epithelium and is also a late feature.

Presence of posterior synechiae is also a feature of late disease. Untreated synechiae might occasionally cause obstruction to aqueous outflow and cause increased intra-ocular pressure.

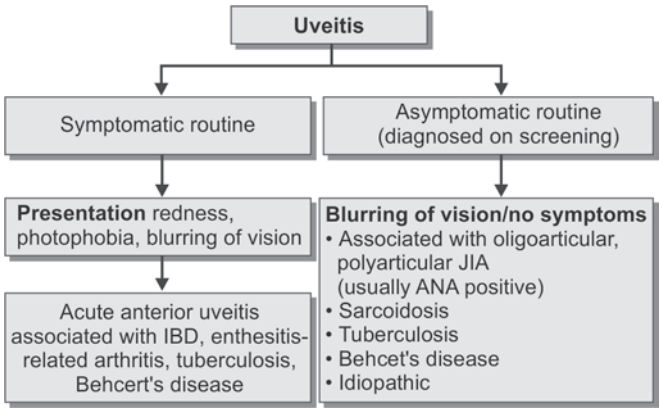
Since chronic uveitis might lead to significant visual morbidity, it is prudent to electively screen children with JIA. Table 5 gives a guideline for screening of children depending upon the risk involved. Uveitis may also be associated with other inflammatory disorders in children like inflammatory bowel disease and reactive arthritis. Uveitis can also in occur in chronic infantile neurological cutaneous and articular syndrome, sarcoidosis, Blau syndrome, Bechet's disease and Kawasaki disease. Algorithm 1 gives provides an outline of the diagnostic possibilities for children presenting with uveitis.

Management

Uveitis associated without arthritis needs to be evaluated and infections like tuberculosis need to be ruled out. Angiotensin converting enzyme levels for sarcoidosis, HLA B51 for Behçet's disease, ANA need to be done if child does not have arthritis. Human leukocyte antigen B27 associated uveitis is usually acute symptomatic but rarely may be

ALGORITHM 1

Approach to a child with uveitis



JIA, juvenile idiopathic arthritis; ANA, antinuclear antibodies; IBD, inflammatory bowel disease.

chronic persistent. Rheumatoid factor positivity generally has a protective role for uveitis.

Treatment

The management of uveitis is done by ophthalmology and rheumatology teams jointly.

Topical glucocorticoid drops with or without mydriatics are the first line agents. Topical therapy for prolonged period is associated with severe ocular complications like cataract and glaucoma.

Second line agent for uveitis unresponsive to topical therapy is methotrexate. It can also be used as a steroid sparing agent with excellent results.

Mycophenolate mofetil, cyclosporine, and tacrolimus are the next line of management.

Severe, unresponsive disease can be managed by tumor necrosis factor alpha blocker, infliximab.

There is also some role of costimulatory blockade, abatacept for resistant uveitis though large trials are still required.

Clinical Pearls

- In children with diagnosed juvenile idiopathic arthritis, routine screening for chronic anterior uveitis is a mandate
- Topical therapy for prolonged period of time can cause significant morbidity and must be avoided.

KEY POINTS

- ☞ Acute anterior uveitis might often be the first presentation of disorders like juvenile spondyloarthropathy and inflammatory bowel disease (IBD)
- ☞ Detailed ophthalmic examination is necessary in every child with juvenile idiopathic arthritis (JIA)
- ☞ Chronic anterior uveitis is asymptomatic and a young child might not be able to complain of blurring of vision
- ☞ In a child with uveitis, diseases like tuberculosis, sarcoidosis, Behçet's, IBD, and JIA must be ruled out
- ☞ Disease-modifying antirheumatic drugs are essential early in the disease course to prevent side effects of topical/oral steroids.

SUGGESTED READINGS

1. Galor A, Thorne JE. Scleritis and periplheral ulcerative keratitis. Rheum Dis Clin N Am. 2007;33:835-54.
2. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. Amer J Ophthalmol. 2005;140:509-16.
3. Nguyen QD, Foster CS. Systemic lupus erythematosus and the eye. Int Ophthalmol Clin. 1998;38:33-60.
4. Okhravi N, Mc Cluskey P. Scleritis. Surv Ophthalmol. 2005;50(4):351-63.
5. Yancey C, White P, Magilavy D, Gewanter H, Lowe B, Passo M, et al. The Guidelines of the Rheumatology and Ophthalmology sections of the American Academy of Pediatrics. Pediatrics. 1993;92:295-6.

CHAPTER 125

Empyema Thoracis: Management Algorithm

Rasik S Shah, Suyodhan A Reddy

INTRODUCTION

Empyema thoracis (ET) is collection of purulent fluid in the pleural cavity, which is either free or localized. Pneumonic infection and the associated inflammation of the pleural lining lead to an exudative parapneumonic pleural effusion, which upon invasion by bacteria becomes empyema. The term "empyema" is derived from the Greek words *pyon*, meaning pus and *empyein*, meaning pus producing. The optimal time and the manner of drainage of empyema was a matter of concern since the times of Hippocrates and Fabricus. In the last two decades, many pediatric surgical centers are increasingly using minimal access techniques in management of ET patients.

EPIDEMIOLOGY

Childhood empyema occurs in 0.7–3.3 per 100,000 worldwide. There is gradual increase in the incidence. The pattern of use of antibiotics and incorporation of polyvalent pneumococcal vaccine (7vPVC) into immunization programs has led to an increase in invasive pneumococcal empyema by nonvaccine serotypes.

ETIOPATHOGENESIS

Empyema thoracis most often occurs as a sequel of bacterial pneumonia; however, it can also occur following pulmonary tuberculosis, trauma, perforation of intrathoracic esophageal, or operations on chest. Lower respiratory tract infection in children may get complicated by parapneumonic fluid collections in 50% of patients. Progression to an established ET occurs in 1 of every 155 cases of pneumonia according to one large pediatric series.

In India, *Staphylococcus aureus* is still the most common isolate from the children of ET. This is followed by *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Although *S. pneumoniae* produces large effusion in 40% of the cases, only 5% eventually progress to frank ET. Tubercular empyema is rare and occurs only in 2% of the cases of tubercular pleural infections. Anaerobes are common in older children who often have predisposing factors like aspiration pneumonia, lung abscess, and poor dental hygiene. *Aspergillus* and *Candida albicans* also have been isolated. Rarely, *Entamoeba histolytica* abscess in the liver may rupture in the pleural cavity and produce ET with *Entamoeba histolytica*.

PATHOPHYSIOLOGY

The smooth and synchronized expansion of the lung in consonance with the expansion of the chest wall is facilitated by a small amount of intrapleural fluid (0.3 mL/kg). This is maintained in a dynamic equilibrium in visceral and parietal pleura by unidirectional flow created by lymphatics. These lymphatics generate a negative pressure of about 7 mmHg and are capable of absorbing large volumes of clear low solute fluids in the pleural space. However, a secondary infection in the pleural space triggers an inflammatory process, which makes the pleural vasculature to become more permeable to inflammatory cells and bacteria. The pleural fluid now transforms into exudates of frank pus, resulting in the classical empyema. This influx is mediated by proinflammatory cytokines, such as tumor necrosis factor, interleukin (IL)-1β, and IL-6, secreted from mesothelial cells. The activation of the coagulation cascade and disruption of enzymes of the fibrinolytic system, such as tissue type plasminogen activator and plasminogen activator inhibitor type 1, results in fibrin deposition and blockage of lymphatic pores leading to further accumulation of fluid. This imbalance of the fibrin produces multiple loculations and formations of fibrinopurulent peel as seen in the later stages of empyema.

Empyema thoracis is classified in to three stages, i.e., exudative, fibrinopurulent, and organizing stage by the American Thoracic Society. The pathological response is divided in three phases that are not sharply distinct but gradually one phase merges into another (Table 1).

TABLE 1: Stages of empyema

Stage	Duration	Cellular content	Glucose ratio fluid/plasma	pH	LDH	Pleural space
Exudative	1–3 days	Low	>60 mg (>0.5)	>7.30	<1,000	Thin sterile, low sediment fluid
Fibrino-purulent	4–14 days	Neutrophilia and fibrin	<60 mg (<0.5)	<7.10	>1,000	Purulent, viscous fluid, loculations, and limiting membranes Organisms isolated
Organized	>14 days	Fibroblasts proliferation leads to thick peel, which encases the lung. The pleural space contains very thick exudates				

LDH, lactate dehydrogenase.

Hamm and light described a stage that proceeds to the stage of exudation, which they termed "pleuritis sicca stage", this is characterized by the presence of pleuritic chest pain and pleural rub. This does not proceed to exudative stage.

CLINICAL FEATURES

Empyema is more common in the poor socioeconomic group. The incidence peaks between 6 months and 3 years of age. Clinical signs vary depending on the type of organism isolated, age of the patient, stage of the effusion, and type of prior antibiotic therapy.

The bacterial pneumonia in children usually presents with cough and fever; development of pleuritic chest pain and dyspnea heralds complication of ET. Children may lie on the affected side in attempt to splint the chest. The breath sounds and respiratory movements' decreases on the side of empyema. There may be shift of the mediastinum. Often scoliosis is seen toward the affected side on both clinical examination and chest X-ray. This occurs initially in an attempt to reduce the pleural pain and later on due to the result of fibrosis of the parietal pleura. In late stages of ET, the ipsilateral chest is collapsed with crowding of ribs leading to obliteration of intercostal space, pulling of mediastinum, and diaphragm on the side of ET and scoliosis. The patients can develop pyopneumothorax due to air leak either from lung parenchyma [parenchymo-pleural fistula (PPF)] or by erosion of bronchus [bronchopleural fistula (BPF)].

INVESTIGATIONS

Investigations are performed to determine quantity and quality of fluid present in the pleural space and its effect on the cardiorespiratory system.

Chest Radiograph

All children with symptoms suggestive of febrile respiratory illness should have a chest X-ray posteroanterior view. Blunting of costophrenic angle and pleural shadowing suggests presence of free fluid in the pleural space. Massive fluid accumulation in the chest may show opacified hemithorax with or without mediastinal shift. Presence of air fluid level suggests either anaerobic infection, or BPF or PPF. Advanced stage of the disease may show fibrosis where the mediastinum is pulled toward the fibrosed pleura. The chest X-ray is not helpful in monitoring the progress of the disease and radiological features lag behind the physiological changes.

Ultrasonography of Chest

The ultrasonography of chest is the most useful investigation; it is noninvasive, does not use ionizing radiation, provides a dynamic assessment of the chest, and can be done repeatedly without fear of any adverse effect. It can differentiate between consolidated lungs from fluid in pleural space. It also detects presence of loculations and fibrin strands, and volume of the fluid in the pleural space. The sonologist can mark the spot for the aspiration of fluid and/or chest-tube insertion. The aspiration of fluid differentiates between sympneumonic effusion and ET. Though ultrasound is useful to stage the ET in children, it is not helpful in predicting its outcome.9

Computed Tomography Scan

The role of routine computed tomography (CT) is controversial. The CT scan often requires general anesthesia or sedation, which may be a limiting factor in some very small and sick child. CT scan also gives lot of radiation. Its role is limited in patients, who are not responding to the treatment. The CT scan precisely shows site of fluid collection, thickness of fibrotic peel, its location, and whether it is on visceral surface of lung or on diaphragm or chest-wall. This information is useful to endoscopic surgeons for the port placement to avoid trauma to the lung and subsequent PPF or BPF. Though the CT scan can demonstrate the lung parenchyma and it pathologies accurately, it is unable to identify the presence of thin fibrinous strands in pleural fluid. Coren et al. reviewed the use of CT scanning in preoperative assessment and found that CT scans were least useful in the preoperative assessment of empyema complicating community-acquired pneumonia.

Clinical Pearls

- X-ray chest posteroanterior view should be done in all children in whom an empyema is suspected
- Ultrasound is the most informative investigation
- Computed tomography scan is reserved for patients who are not responding to treatment or as a preoperative investigation.

Hematological Investigations

The total blood count may reveal anemia, leukocytosis with polymorphonuclear predominance, and thrombocytosis and raised C-reactive protein. The falling levels of white blood cell count and C-reactive protein are indicative of clinical improvement. Thrombocytosis is common in many chronic

inflammatory conditions including empyema. However, low platelet count with low hemoglobin in a child with empyema should alert the physician about possibility of the hemolytic uremic syndrome, which often develops secondary to neuraminidase release by *Streptococcus pneumonia*.

The coagulation studies are usually normal in healthy children with normal liver. However, children with impaired liver and chronic malnutrition may have abnormal blood coagulation. Single screening of coagulation should suffice at the time of initial venous cannulation.

Clinical Pearl

- Resolution of fever, falling levels of total leucocyte counts and C-reactive protein are favorable indicators.

Pleural Fluid Analysis

Pleural fluid tapping is highly informative, however, the procedure is challenging as it might require sedation in a sick child. Small collections are best left alone. The fluid is examined for Gram staining, aerobic and anaerobic culture, pH, specific gravity, protein content, glucose estimation, and LDH levels. The specimen should be sent for microscopy and culture. The reported rate of isolating a pathogen varies and depends on the prior antibiotic usage. If facilities permit 16s ribosomal RNA ploymerase chain reactions (PCR) should be done and suitable antibiotics should be instituted. The fluid should also be cultured for *Mycobacterium tuberculosis.*.

Clinical Pearls

- Pleural fluid is sent for microscopy, cytology and culture
- Polymerase chain reaction if available should be used
- There is no role of biochemical markers in children.

MANAGEMENT

The broad principles in management of empyema include treatment to stop ongoing sepsis, restoring the normal lung volume, and reestablish the physiological pleural fluid circulation. The child's hemodynamic status should be stabilized with oxygen therapy, parenteral fluids, antipyretics, and analgesia.

Clinical Pearl

- Sterilize and evacuate the thorax at the earliest

Antibiotics

Antibiotics alone have a role in small effusions in which the child has no respiratory compromise. The choice of antibiotic should be based on local policy on pneumonia guidelines and knowledge of both community and hospital acquired pathogens. The antibiotics are selected empirically and changed according to the Gram staining and culture sensitivity of the aspirated pus. Broad-spectrum antibiotics are used to ensure adequate cover for *S. pneumonia,* and consideration should be given to antistaphylococcal cover, particularly if pneumatoceles are present. Adequate anaerobic cover should be given when there is a clinical suspicion for aspiration pneumonia. Once the child is afebrile then child can be shifted to oral therapy, which can extend up to 6 weeks.

Pleural Cavity Drainage

Clinical Pearls

Modalities for Drainage

- Multiple needle thoracocentesis
- Tube drainage of chest with or without fibrinolytics
- Video-assisted thoracic surgery
- Open thoracotomy.

Timing of Drainage

The timing of pleural cavity drainage should be individualized depending upon the local expertise and the balance of noninvasive monitoring and expectant management. The decision to intervene and drain the fluid is taken when the fluid analysis is suggestive of empyema and/or if child develops respiratory distress (Algorithm 1).

Options for Drainage

Aspiration is done under local anesthesia with sedation at the most dependent site or in the fifth intercostal space in midaxillary line. In the exudative stage, it may be possible to aspirate ET completely; however, as the pus becomes thicker and flakes of fibrinopurulent material starts forming, it is not possible to aspirate the ET completely. Some studies have compared the efficacy of repeated thoracocentesis to that of chest tube drainage and found both comparable. These studies concluded that repeated needle aspirations are more traumatic; require multiple anesthesia and ultrasonography assistance. These studies recommend early chest tube insertion.

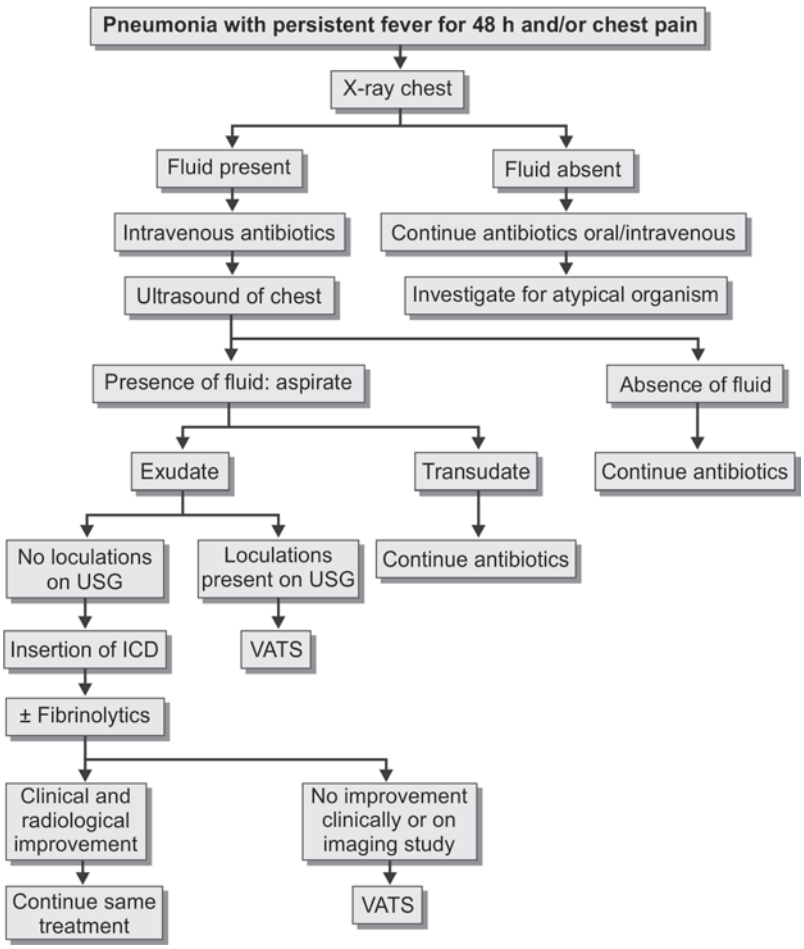
Chest tube drainage along with parenteral antibiotic is the standard management in the exudative stage and in fibrinopurulent stage. Addition of fibrinolytics shortens the duration of the chest drainage and improves the clinical outcome. Adequate chest drainage and good broad-spectrum antibiotics resolve the fever and leukocytosis, with almost complete lung reexpansion as seen on X-ray and/or sonography. The chest drainage should be continued till drainage decrease to less than 10–15 mL/day, which usually takes 7–14 days. The successful resolution with conservative management has been reported in 65–82% of the patients, and rest will require surgical therapy.

Clinical Pearl

- More than two-thirds of early empyema can resolve with standard management of antibiotics and chest tube drainage. Remaining needs surgical intervention.

ALGORITHM 1

Management algorithm for empyema in children



USG, ultrasonography; ICD, intercostal drainage; VATS, video-assisted thoracoscopic surgery.

Pepperpoint et al. compared and reviewed the outcomes in terms of length of hospital stay and the need for further intervention in children with empyema treated either with a stiff large bore tube or with small bore pig tail catheter. The outcomes were significantly better in children who received small bored catheter. It has been observed that the most of the patients in India presents late and they do better with large bore chest drain then pigtail catheter.

Satish et al. in their study conducted in the secondary referral center on 14 children concluded that chest drainage along with antibiotics is sufficient to treat empyema. They also suggested there is no need for surgical decortications in children. However, in this study, the physiological and radiological resolution was obtained up to 16 months. The prolonged hospital stay, coupled with the extraordinarily long recovery of lung has significant economic, social, and academic implications of a growing child. Spencer in his editorial comment observed, "it is not time to put the knife down".

As the duration of the empyema advances, there is increased fibrin formation and this result in loculated pus pockets. Use of fibrinolytics in pleura is to lyse the fibrin strands, clear the lymphatics, and liquefy the pus. The literature is replete with case series describing the management using streptokinase, urokinase, aleptase, or tissue plasminogen activator in various different protocols.

In fibrinopurulent stage with loculations and in organizing stage, the simple chest drain or cyclical irrigation is unlikely to work and they would need either formal decortication or video-assisted thoracoscopic surgery (VATS). In fibrinopurulent stage, it is more of pleural debridement and breaking up of the loculations, which ensures adequate drainage. This can be safely accomplished by VATS. Open decortication is required in a miniscule number of advanced cases of empyema. The term decortication refers to the removal of the thick fibrotic parietal and visceral pleural peel found in the late chronic disease is accomplished with open thoracotomy either with or without rib resection.

Clinical Pearl

- Early surgical intervention allows faster recovery and rapid lung expansion.

The term primary and secondary VATS is used for the procedures performed before or after the trial of standard management, respectively. VATS offsets many disadvantages of open thoracotomy and provides excellent vision of the entire hemithorax. The primary VATS allows determination of the stage of the disease, breaking of all loculi with complete evacuation of thick pus, and fibrinopurulent material. In early stage, it may reduce the bacterial load and chest drain is inserted in the proper dependent position. In addition, VATS gives visual impression of condition of underlying lung, its capacity to expand, and presence, site, and size of PPF or BPF. However, it may be difficult to perform formal resection of lung parenchyma to control the air leak using VATS in small children. The almost complete removal of thick pus and fibrinopurulent material results in early resolution of fever, chest drain is required for short duration and postprocedure hospitalization is reduced to 6–7 days. VATS causes minimal disturbance in the anatomy of nerves, muscles, and ribs. The integrity of the chest wall and the dynamics of the respiration are not disturbed. Kyphoscoliosis is avoided in children who undergo VATS. The less invasive nature of VATS produces less pain and better postoperative lung movements. This finally translates into early recovery and excellent cosmesis. The aesthetic appearance and the normal anatomy of the spine and the rib cage improve the child's posture and self esteem. The above-mentioned benefits make VATS as an attractive option in treatment for empyema in children. Moreover, the VATS reduce the cytokine response of the body in comparison to open thoracotomy.

However, VATS needs general anesthesia, operating room, endoscopic equipment, and team of experienced anesthetist and endoscopic surgeon. Some of the very sick patients undergoing VATS may need postprocedure careful monitoring, preferably in pediatric intensive care unit. The primary VATS in ET have been reported to have the best outcome. The author recommends primary VATS if patient presents late (>7 days history) or if there are loculations on imaging studies as the standard management is likely to fail. If thick fibrotic peel does not allow dissection to proceed to create enough space then the open decortication by minithoracotomy with or without rib resection should be performed.

Open thoracotomy and decortication involves opening of the thorax posterolaterally and excision of the thickened pleural encasing the lung. Lung pathologies like lung abscesses, necrotic lung, and BPF, if any, can be addressed simultaneously. It is an excellent modality of treatment useful in the treatment of advanced stage of empyema. Long-term aftereffects of open thoracotomy are often crippling.

Alexiou et al. reviewed their data of 44 children and concluded that open decortications are an excellent option for treating of advanced empyema. Fibrinolysis and VATS should be considered on their own merits, and should not be based on the adverse outcomes of open thoracotomy.

In the past, VATS was used after the failure of medical therapy, now it is increasingly used as primary therapy. In an study from Dallas on 139 children, Doski et al. demonstrated that children who underwent primary VATS significantly reduced hospital stay compared to those who had secondary VATS or open decortications for failed medical treatment.

Cohen et al. compared results of primary VATS with chest drainage alone and found significant reduction in the hospital stay (7.4 vs. 15.4 days) and removal of chest drain (4.0 vs. 10.2 days) in VATS group. In addition, 39% of children with chest drainage alone required some other form of surgical intervention. This study clearly demonstrates the superiority of VATS over chest drain alone. This observation has been confirmed from different centers. There are no studies comparing primary VATS with open decortication in children. Subramanium et al. demonstrated reduced hospital stay in VATS group of children in comparison to the open thoracotomy group in children who were referred for the failure of medical treatment.

Gates et al. carried out a systematic review of 44 retrospective studies to assess the superiority of VATS over chest drainage alone, fibrinolysis, or thoracotomy. They concluded VATS and open decortication led to early recovery in children. The study also identifies the lack of properly designed study to answer the question of superiority of VATS over the other available modalities of treatment.

Clinical Pearl

- Multiple studies throughout the world have confirmed the safety, efficacy, and cost effectiveness of video-assisted thoracoscopic surgery in the treatment of empyema in children.

KEY POINTS

- ☞ Empyema thoracis is a complex pediatric surgical disease and the best standard of care involve pediatric surgeon as soon as it is suspected
- ☞ Management needs to be individualized depending upon the presentation and stage of disease
- ☞ For patient presents early (<7 days of symptoms), standard management can be offered in the form of intravenous antibiotics and intercostal drainage
- ☞ Patients presenting late (>7 days of symptoms), or having loculations on imaging studies (X-ray or ultrasonography of chest) should be offered primary video-assisted thoracoscopic surgery
- ☞ Patients who fails to respond to standard management clinically and radiologically in 48–72 hours should be offered secondary video-assisted thoracoscopic surgery
- ☞ Patients having chronic disease with crowding of ribs should be offered an open surgery
- ☞ Video-assisted thoracoscopic surgery in treatment of empyema has decreased morbidity and mortality of the disease
- ☞ In India, due to limited availability of resources and the endoscopic surgical expertise, many patient who fails to received standard care may need either referral to higher center or an open surgery at appropriate time.

SUGGESTED READINGS

1. Alexiou C, Goyal A, Firmin RK, Hickey MS. Is open thoracotomy still a good treatment option for the management of empyema in children? Ann Thorac Surg. 2003;76:1854-8.
2. Balfour-Lynn IM, Abrahamson E, Cohen G, Hartley J, King S, Parikh D, et al. BTS guidelines for the management of pleural infection in children. Thorax. 2005;60(1):1-21.
3. Chan W, Keyser-Gauvin E, Davis GM, Nguyen LT, Laberge JM. Empyema thoracic in children: a 26-year review of the Montreal Children's Hospital experience. JPS. 1997;32(6):870-2.
4. Chiu CY, Wong KS, Huang JL Tasi MH, Lin TY, Hsieh SY. Proinflammatory cytokines, fibrinolytic system enzymes, and biochemical indices in children with infectious para-pneumonic effusions. Pediatr Infect Dis J. 2008;27(8):699-703.
5. Chonmaitree T, Bwell KR. Parapneumonic pleural effusion and empyema. Review of a 19 year experience, 1962-1980. Clin Pediatr. 1983;72:414-9.
6. Cohen G, Hjortdal V, Ricci M, Jaffe´ A, Wallis C, Dinwiddie R, et al. Primary thoracoscopic treatment of empyema in children. J Thorac Cardiovasc Surg. 2003;125:79-84.
7. Coren ME, Ng M, Rubens M, Rosenthal M, Bush A. The value of ultrafast computed tomography in the investigation of pediatric chest disease. Pediatr Pulmonol. 1998;26:389-95.
8. Doski JJ, Lou D, Hicks BA, Megison SM, Sanchez P, Contidor M, et al. Management of parapneumonic collections in infants and children. J Pediatr Surg. 2000;35:265-8.
9. Gates RL, Hogan M, Weinstein S, Arca MJ. Drainage, fibrinolytics, or surgery: a comparison of treatment options in pediatric empyema. J Pediatr Surg. 2004;39:1638-42.
10. Hamm H, Light RW. Parapneumonic effusion and empyema. Eur Respir J. 1997;10(5):1150-6.
11. Hoff SJ, Noblett WW, Heller RM, Pietsch JB, Holcomb GW Jr, Sheller JR, et al. Post pneumonic empyema in childhood: selecting appropriate therapy. J Pediatr Surg. 1989;24:659-64.
12. Hull J, Thomson A. Empyema thoracis: a role for open thoracotomy and decortication. Arch Dis Child. 1999;80:581.
13. Jaffe A, Balfour-Lynn IM. Management of empyema in children. Pediatr Pulmonol. 2005;40(2):148-56.
14. Jaffe A, Calder AD, Owens CM, Stanojevic S, Sonnappa S. Role of routine computed tomography in paediatric pleural empyema. Thorax. 2008;63(10): 897-902.
15. Jaffé A, Cohen G. Thoracic empyema. Arch Dis Child. 2003;88:839-41.
16. McAvin JC, Reilly PA, Roudabush RM, et al. Sensitive and specific method for rapid identification of Streptococcus pneumoniae using real-time fluorescence PCR. J Clin Microbiol. 2001;39(10):3446-51.
17. Merry CM, Bufo AJ, Shah RS, Schropp KP, Lobe TE. Early definitive Intervention by thoracoscopy in pediatric empyema. JPS. 1999;34:178-80.
18. Mitri RK, Brown SD, Zurakowski D, Chung KY, Konez O, Burrows PE, et al. Outcomes of primary image-guided drainage of parapneumonic effusions in children. Pediatrics. 2002;110:e37.
19. Nyman AG, Pitchumani S, Jaffe A, Sonnappa S. Pneumococcal empyema and haemolytic uraemic syndrome in children: experience from a UK tertiary respiratory centre. Arch Dis Child. 2009;94(8):645-6.
20. Peters RM. Empyema thoracis: historical perspective. Annals Thorac Surg. 1989:48:306-8.
21. Pierrepoint MJ, Evans A, Morris SJ, Harrison SK, Doull IJ. Pigtail catheter drain in the treatment of empyema thoracis. Arch Dis Child. 2002;87:331-2.
22. Satish B, Bunker M, Seddon P. Management of thoracic empyema in childhood: does the pleural thickening matter? Arch Dis Child. 2003;88:918-21.
23. Shoseyov D, Bibi H, Shatzberg G, Klar A, Akerman J, Hurvitz H, Maayan CI. Short-term course and outcome of treatments of pleural empyema in pediatric patients: repeated ultrasound guided needle thoracocentesis vs. chest tube drainage. Chest. 2002;121:836-40.
24. Singh M, Singh SK, Chowdhary SK. Management of empyema thoracic in children. Indian Pediatrics. 2002;39:145-57.
25. Sonnappa S, Cohen G, Owens CM, van Doorn C, Cairns J, Stanojevic S, et al. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. Am J Respir Crit Care Med. 2006;174(2): 221-7.
26. Sonnappa S, Jaffe A. Treatment approaches for empyema in children. Paediatr Respir Rev. 2007;8:164-70.
27. Spencer D. Empyema thoracis: not time to put down the knife. Arch Dis Child. 2003;88:842-3.
28. Subramaniam R, Joseph VT, Tan GM, Goh A, Chay OM. Experience with video-assisted thoracoscopic surgery in the management of complicated pneumonia in children. J Pediatr Surg. 2001;36:316-9.
29. Telunder RL, Moir CR. American Thoracic Society. Management of nontuberculous empyema. Am Rev Respir Dis. 1962;85:935-6.
30. Yim AP, Wan S, Lee TW, Arifi AA. VATS lobectomy reduces cytokine responses compared with conventional surgery. Ann Thorac Surg. 2000;70:243-7.

CHAPTER 126

Evaluation of Acute Abdominal Pain in Children

Ketan P Parikh

INTRODUCTION

The abdomen has often been labeled as a Pandora's box. This analogy is rooted in the fact that in many situations, the clinical presentation and investigative conclusions are rivaled by the finally ascertained diagnosis. Thus, every patient of an acute abdominal pain needs to be evaluated systematically to ascertain the most likely etiology to avoid long-term morbidity or an occasional mortality.

The term acute abdominal pain refers to a sudden, severe pain in the abdomen of short duration—usually of 24–48 hours. In contrast the term acute abdomen refers to a clinical condition with other manifestations which may include (besides the acute abdominal pain) a variety of other symptoms more particularly: vomiting, abdominal distension, fever, constipation, or diarrhea besides other symptoms. There may be an element of general toxicity due to dehydration or septicemia necessitating a more detailed assessment.

PATHOPHYSIOLOGY

Clinically, three categories of pain may arise from the abdomen:

- Visceral (splanchnic) pain: it results from stimulation of a viscous with a noxious stimulus like stretching or ischemia. It is usually dull, poorly localized, and is experienced in the midline. Pain arising from foregut structures (e.g., lower esophagus, stomach) is generally felt in the epigastrium, from midgut structures (small intestine) to the umbilical area and from hindgut structures to the hypogastrium
- Parietal pain: it follows a noxious stimulation of the parietal peritoneum. It is experienced with inflammation of the parietal peritoneum. It is usually sharp, discrete, and localized, and aggravates on coughing or movement
- Referred pain: it has characteristics of parietal pain but is felt in remote areas supplied by the same dermatome as the diseased organ. A classic example: abdominal pain experienced due to the supradiaphragmatic irritation of pleura due to a lobar pneumonia.

The fact that abdominal pain is so elusive is often a cause for it being labeled as functional or psychogenic in some cases. However, it needs to be emphasized that the labeling of this pain as psychogenic should be an opinion of exhaustive exclusion rather than a default assumption.

In spite of the multitude of investigative armamentarium available, evaluation of a child with an acute abdomen relies significantly on the clinical assessment and its correlation with the investigations. In doubtful situations, repeated physical examination by the same physician is often useful.

- ☞ Visceral pain: usually dull, poorly localized and in the midline
- ☞ Parietal pain: sharp, localized.

PAIN HISTORY

The chronology of the clinical presentation and the age of the child are important in the evaluation. In the acute surgical abdomen, pain generally precedes vomiting, while the reverse is true in medical conditions.

Most preadolescents have a poor sense of onset or location of pain. In children who cannot verbalize, the initial symptoms of nausea or periumbilical (visceral) pain may go unnoticed, and thus they often present at the second stage of visceral pain. A neonate or an infant with abdominal pain may express in the form of excessive crying, transient apneic spells or even grunting. These subtle symptoms require astute supervision to raise an early alarm to avoid missing life-threatening surgical emergencies.

- ☞ Pain preceding vomiting: possibly surgical abdomen
- ☞ Vomiting preceding pain: more likely medical abdomen.

Associated symptoms which have a significant bearing are:

- Vomiting (Table 1):
  - Nonbilious vomiting:
    - Common with a routine gastroenteritis

TABLE 1: Associated clinical features in a patient with acute abdominal pain

Vomiting	Before onset of pain	Possibly medical cause
	After onset of pain	More likely to be surgical cause—e.g., appendicitis/intestinal obstruction
	Bilious	More likely to be surgical cause—e.g., intestinal obstruction
	Nonbilious	May be either medical condition (gastritis/hepatitis, etc.) or early surgical cause
Abdominal distension	After excessive crying especially in a small child	Aerophagia
	With acute constipation	Possibly surgical, e.g., intestinal obstruction
	Upper abdominal distension	Possibly an upper abdominal obstruction
	With diarrhea	Severe watery → ?enterocolitis Persistent but small quantity → ?peritonitis
Constipation	Absolute (feces + flatus)	Intestinal obstruction
	Passing more flatus	Aerophagia (possibly supradiaphragmatic cause)
Fever	If after 1 or 2 days of abdominal pain	Surgical cause like appendicitis/peritonitis, etc.
	If precedes abdominal pain	More likely to be inflammatory like enterocolitis
Loose motions	If feculent	Enterocolitis
	Mainly mucus/blood	Intussusception/peritonitis/high intestinal obstruction
Dysuria	Abnormal ultrasonography	Maybe renal colic
	Normal ultrasonography	Maybe appendicitis, especially if pain is right sided
Gait	Walking with stoop on one side	Appendicitis/psoas irritation
Abdominal movements	Restricted	?Peritonitis
Cough/shortness of breath	—	Pleural pathology
Joint pains/skin purpura	—	?Henoch–Schönlein purpura

  - It is also an early feature of a surgical abdomen (an intussusception) or an inflammatory cause (like an acute appendicitis)
  - Persistent nonbilious vomiting along with abdominal pain at any age may also be seen in peritonitis. These patients may have fever/abdominal distension and constipation. A child with meconium peritonitis with secondary bacterial peritonitis may also have a periumbilical mottling besides radiological features of calcification in a case of intestinal obstruction/peritonitis (Fig. 1)
  - Some of the urogenital causes of acute abdomen may also have nonbilious vomiting:
    - Pyelonephritis—hypertension, urine examination, abdominal USG
    - Testicular torsion—clinical examination
    - Ovarian torsion—USG or other imaging
    - Renal colics—dysuria/USG
    - Bilious vomiting at almost any age signifies an intestinal obstruction unless proved otherwise
- Abdominal distension: it is usually a late sign in most cases of acute abdomen. It may result from:
  - Gas (aerophagia)—predominant gaseous distension is more a feature of hypoperistalsis
  - Intestinal obstruction—usually distension is a late symptom and may present as visible/palpable loops of bowel

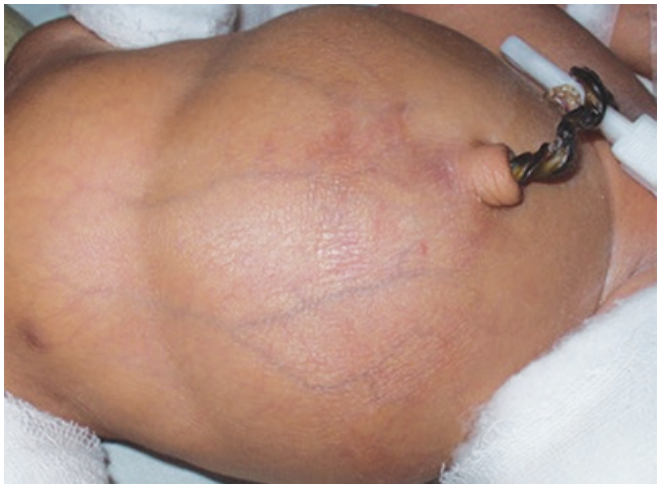


Fig. 1: Mottling of the abdominal wall in an infected meconium peritonitis

  - Fluid in the peritoneal cavity—in an acute abdomen this may suggest peritonitis
  - If accompanied by acute constipation or obstipation—surgical cause
  - A neonate with a scaphoid abdomen or distension restricted to upper half could possibly either be:
    - A high bowel atresia (duodenal/high jejunal)

  - A midgut volvulus due to an intestinal malrotation especially if there is a delayed onset of intestinal obstruction
    - In either case, a surgical exploration would be needed; a delay in surgically exploring a case of midgut volvulus could lead to extensive gangrene of the entire midgut which is incompatible to normal life without life-long total parenteral nutrition/intestinal transplantation
    - In those cases where the abdominal distension is more generalized, a lower intestinal obstruction may be considered
  - If accompanied with diarrhea:
    - Either severe enterocolitis (there would also be frequent passage of flatus) or peritonitis (there is usually infrequent passage of flatus and minimal fecal content) is a strong indication for a surgical opinion. Bogginess in the prerectal space on a per-rectal examination would almost be diagnostic of a pelvic peritonitis
    - An acute appendicitis in a pre-school child may present directly as peritonitis because of the subtlety of the early symptoms and the rapid progression of the pathology at this age
- Constipation: unlike chronic constipation, acute constipation usually has an organic cause:
  - Absolute constipation (obstipation—failure to pass feces/flatus)—strongly suggests a surgical cause of acute abdomen
  - Frequent passage of flatus in a patient with abdominal distension—possibly medical cause/pneumonia
  - Chronic constipation preceding abdominal pain—more likely primary constipation
  - Constipation following vomiting and abdominal pain—more likely surgical. Child may pass 1 or 2 normal stools and constipation may set in later once the bowel distal to the obstruction is completely evacuated. In neonates with congenital bowel obstruction, there may be a history of passage of some meconium, but in most cases, direct questioning of the neonate's attendant may reveal that this meconium was pale colored. In those cases where the neonates acute abdomen has set in a few days after the passage of normal meconium, the possibility of volvulus with malrotation becomes higher
  - In the occasional patient with high obstruction and peritonitis, the baby may pass loose motions due to peritoneal irritation of the distal bowel; however, this would be predominantly mucoid and not bile containing
- Fever:
  - If the acute abdominal pain follows a febrile illness, it is likely to be secondary to gastroenteritis or gastritis resulting from the medications
  - However, if fever follows, an acute abdominal pain episode for 1–3 days—possibility of localized or generalized peritonitis/liver abscess or some other inflammatory pathology of the abdomen or even chest
- Loose motions: note the content of loose motions:
  - If feculent—more chances of enteritis/colitis
  - If mucoid—need to consider surgical causes
- Bleeding per rectum:
  - In infants—typical currant jelly stools (mucoid mixed with blood): high chances of intussusception
  - If content is predominantly altered blood with mild colics, consider bleeding due to a Meckel's diverticulum
  - After 2 years of age—mild bleeding with feces with abdominal pain (not severe)—there is possibility of rectal juvenile polyps leading to localized intussusception
- Dysuria:
  - In case with lateralized colics—renal colics
  - If right-sided pain with dysuria, the possibility of acute appendicitis with ipsilateral ureteric/vesical irritation can be a possibility and needs to be ruled out
- A history of recent trauma may indicate the cause of pain
  - Additional history:
    - Cough or shortness of breath, and chest pain point to a thoracic source
    - Polyuria and polydipsia suggest diabetes mellitus
    - Joint pain, rash, and smoke-colored urine suggest Henoch-Schönlein purpura
    - High fever with toxicity acute hemolytic syndromes like malaria/dengue which may mimic an acute abdomen
    - Medication: a detailed drug history especially salicylates/nonsteroidal anti-inflammatory drugs/steroids
    - Gynecologic history: relevant especially in adolescent girls

Past history: all previous hospitalizations or significant illnesses, e.g., sickle cell anemia/porphyria. A history of previous surgery or peritonitis may suggest adhesive obstruction.

Family history: family history of sickle cell/or cystic fibrosis may indicate the diagnosis.

CLINICAL EXAMINATION

General Examination

A throat examination to identify enlarged tonsils leading to a swallowed gastrointestinal infection, a chest examination to rule out a pleural/pulmonary pathology is important complimentary clinical guide.

Gait

While a child with colics writhes with pain, children with peritonitis remain quite still and resist movement. A patient with acute appendicitis typically walks with a stoop to the right.

Vital Signs

Dehydration (severity needs to be assesed), fever if any. Kussmaul's respiration indicates diabetic ketoacidosis.

Abdominal Examination

The abdominal movements should be observed, and the patient should be asked to distend the abdomen and then flatten it. Restricted abdominal movements indicate a peritoneal irritation in that area:

- Visible contusions would suggest a traumatic etiology
- A definite examination of the hernial orifices is mandatory in any case of acute abdominal pain since a strangulated hernia may present as an acute abdomen (Fig. 2)
- Mottling of the abdomen may indicate an inflammatory etiology especially in a neonate (Fig. 1)
- Tenderness of abdomen needs to be evaluated with the palmar (flat) surface of the fingers rather than the tips of the fingers (Figs 3 and 4). In a crying child, it is best evaluated between breaths whereas other children may be asked to take deep breaths with an open mouth to relax the abdominal muscles. Since smaller children are not able to localize parietal pain well, guarding/rigidity is more relevant than tenderness
- Deeper palpation is necessary to discover masses and organomegaly

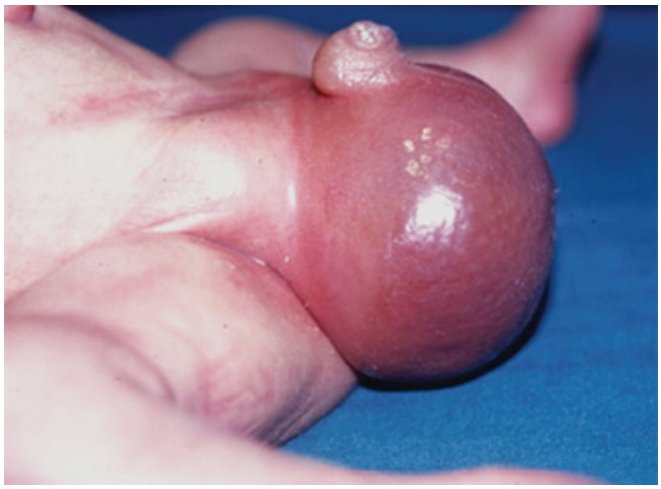


Fig. 2: Neonatal peritonitis presenting as acute scrotum due to the patent processus vaginalis

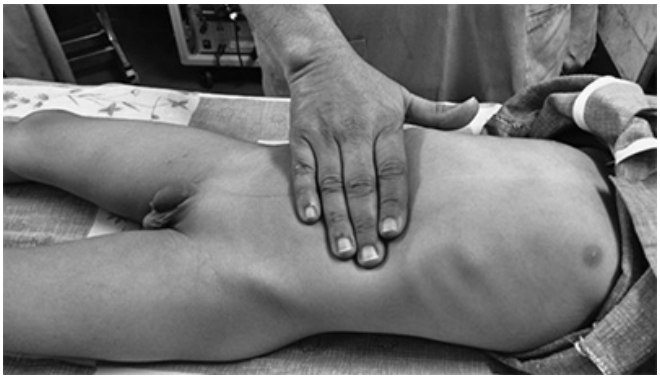


Fig. 3: Demonstrating the correct method of palpation of abdomen (with the flat of the hand)

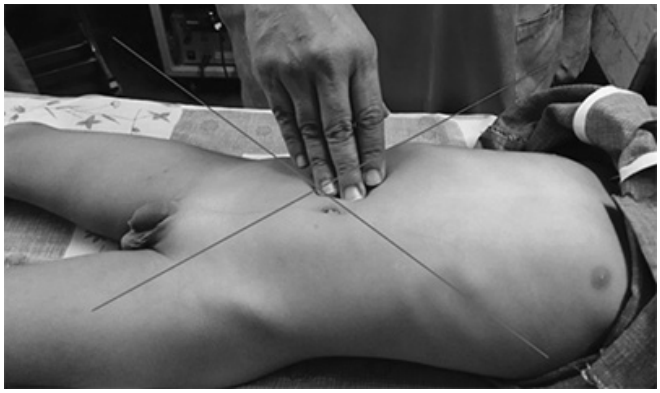


Fig. 4: Avoidance of palpating the abdomen with the tips of the fingers

- A per rectal examination may reveal a loaded rectum leading to constipation and abdominal pain/a bogginess in the pelvis indicative of a peritonitis/blood in the rectum or a palpable rectal polyp.

INVESTIGATIONS (TABLE 2)

These should be tailored to the patient's symptoms and clinical findings.

TABLE 2: Investigative algorithm in a case of acute abdominal pain

White blood cell count	Marginally high	Appendicitis/intestinal obstruction
	Very high	Perforated appendicitis/ peritonitis/liver abscess
	Normal/low	Hepatitis/mesenteric adenitis/viral infections
Urinalysis	Pyuria/hematuria	Renal etiology/appendicitis
Erect abdominal/ chest film	Gas under diaphragm	Major G.I. perforation
	Fluid levels	Bowel obstruction/paralytic ileus
	Ground glass appearance	Peritonitis
	Raised diaphragm (rt)	? Liver abscess
	Pleural/pulmonary shadow	Consolidation/diaphragmatic hernia/pleural effusion
Abdominal ultra-sonography (operator dependent)	Highly sensitive	Ovarian pathology/ renal pathology/ hepatic inflammation/ pancreatic inflammation/ intussusception
	Poor sensitivity	Maybe negative in many bowel pathologies including appendicitis
Diagnostic laparoscopy	—	Possible only if bowel distension is not severe

- Hemogram: leukocytosis, especially in the presence of a shift to the left and toxic granulations in the peripheral smear, indicates an infection
- Urinalysis: pyuria, hematuria—may suggest a renal cause or a gastrointestinal cause irritating the urinary tract, e.g., appendicitis
- Erect/lateral decubitus—plain abdominal films:
  - Gas under diaphragm—major gastrointestinal perforation
  - Fluid levels—bowel obstruction (Figs 5 and 6)
  - Ground glass appearance with or without fluid levels—peritonitis (Fig. 7)
- Chest radiographs: gas under diaphragm/pneumonia/raised diaphragm due to a liver abscess.
- Abdominal ultrasonography (results are operator dependent): most useful in diagnosing gynecologic pathology such as ovarian cysts, ovarian torsion, or advanced periappendiceal inflammation (Fig. 8)
- Abdominal computed tomography: involves radiation exposure and may require the use of contrast agents.

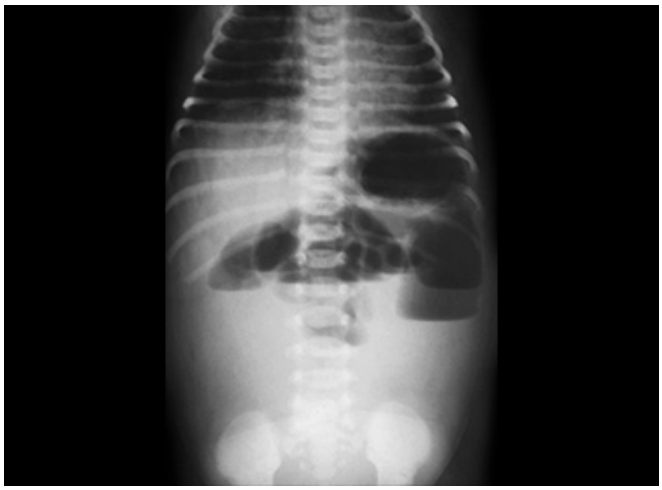


Fig. 5: Multiple fluid levels (mid-intestinal obstruction)

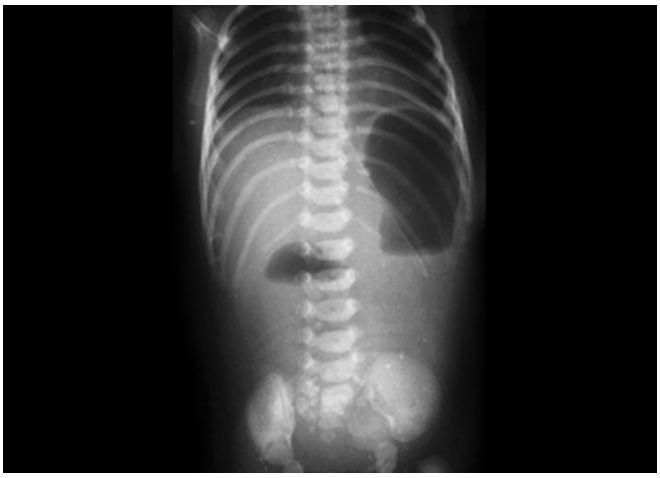


Fig. 6: Double-bubble shadow of duodenal obstruction

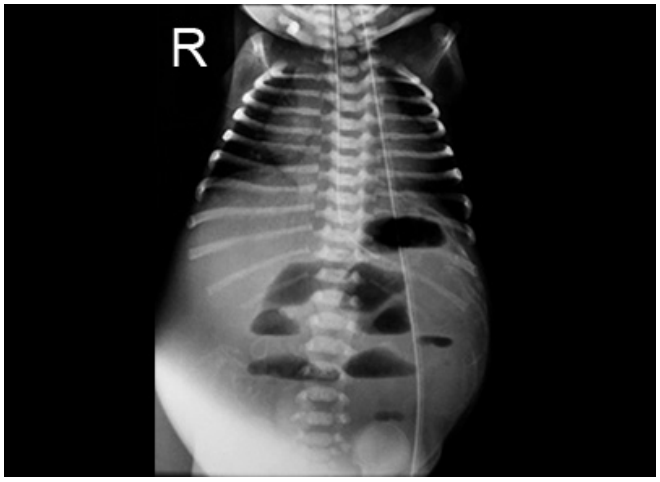


Fig. 7: Central fluid levels surrounded by groundglass appearance of peritonitis

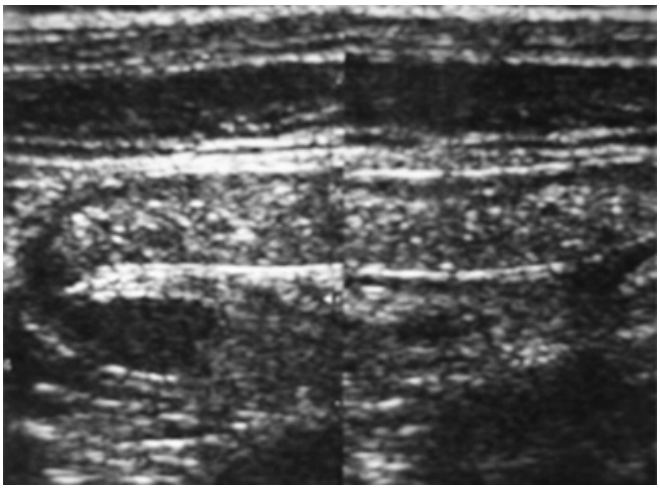


Fig. 8: Ultrasonographic picture of an acutely inflamed appendix

computed tomography may be necessary if excessive bowel gas precludes ultrasonographic examination
- Diagnostic laparoscopy: it is increasingly being used prior to a surgical intervention and thus avoids a formal laparotomy in selected cases. Some of these may include acute appendicitis, Henoch-Schonlein pupura, Meckels' diverticulitis, idiopathic omental necrosis, diagnosing a nonviable bowel, loop, etc. (Figs 9–11).

Specific Conditions Causing Acute Abdomen Pain

The specific conditions causing acute abdomen pain are given in table 3.

Infantile Colic

Infantile colic affects about 20% of infants during the first few months of life. Typically, the affected children scream, draw their knees up against their abdomen, and appear to be in

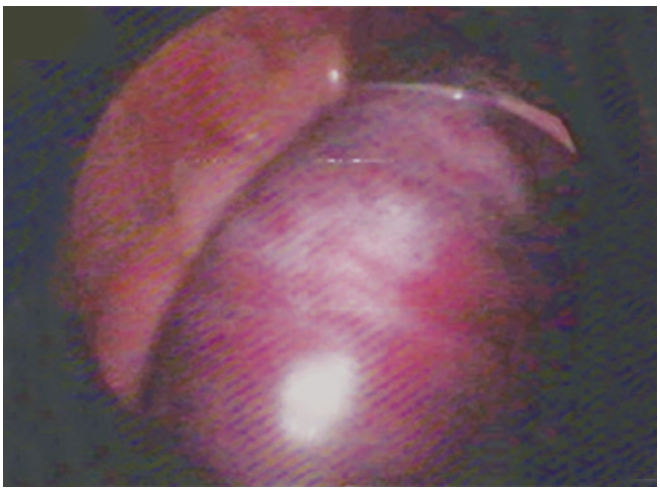


Fig. 9: Laparoscopic view of gangrenous bowel

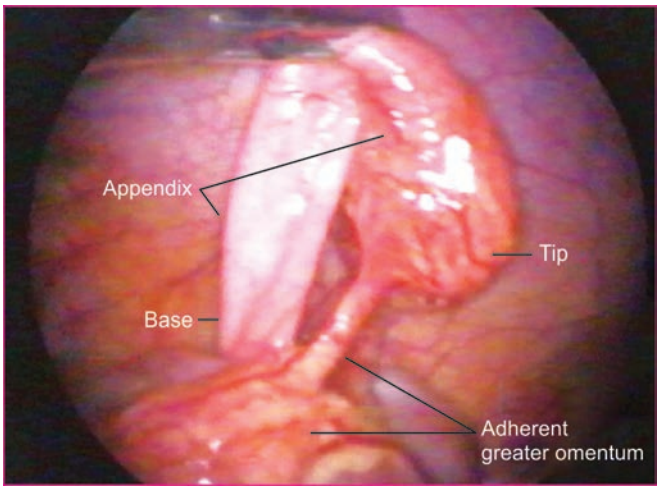


Fig. 10: Laparoscopic view of an acutely inflamed appendix (covered with surrounding omentum

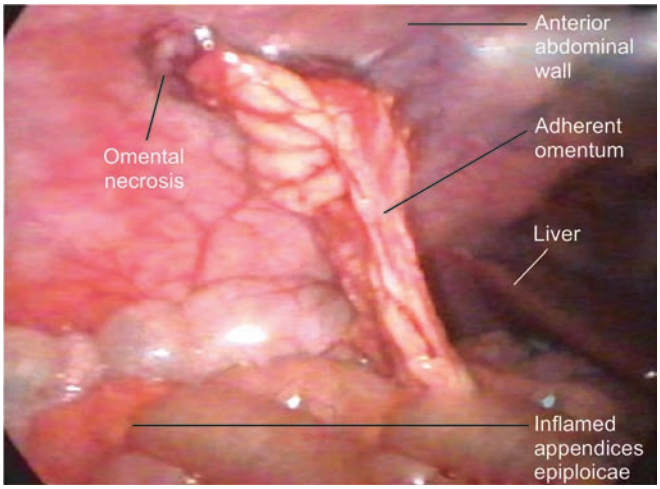


Fig. 11: Idopathic omental torsion with necrosis of the omentum

severe pain. There may be associated symptoms like vomiting; however, this is rarely persistent. Most infantile colics subside within a few hours. The closest differential which one needs to be aware of and needs to be eliminated is intussusception and volvulus with malrotation. In case of persistence of symptoms beyond 1–2 hours or in case of bilious vomiting, bleeding per rectum, an abdominal ultrasonography should be asked for as a screening test.

Gastroenteritis

Gastroenteritis is one of the most common causes of abdominal pain in children. Vomiting and/or diarrhea are usually associated and there may also be fever. Differentiation from an intussusception is done by the fact that in intussusception, the stools usually does not contain fecal matter after one or two motions and there is only blood and/or mucus.

Appendicitis

Appendicitis is the most common surgical condition in children with acute abdomen.

Western literature places the incidence as approximately 1 in 15 persons. While older children may show the classical pain—vomiting-fever chronology, younger children may present directly as peritonitis. Most children have the pain mainly in the periumbilical area with a few vomits and the pain then shifts to the right side only after localized peritonitis sets in. In spite of the various investigative modalities, acute appendicitis still remains a clinical diagnosis and investigations only have a supportive role.

Mesenteric lymphadenitis often mimics appendicitis. Being primarily an adenoviral infection, fever is a more prominent symptom. Generalized lymphadenopathy on abdominal ultrasonography may be a feature with high fever may suggest the same.

TABLE 3: Causes of abdominal pain according to age

Infants	Almost any age	Older children
• Infantile colic • Volvulus	• Gastroenteritis • Appendicitis • Urinary tract infection • Incarcerated hernia • Peritonitis • Cholecystitis • Hepatitis • Pancreatitis • Inflammatory bowel disease • Trauma • Mesenteric lymphadenitis • Henoch-Schönlein purpura • Intestinal obstruction • Sickle cell crisis • Meckel's diverticulum	• Ovarian/testicular torsion • Pelvic inflammatory disease • Mittelschmerz • Diabetic ketoacidosis • Porphyria

Abdominal Trauma

Abdominal trauma can be accidental or intentional. There may be a bowel perforation, intramural hematoma, laceration, or hematoma of the liver or spleen, and avulsion of intra-abdominal organs or vascular pedicles. These patients may benefit from an abdominal computed tomography scan in addition to an abdominal ultrasonography. Diagnostic laparoscopy has a definite role in selected patients.

Intussusception is common around 8–10 months of age and occurs due to a hypertrophied Peyer's patch (acting as a lead point). Such a hypertrophy may occur due to a change in the bacterial flora during weaning or gastrointestinal infection or due to ingestion of infected respiratory secretions.

Clinically:

- There may be a prior history of an upper respiratory tract infection
- Colics: pain occurs in short bursts with intermittent periods of remission
- Vomiting: bilious only in late cases
- Red currant jelly stools: usually with no fecal matter after 1–2 times (a differentiating feature from dysentery)
- On abdominal palpation: intussusception may be felt as banana-shaped mass with the concavity toward the umbilicus. Occasionally the mass can be felt per rectally
- In late cases: features of septicemia and peritonitis.

Investigations:

- Ultrasound of the abdomen can be diagnostic
- Alternatively, a barium enema: the coiled spring sign or the claw sign.

Intestinal Obstruction

Intestinal obstruction is uncommon in older children unless there is a previous history of abdominal surgery. Additional causes include volvulus, intussusception, incarcerated hernia, congenital, or postinflammatory bands including intestinal tuberculosis. An erect abdominal X-ray would be diagnostic in most cases. A trial of conservative management under surgical supervision may be indicated in case there is no suspicion of bowel ischemia. Pain not responding to antispasmodics, tender/palpable loop of bowel, evidence of perforation/ischemia on imaging, and failure of conservative treatment for more than a few days will be indications for surgical intervention.

Pelvic inflammatory disease or primary peritonitis is typically seen in females and the diagnosis is more on laparoscopic/surgical exclusion of known causes of peritonitis.

Indications for surgical consultations in children with acute abdominal pain:

- Severe or increasing abdominal pain with progressive signs of deterioration
- Bile-stained or feculent vomitus
- Involuntary abdominal guarding/rigidity
- Rebound abdominal tenderness
- Marked abdominal distension with diffuse tympany
- Signs of acute fluid or blood loss into the abdomen
- Significant abdominal trauma
- Suspected surgical cause for the pain
- Abdominal pain without an obvious etiology.

Clinical Pearls

- In the acute surgical abdomen, pain generally precedes vomiting, while the reverse is true in medical conditions
- While a child with colics writhes with pain, children with peritonitis remain quite still and resist movement
- Bilious vomiting at almost any age signifies an intestinal obstruction unless proved otherwise.
- Constipation following vomiting and abdominal pain—more likely surgical
- If fever follows an acute abdominal pain episode for 1–3 days—possibility of localized or generalized peritonitis or some other inflammatory pathology
- Restricted abdominal movements indicate a peritoneal irritation in that area
- A definite examination of the hernial orifices is mandatory in any case of acute abdomen
- A patient with acute appendicitis typically walks with a stoop to the right.

KEY POINTS

- ☞ While, the term "acute abdominal pain" refers to a sudden, severe pain in the abdomen of short duration, the term "acute abdomen" refers to a clinical condition with other manifestations which may include (besides the acute abdominal pain) vomiting, abdominal distension, fever, constipation, or diarrhea
- ☞ Labeling of abdominal pain as psychogenic should be an opinion of exhaustive exclusion rather than a default assumption
- ☞ Tenderness of abdomen needs to be evaluated with the palmar (flat) surface of the fingers rather than the tips of the fingers
- ☞ Plain vertical abdominal X-ray is as important as abdominal ultrasonography in the evaluation of acute abdominal pain
- ☞ An acute appendicitis in a preschool child may present directly as peritonitis because of the subtlety of the early symptoms and the rapid progression of the pathology at this age.

SUGGESTED READINGS

1. Cope Z Early diagnosis of the acute abdomen. Oxford University Press; 2005.
2. Fleisher GR, Ludwig S, editors. Textbook of pediatric emergency medicine. Lippincott Williams and Wilkins; 6th revised edition.
3. Paterson-Grown S, Ellis BW, Paterson-Brown S. Hamilton baileys emergency surgery. 13th ed. Boca Raton: CRC Press; 2015.

CHAPTER 127

Management of Undescended Testis: Cryptorchidism

Rasik S Shah, Suyodhan A Reddy, Nachiket M Joshi

INTRODUCTION

Undescended testis (UDT) or cryptorchidism is the most common congenital abnormality of the genitourinary tract. It comprises of true cryptorchid or UDT, ectopic testis, absent testis, atrophic testis, retractile testis, and ascended testis. It is important to differentiate the aforementioned conditions, as their individual management is different.

TERMINOLOGY

- Cryptorchidism: cryptorchidism, by definition, means absence of one or both testis in the scrotum
- True UDT: the testis, which has failed to descend along its normal pathway from the retroperitoneum to the scrotum, is known as true UDT. If the testis remains in abdominal cavity then it is known as abdominal UDT; if it comes out of internal ring and goes back to the abdomen, then it is known as emergent UDT; if it is in inguinal canal, then it is known as intracanalicular UDT; if it is just outside the external ring, then it is known as suprascrotal UDT.
- Ectopic testis: the testis, which has normally descended from retroperitoneum up to the external ring subsequently gets deviated to an aberrant position, is known as ectopic testis. It may be palpable in the superficial inguinal pouch (most common), suprapubic region, femoral triangle, or perineum. Rarely, testis travels via opposite internal ring into contralateral scrotal compartment and then it is known as transverse testicular ectopia.
- Absent testis: testis which embryologically has failed to develop is known as absent testis.
- Atrophic testis: the testis was developed normally and at some stage, it has undergone atrophy secondary to vascular compromise. If it occurs in the prenatal period, then it is also known as the vanishing testis syndrome or testicular regression syndrome.
- Retractile testis: the testis normally descends to the scrotum at birth; however, the hyperactive cremasteric reflex pulls the testis into suprascrotal position. This testis can be manipulated into a dependent scrotal position, by making the patient relax his cremasteric muscle. The testis will remain there as long as the cremasteric muscles are relaxed.
- Ascended testis: the testis, which has been documented to be in the scrotum in neonatal period, is found to be at higher position in later childhood is known as the ascended testicle.

PATHOGENESIS

The factors responsible for normal testicular descent are not well understood. The intra-abdominal phase of descent is thought to be androgen-independent and is mediated by a polypeptide "descendin". The testis passes through the inguinal canal in 28th week of gestation; it is believed to be the combined result of interactions between mechanical, hormonal, and neurotransmitters. Changes in abdominal pressure, patency of the processus vaginalis, gubernacular regression, androgens, gonadotropins, Müllerian inhibiting substance (MIS), and calcitonin gene-related peptide are all thought to play a role.

The pathogenesis of UDT is less understood than that of normal testicular descent. Alterations in any of the factors that contribute to normal testicular descent may theoretically result in UDT. Gonadotropin deficiencies *in utero*, decreased MIS, and increased expression of estradiol in the placenta have been proposed as contributing factors.

EPIDEMIOLOGY AND RISK FACTORS

At birth, 2–5% of full-term and 25–30% of premature male infants are born with an UDT. Of these, in approximately 70%, the testis descends spontaneously within first 2–3 months of life and is unlikely to descend after 3 months. At 1 year of age, the prevalence of UDT is around 0.8–1%, which is similar to that in adults.

The prevalence of UDT varies geographically, which may be due to genetics or environmental factors. Prematurity, being small for gestational age at birth, and birth weight less than 2.5 kg are common risk factor. Prenatal exposure to endocrine disruptors (e.g., diethylstilbestrol, pesticides) also has been associated with cryptorchidism in some studies.

Associated Conditions

Cryptorchidism usually is an isolated finding. However, it may occur in association with endocrine disorders, genetic syndromes, and morphologic abnormalities, especially if it is bilateral. Associated conditions are shown in box 1.

Clinical Pearl

- Patients having undescended testis and hypospadias have high incidence of underlying disorders of sexual development.

CLINICAL FEATURES

Clinical features of cryptorchidism include an empty, hypoplastic, hypopigmented, and poorly developed rugae of scrotum or hemiscrotum. Inguinal fullness may be present.

In approximately 10%, it is a bilateral condition. Bilateral UDT are more commonly associated with other conditions. Unilateral UDT is more common on left side.

The most common location for an UDT is just outside the external ring (superficial inguinal pouch), followed by the inguinal canal (intracanalicular), and finally intra-abdominal. The testis is not palpable in 20% of patients with UDT.

The growth of unilateral UDT is impaired compared with the normally descended contralateral testis, whether it descends spontaneously or it is surgically brought in scrotum. Treatment before 1 year of age is associated with partial catch-up of growth.

Box 1: Associated conditions

- Prune belly syndrome
- Myelomeningocele
- Cerebral palsy
- Disorders of sexual development
- Genetic disorders with diminished testosterone production
  - Kallamann syndrome
  - Klinefelter syndrome
  - Prader-Willi syndrome
  - Androgen insensitivity syndrome
- Genetic disorders
  - Noonan's syndrome
- Primary hypogonadism with increased gonadotropin levels
  - Laurence-Moon syndrome
- Other genetic disorders
  - Trisomy 18
- With no effect on testosterone and gonadotropin levels
  - Trisomy 13
  - 22q11.2 deletion syndrome
  - 1p36 deletion syndrome
  - Beckwith-Wiedemann syndrome Smith-Lemli-Opitz syndrome Cornelia de Lange syndrome, etc.

COMPLICATIONS AND SEQUELS

Complications and sequels of UDT include inguinal hernia, testicular torsion, testicular trauma, subfertility, and testicular cancer. The potential seriousness of these complications and sequels demands early referral for definitive treatment (Box 2).

Inguinal Hernia

The UDT have an associated patent processus vaginalis in about 60% cases. Inguinal hernia in UDT can present at any age with the typical symptoms or complications, including incarceration.

Testicular Torsion

Testicular torsion is approximately ten times more common in UDT than in normal scrotal testis, but the true relative risk is not known. The rate of salvage of torsion in cryptorchid testis is decreased compared to that in normally descended testis, perhaps related to delay in diagnosis.

If patient with inguinal testis develops the torsion, then he will present with local swelling and tenderness with an empty ipsilateral hemiscrotum. If patient with intra-abdominal testis develops torsion, then he will present as an acute abdomen with empty one side of scrotum and usually diagnosis of torsion is made only at the time of abdominal exploration.

Testicular Trauma

Testis located in the inguinal canal is at increased risk of blunt traumatic injury from compression against the pubic bone.

Subfertility

Men with a history of UDT have lower sperm counts, sperms of poorer quality, and lower fertility rates than men with normally descended testis. Impaired spermatogenesis is probably related to underlying genetic, hormonal, and developmental abnormalities, some of which may be partially reversible through early surgical intervention. Sperm counts in adulthood are directly related to prepubertal germ cell counts and type of cell (gonocyte versus adult dark spermatogonia) at the time of orchidopexy. The local milieu reduces the number of Leydig cells, which produce testosterone. Testosterone plays an important role in maturation of gonocyte to dark adult spermatogonia. This affects both quality and quantity of the mature germ cells in the testis.

The degree of germ cell dysfunction increases with bilateral involvement and with increasing duration of suprascrotal location. Intra-abdominal and intracanalicular UDT are affected similarly, probably related to the damaging effect of higher temperatures outside the scrotum on spermatogenesis.

Elevated serum gonadotropin [follicle stimulating hormone (FSH) and luteinizing hormone (LH)] concentration and

Box 2: Complications and sequels of undescended testes

- Hernia
- Torsion
- Trauma
- Subfertility
- Testicular cancer with late detection

decreased serum inhibin B concentration are endocrinologic markers of testicular dysfunction.

Testicular Cancer

Men with a history of UDT have an increased risk of developing testicular cancer compared with men in the general population in whom the age adjusted incidence is approximately 5.4 per 100,000. The epidemiological data points toward a definite relationship between the intrauterine, perinatal development and UDT.

The risk of developing testicular cancer is further increased in men with bilateral cryptorchidism (which may be associated with endocrinologic abnormalities or abnormal karyotype) and intra-abdominal UDT.

A history of cryptorchidism is also a risk factor for developing intratubular germ cell neoplasia of unclassified type, a premalignant condition, which is also called carcinoma in situ, or testicular intraepithelial neoplasia.

Surgical repositioning of the testis (orchidopexy) before puberty appears to decrease the risk of testicular cancer, but does not completely eliminate it. Testicular malposition is not the only factor in the development of testicular cancer in men with a history of cryptorchidism because surgical repositioning does not completely eliminate the risk.

Clinical Pearl

- Children who has been operated for orchidopexy should be taught self-examination for early detection of testicular carcinoma.

MANAGEMENT

The patients of UDT should be worked up for anesthesia fitness preoperatively. Other hormonal investigations are optional and may be performed depending upon local institutional policy. Imaging studies for locating testis are not required, as they have limited specificity and sensitivity. In addition, these investigations induce confusion in minds of parents. On imaging, if the testis is not visualized and surgeon recommends surgery, then they start thinking although that testis is not seen and even then the surgeon still wishes to operate. If the surgeon explains why surgery is essential, then the parents might raise the query that if the surgeon has already decided to operate upon then what was the need to doing imaging studies. In order to avoid confusion, it is safer not to order investigations for locating testis.

The goal is to bring the apparently normal looking testis into the scrotum from its abnormal position and to prevent the complications. It is essential to pex testes into scrotum to prevent postoperative ascent. Small atrophic testes should be removed.

The testis in scrotal position is less likely to undergo torsion or blunt traumatic injury. In addition, it also permits easier self-examination for early detection of malignancy. If orchidopexy is performed early, it may reduce the risk of infertility and testicular cancer. The testis in normal scrotal position is likely to provide improved body satisfaction, although the psychological impact of abnormal testicular position has not been studied.

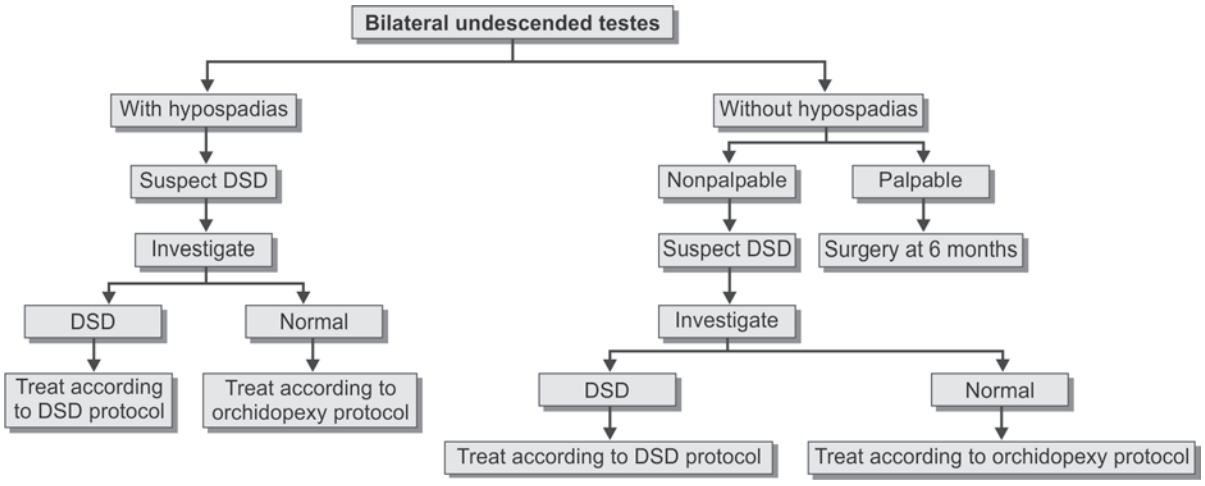
Hormonal therapy has been tried in past, but it has not proven to be efficacious in inducing testicular descent.

Bilateral Undescended Testis

If the patients have bilateral palpable UDT without hypospadias, then they should be operated after the age of 6 months. If the patients have bilateral nonpalpable UDT or if UDT is associated with hypospadias, then they should be investigated for disorders of sex differentiation (DSD). If investigations are in line of a normal boy, then the orchidopexy should be performed after the age of 6 months. Authors operate on both sides in the same sitting even when they are nonpalpable, though some institutes have protocol of operating on one side first and then on other side. If investigations are suggestive of DSD, then one should follow DSD protocol (Algorithm 1).

ALGORITHM 1

Management algorithm for bilateral undescended testis



DSD, disorders of sex differentiation.

Surgical Treatment

Timing of surgery: The spontaneous descent is less likely to occur after 3 months of age and it has recommended that children with UDT should be operated as soon as possible after 6 months of age to prevent the complications. In children with ascended testicle, surgery should be performed as soon as possible after diagnosis is established.

Early orchidopexy before 2 years (ideally before 1 year) of age is associated with improved testicular growth and fertility potential.

If a patient with UDT presents with inguinal hernia, then orchidopexy with repair of inguinal hernia should be performed at the time of presentation (Algorithm 2).

Clinical Pearl

- Orchidopexy should be performed any time after the age of 6 months, the earlier the better to prevent its complications. Undescended testes presenting with inguinal hernia should be operated at the time of diagnosis.

Palpable Testis

Patients with palpable UDT should undergo open orchidopexy. The surgery is usually carried out as a day care procedure under laryngeal mask and caudal anesthesia. An incision is taken in the lower skin crease in the groin. The testis along with the cord structures are mobilized, herniotomy (if hernial sac is present) is performed and testis is manipulated into the scrotum and sutured in place. Usually palpable testis can be brought down to the scrotum as the cord structures have adequate length. Sometimes, even palpable (especially emergent) UDT has short cord and they may not come down to scrotum without tension and can ascend postoperatively into higher position needing second surgery. The exact incidence of such a scenario has not been reported, but it is likely to be in range of 2–3% (personal experience).

Clinical Pearl

- Palpable undescended testes (UDT) should undergo open surgery and nonpalpable UDT should undergo laparoscopic surgery

Nonpalpable Testis

The nonpalpable testis can be abdominal, atrophic, or absent. It is difficult to differentiate between these conditions preoperatively and parents of these patients should be explained about possible outcome of surgery, i.e., single stage orchidopexy, two stage orchidopexy, or orchiectomy depending upon the operative findings. Even patients with nonpalpable UDT can be operated as a day care surgery, but they need to be preferably scheduled as first case in the morning.

The first step is to perform examination under anesthesia and if testis is palpable, then to proceed with standard open orchidopexy. If the testis is confirmed to be not palpable, then proceed with the next step, i.e., laparoscopic surgery.

Following are the advantages of laparoscopic surgery over open procedure in nonpalpable UDT:

- Probability of missing the high testis and testis in abnormal position (retrovesical) is almost nil
- Laparoscopic mobilization of testicular vessels is far superior as compared to open mobilization. The incidence of postoperative ascent and atrophy is less common compare to open surgery.

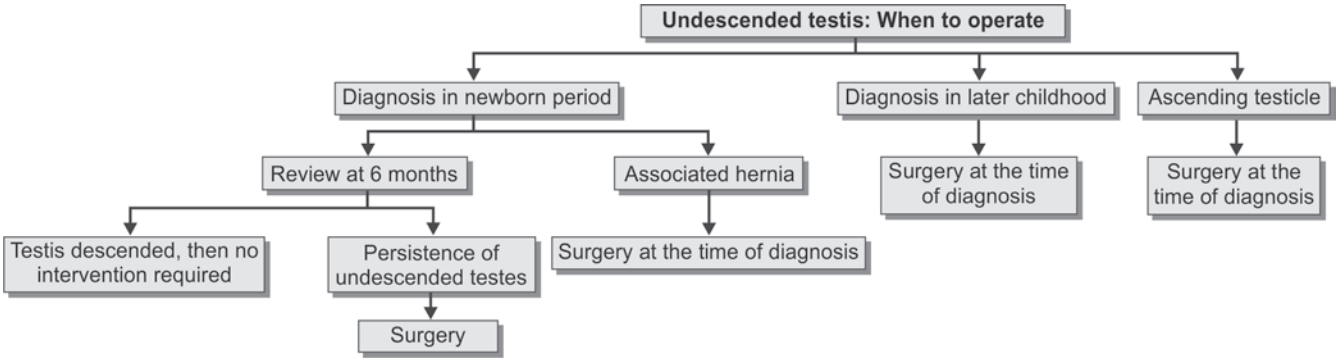
In a place, where option of laparoscopic pediatric surgery is not available, surgeon may proceed with open surgery by lower inguinal crease incision. If the testis is not found in the groin, then the peritoneal exploration may be performed by extending the groin incision laterally or to reverse the patient from anesthesia and refer the patient to the higher center. If cord structures or testicular remnants are found, they are removed and the procedure is terminated.

The diagnostic laparoscopy is a safe procedure in experienced hands. The laparoscope is placed via the umbilicus and following observations are carried out, patency of the processus vaginalis, location of testis, testicular vessels, vas deferens, gubernaculum, and presence of Müllerian structures. The findings on laparoscopy decide the further plan of action (Algorithm 3).

The presence of blind ending vas and vessels in the retroperitoneum (usually 2–3 cm proximal to the internal ring) is suggestive of vanishing testis syndrome. In this situation, nothing further needs to be done for the UDT, though fixation of contralateral testis to prevent torsion and loss of only testicular tissue remains controversial at present. Authors routinely

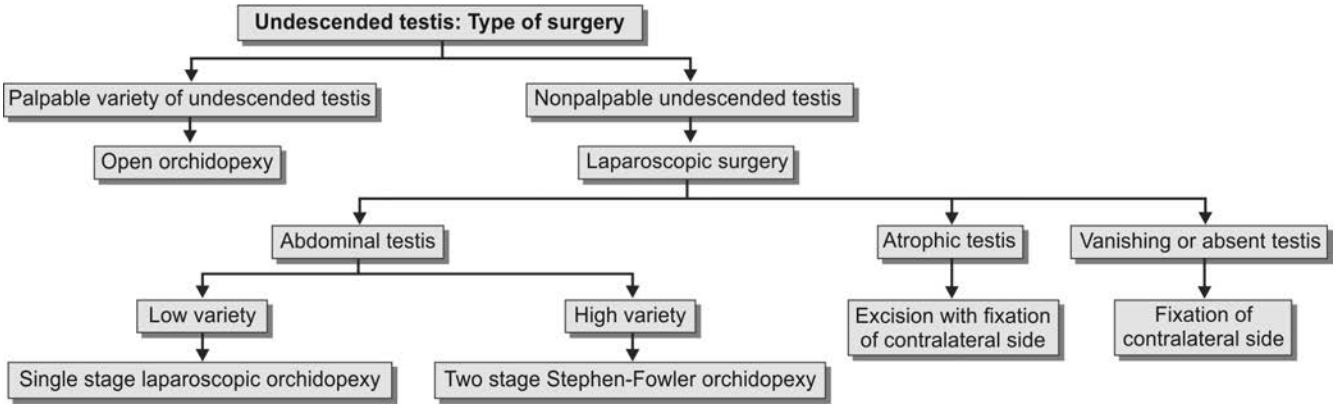
ALGORITHM 2

Timeline for surgery in undescended testis



ALGORITHM 3

Treatment algorithm for undescended testis



fix the contralateral testis in such a scenario. In addition, if facilities are available, then surgeon can insert the testicular prosthesis on the ipsilateral side at the time of surgery or later on at puberty. If the prosthesis is inserted in a young child, then it may need to be revised at the time of puberty to match the normal contralateral testicular size. The psychological assessment of these young adults with or without prosthesis has not been performed, but logically the person with normal feel of scrotum is likely to have better self-esteem.

On laparoscopy, if vas and vessels are entering internal ring, then patient is likely to have atrophic testis either in the inguinal canal or in the scrotum. This patient should undergo excision of atrophic testicle either laparoscopically (if hernial sac is open and atrophic testis is visualized) or by an open inguinal incision along with fixation of contralateral testis by scrotal incision to prevent torsion and loss of only testicular tissue.

On laparoscopy, if apparently normal looking testis is seen, then surgeon needs to decide whether to bring the testis to scrotum in one or two operations. This decision is based on following factors:

- Age of patient
- Distance of testis from the internal ring
- Mobility of testicular vessels.

In infants, length of the inguinal canal is much shorter than the older children and it is easy to bring the testis in scrotum. The term low abdominal testis is used when the distance of testis from the internal ring is less than 2.5 cm (Fig. 1). The term high abdominal testis is used when the distance of testis from internal ring is more than 2.5 cm. In children who are less than 5 years old with low abdominal testis and mobile vessels, usually the testis can be brought down in single operation. The success rate of single stage orchidopexy is more than 95%.

The children with high abdominal testis, age more than 5 years, and short testicular vessels usually needs two stage Stephen-Fowler (SF) orchidopexy. In the first stage, the testicular vessels are controlled either using bipolar diathermy, clipped or with an ultrasonic scalpel and then transected. This is performed approximately 2.5 cm away from the testis. This allows the development of collaterals between artery to vas deferens and testicular vessels (Fig. 2).

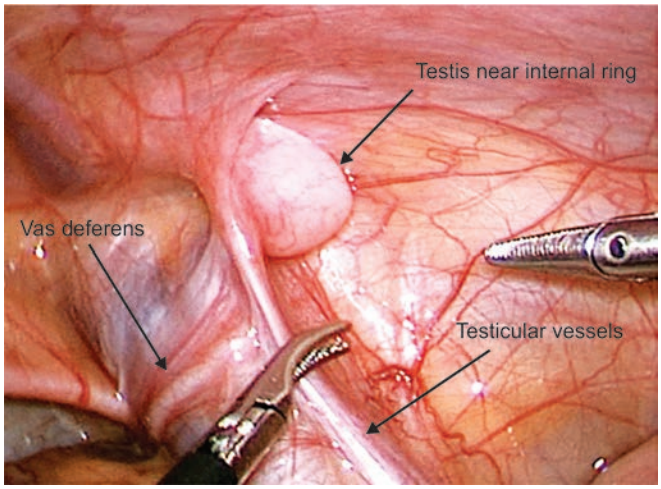


Fig. 1: Laparoscopic findings in the low abdominal testis near the internal ring

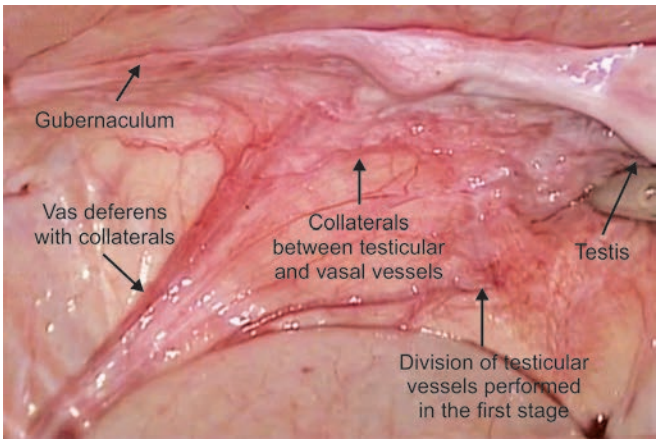


Fig. 2: Laparoscopic findings during second stage of Stephen-Fowler orchidopexy showing collaterals between artery to vas deferens and testicular artery

The second stage SF orchidopexy is usually performed after 6 months, wherein the testis is brought down to scrotum on the pedicle of vas. The two stage orchidopexy has success rate of more than 80%.

In past for high abdominal testis, microvascular surgery was performed by anastomosis of testicular artery with inferior epigastric artery but has limited success and is not popular.

Retractile Testis

A retractile testes should be under careful surveillance. The probability of spontaneous descent is 58 % in boys older than 7 years and 21% in boys younger than 7 years. It has 32% risk of becoming an ascending UDT. Surgical repositioning of the testis should be done if the testes become ascended testes (acquired cryptorchidism) or there is significant loss of testicular volume in comparison to contralateral testes.

Clinical Pearl

- Retractile testis needs a close supervision and 32% becomes ascended testicle needing surgery.

Ascended Testicle

Ascended testicle should be surgically positioned at the time of presentation. Ascended testes are seen in mid-childhood, are usually unilateral, and are present in distal inguinal canal. Ascended testis is prone to the same germ cell maldevelopment seen in congenital cryptorchidism.

LONG-TERM OUTCOME OF THE ORCHIDOPEXY

Testicular Atrophy

Testicular atrophy is a serious negative outcome of the orchidopexy. It is reported in 1% in ectopic testis, up to 5% of the distal testis, and in up to 9% of cases in intra-abdominal testis. The preoperative location of testes, torsion, and anomalies of vas deferens determines the occurrence of postorchidopexy testicular atrophy. Inadvertent trauma to the testicular vessels, postoperative edema, and local infections may also play a role in testicular atrophy. The resultant postoperative ischemia leads to complete or partial atrophy of the testis.

Fertility

Adults with bilateral UDT have azoospermia in almost 100% of cases, while more than 20% adults will have normal sperm counts when their orchidopexy was done in early childhood. Adults who underwent orchidopexy generally have low sperm count and have poor semen quality. This subfertility is not completely compensated by the contralateral descended testis. The fertility is further compromised if both testes are undescended and if the treatment is delayed. In bilateral UDT, the studies quotes normal sperm counts in up to 76% of cases when the orchidopexy was done between 10 months and 4 years of age and in up to 26% of cases who underwent orchidopexy in the age group 4–14 years of age. The timing of the surgery does not influence fertility in unilateral cryptorchidism. Though the fertility is not impaired, there are distinct benefits of early surgical orchidopexy.

Malignancy

Adult men with history of UDT have higher probability of developing a testicular malignancy. The risk increases to 32 fold in comparison to the general population. The intra-abdominal testis has the highest risk of developing malignancy, which is five times higher than that of inguinal UDT. The risk of malignancy is higher in bilateral UDT. The children who undergo orchidopexy after puberty are twice at the risk of developing the malignancy than those who undergo orchidopexy before puberty. The incidence of malignant degeneration in contralateral descended testis is about 8–15%.

KEY POINTS

- ☞ One percent of male child suffers from undescended testes (UDT) at the age of 1 year
- ☞ Imaging studies are not reliable and are not advocated to locate UDT
- ☞ Surgery is performed to prevent the complications, e.g., hernia, torsion, trauma, subfertility, and malignancy
- ☞ Clinically, UDT should be classified as palpable and non-palpable variety
- ☞ Surgery should be performed after the age of 6 months
- ☞ UDT presenting with hernia should be operated at the time of diagnosis
- ☞ Retractile testis needs a close supervision
- ☞ In 32% of patients diagnosed to have retractile testis, becomes ascended testicle and needs surgery
- ☞ Palpable UDT should undergo an open surgery
- ☞ Nonpalpable UDT should undergo laparoscopic surgery
- ☞ There is no role of hormonal treatment
- ☞ Insertion of testicular prosthesis should be considered in patients with absent or atrophic type of UDT to prevent psychological issues and to improve the self-body image
- ☞ All children undergoing orchidopexy should be taught self-examination for early detection of malignancy.

SUGGESTED READINGS

1. Abaci A, Catli G, Anik A, Bober G. Epidemiology, classification and management of undescended testes: does medication have any value in its treatment? J Clin Res Pediatr Endocrinology. 2013;5(2):65-72.
2. Agarwal PK, Diaz M, Elder JS. Retractile testis is it a normal variant? J Urol. 2006:175(4):1496-9.
3. Al-Zahem A, Shun A. Routine contralateral orchidopexy for children with a vanished testis. Eur J Pediatr Surg. 2006;16(5):334-6.
4. Alagaratnam S, Nathaniel C, Cuckow P, Duffy P, Mushtaq I, Cherian A, et al. Testicular outcome following laparoscopic second stage Fowler-Stephens orchidopexy. J Pediatr Urol. 2014;10(1):186-92.

5. Baker LA, Docimo SG, Surer I, Peters C, Cicek L, Diamond DA, et al. A multi-institutional analysis of laparoscopic orchidopexy. BJU Int. 2001;87:484-9.
6. Barthold JS, Gonz lez R. The epidemiology of congenital cryptorchidism, testicular ascent and orchidopexy. J Urol. 2003;170:2396-401.
7. Belkar AM. Urologic microsurgery current perspectives: II. Orchiopexy and testicular homotransplantation. Urology. 1980;15(2):103-7.
8. Biers SM, Malone PS. A critical appraisal of the evidence for improved fertility indices in undescended testes after gonadotrophin-releasing hormone therapy and orchidopexy. J Pediatr Urol. 2010;6(3):239-46.
9. Ein SH, Nasr A, Wales PW, Ein H. Testicular atrophy after attempted pediatric orchidopexy for true undescended testis. J Pediatr Surg. 2014;49(2):317-22.
10. Favorito LA, Costa WS, Sampaio FJ. Relationship between the persistence of the processus vaginalis and age in patients with cryptorchidism; International. Braz J Urol. 2005; 31(1):57-61.
11. Fedder J. History of cryptorchidism and ejaculate volume as simple predictors for the presence of testicular sperm. Syst Biol Reprod Med. 2011;57(3): 154-61.
12. Giwercman A, Bruun E, Frimodt-MIler C, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. J Urol. 1989;142:998-1001.
13. Giwercman A, Grindsted J, Hansen B, Jensen OM, Skakkebk NE. Testicular cancer risk in boys with maldescended testis: a cohort study. J Urol. 1987;138:1214-6.
14. Lee PA, Coughlin MT, Bellinger MF. Inhibin B: comparison with indexes of fertility among formerly cryptorchid and control men. J Clin Endocrinol Metab. 2001;86(6):2576-84.
15. Lee PA, Coughlin MT. Fertility after bilateral cryptorchidism. Evaluation by paternity, hormone, and semen data. Horm Res. 2001;55:28-32.
16. Lee PA. Fertility in cryptorchidism. Does treatment make a difference. Endocrinol Metab Clin North Am. 1993;22(3):479-90.
17. Lip SZ, Murchison LE, Cullis PS, Govan L, Carachi R. A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. Arch Dis Children. 2013;98(1):20-6.
18. Ludwikowski B, Gonz lezR. The controversy regarding the need for hormonal treatment in boys with unilateral cryptorchidism goes on: a review of the literature. Eur J Pediatr. 2013;172(1):5-8.
19. Mano R, Livne PM, Nevo A, Sivan B, Ben-Meir D. Testicular torsion in the first year of life characteristics and treatment outcome. Urology. 2013;82(5):1132-7.
20. Mathers MJ, Sperling H, Rubben H, Roth S. The undescended testis: diagnosis, treatment and long-term consequences. Dtsch Artzbel Int. 2009;106(33):527-32.
21. McAleer IM, Packer MG, Kaplan GW, Scherz HC, Krous HF, Billman GF. Fertility index analysis in cryptorchidism. J Urol. 1995;153:1255-8.
22. Miller KD, Coughlin MT, Lee PA. Fertility after unilateral cryptorchidism. Paternity, time to conception, pretreatment testicular location and size, hormone and sperm parameters. Horm Res. 2001;55:249-53.
23. Osifo DO, Osaigbovo EO. The prevalence, postnatal descent, and complications of undescended testes among children who underwent neonatal circumcision in Benin City, Nigeria. J Pediatr Surg. 2009;44(4):791-6.
24. Osime O, Momoh M, Elusoji S. Torsed intraabdominal testis: a rarely considered diagnosis. Cal J Emerg Med. 2006;7(2):31-3.
25. Pettersson A, Richiardi L, Nordenskjoid A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med. 2007;356(18):1835-41.
26. Virtanen HE, Bjerknes R, Cortes D, Jrgensen N, Rajpert-De Meyts E, Thorsson AV, et al. Cryptorchidism: classification, prevalence and long-term consequences. Acta Paediatr. 2007;96(5):611-6.
27. Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. Int J Cancer. 2000;87:438-43.
28. Zilberman D, Inbar Y, Heyman Z, Shinhar D, Bilik R, Avigad I, et al. Torsion of the cryptorchid testis can it be salvaged? J Urol. 2006;175(6):2287-9; discussion 2289.

CHAPTER 128

Acute Scrotum

Mohan K Abraham

INTRODUCTION

Acute scrotum is an alarming condition both for the parents and the child. Since the most common cause in children is torsion of the testis, emergency management is indicated. Epididymo-orchitis and trauma can also present as acute scrotum. However, these conditions are rarer and torsion should be ruled out first.

DEFINITION

Any sudden swelling of the scrotum, unilateral or bilateral with redness and edema, should be considered as acute scrotum.

ETIOLOGY

Etiology can be divided into infective causes like epididymo-orchitis, allergic causes like idiopathic scrotal edema or ischemic causes like torsion testis and torsion of the appendages of the testis. Epididymo-orchitis is usually due to ascending infection through the vas because of a urinary tract infection. There are two peaks when torsion of the testis occurs; one is in the new born period and another at puberty. Lack of fixation in the new born period and over activity of the cremaster muscle has been attributed to the increased incidence during these periods. Torsion is mostly extravaginal in the new born period where the twist occurs in the cord. Torsion is intravaginal in the rest of life. Intravaginal torsion is due to high investment of tunica vaginalis which gives rise to a bell clapper deformity. Here, the mesentery of the testis is narrow and testis hangs like a bell-clapper in a church bell predisposing it to torsion. The appendages of the testis can also undergo torsion when signs and symptoms are minimal. Idiopathic scrotal edema is another condition that mimics acute scrotum. Absence of tenderness and normal testis felt on palpation or a normal testis without edema and good blood flow seen by ultrasound distinguishes this from other conditions.

CLINICAL FEATURES

History

History gives a clue in most of the conditions. Pain of sudden onset may indicate torsion. Torsion is commonly seen in postpubertal or new born age. Torsion of appendages of the testis occurs in the prepubertal age. History of trauma does not rule out torsion. If pain from trauma lasts more than 1 hour, torsion should be considered. History of urinary tract infection, surgery for hypospadias, or sexual activity may be obtained in epididymo-orchitis. Fever also may be present in case of epididymo-orchitis. Pain of epididymo-orchitis is gradual in onset. Henoch–Schönlein purpura can also present with acute scrotum, but the lesions in other parts of the body will point to the diagnosis. Obstructed hernia can also mimic acute scrotum. History of a reducible swelling existing before the onset of acute scrotum will point to the diagnosis.

Clinical Examination

It is important to gain the confidence of the child or mildly sedate the child before starting the examination. This will facilitate proper examination. Abdominal examination including the inguinal area should be done first. Incarcerated hernia will have a swelling extending into the inguinal canal. A thickened and tender spermatic cord in the inguinal canal will indicate epididymo-orchitis.

Examination of the Scrotum

In idiopathic scrotal edema, both the sides are involved but tenderness is absent. In torsion and epididymo-orchitis, the involvement is unilateral to start with and becomes bilateral as time passes. A testis felt in the root of the scrotum or a testis with a transverse lie should warn about the possibility of torsion. Absence of cremasteric reflex indicates torsion. This is elicited by stroking the medial side of the thigh which gives

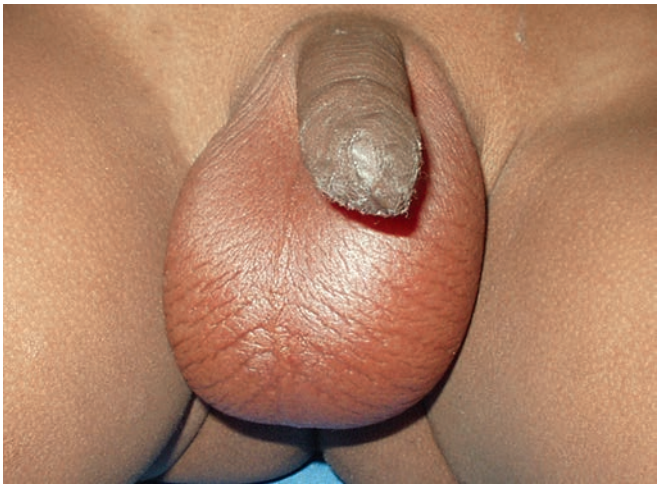


Fig. 1: Showing red edematous scrotum on left side due to torsion

rise to ipsilateral elevation of testis because of the contraction of cremaster muscle. Pain duration less than 24 hours, nausea or vomiting, a high position of the testis, and an abnormal cremasteric reflex has a positive predictive value for torsion. Testis should be examined carefully. Testis should be held between thumb and two fingers. Epididymis should be felt as a soft linear structure on the posterior lateral aspect of the testis. If this is tender and swollen, then epididymitis should be thought of. Tenderness limited to the upper pole of the testis suggests torsion of the appendage of the testis. A small area of bluish discoloration at the upper pole, also known as blue dot sign, also represents torsion of an appendage of the testis. Testis is swollen and tender in early torsion and epididymo-orchitis. Tenderness may disappear once complete gangrene of the testis has set in. As time passes, the erythema and edema involves both sides of the scrotum (Fig. 1). Palpation of the testis will reveal a hard enlarged testis on the affected side.

Elevation of testis may give relief of pain in case of epididymo-orchitis, but not in torsion.

INVESTIGATIONS

- Urine analysis: if pyuria is present, it may suggest epididymo-orchitis
- Ultrasound: conventional ultrasound has not been found useful. Color Doppler has improved the diagnostic accuracy in expert hands. However, Doppler may miss a partial torsion which will eventually lead to testicular loss. A hypervascular enlarged epididymis can occur in 5% of torsion cases. Color Doppler can avoid surgery in cases of increased or normal blood flow; in rest of the cases, exploration may be needed
- Nuclear scanning: nuclear scanning is highly accurate in demonstrating torsion as a photopenic area. However, this is not widely available and consumes time which may lead to testicular gangrene. Moreover, it gives a small dose of radiation also
- Near infrared spectroscopy: though some usefulness was seen in animal studies, in human studies it failed to demonstrate any difference in tissue saturation between testis that had undergone torsion and normal testis.

Clinical Pearl

- There is no investigation that is completely reliable to rule out torsion in a reasonable time frame.

MANAGEMENT

Epididymo-orchitis

Empirical antibiotics are given till urine culture and sensitivity is obtained. Bed rest and scrotal elevation will lessen the pain. If urine culture is positive, then child will need further work up to look for any underlying anatomical abnormality.

Idiopathic Scrotal Edema

Bed rest and scrotal elevation will be enough. Edema will subside in 48–72 hours.

Torsion of Testis

Points to consider in the management of torsion are:

- Duration of torsion. Some studies have shown that testicular atrophy occurred in all cases where the symptom duration was more than 24 hours
- Triggering of immune mechanism because of loss of blood testicular barrier due to ischemia is a matter of concern. This can result in damage to the normal testis and infertility.

Testicular torsion is a surgical emergency and no time should be wasted between diagnosis and exploration. Scrotal exploration is done and the testis is fixed to the dartos with nonabsorbable sutures. Alternatively, it can be put in a dartos pouch to prevent torsion. However, suture fixation has the potential danger of violating testicular barrier and triggering an immune response damaging the contralateral testis. Contralateral side also needs to be fixed to prevent torsion because the bell clapper deformity can be bilateral. There is some controversy regarding the fixation of the contralateral testis in newborn torsion. Neonatal torsions are usuallyextra vaginal and bilateral involvements are not usually seen in these cases. However, most surgeons favor fixing the contralateral side since bilateral torsions are known to occur. If testis is found to be ischemic as evidenced by dark discoloration, testis should be detorsed and warm sponges applied to see if there is regaining of color (Fig. 2). If there is no improvement in color, testis can be incised to see the state of testicular tissue inside. If the testis is found to be gangrenous, orchiectomy is indicated. Contralateral side testis should be fixed in the dartos pouch to prevent torsion.

Drugs have been studied in experimental animal models to reduce the ischemia reperfusion injury. These include allopurinol, calcium channel blockers, oxypurinol, and superoxide dismutase. But, none of these studies have produced enough evidence to allow its usage in human beings.

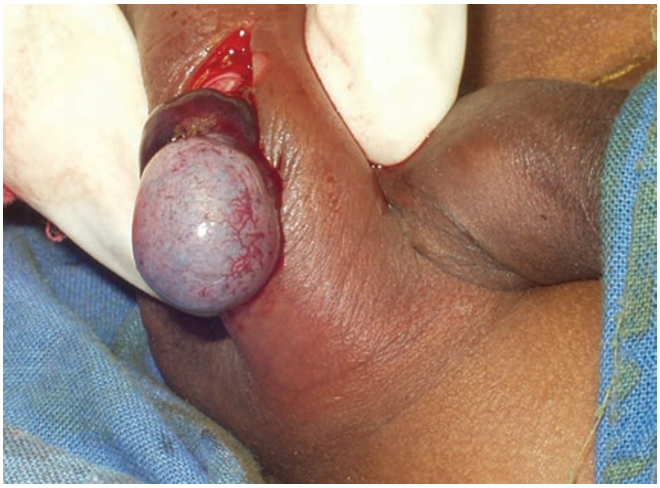
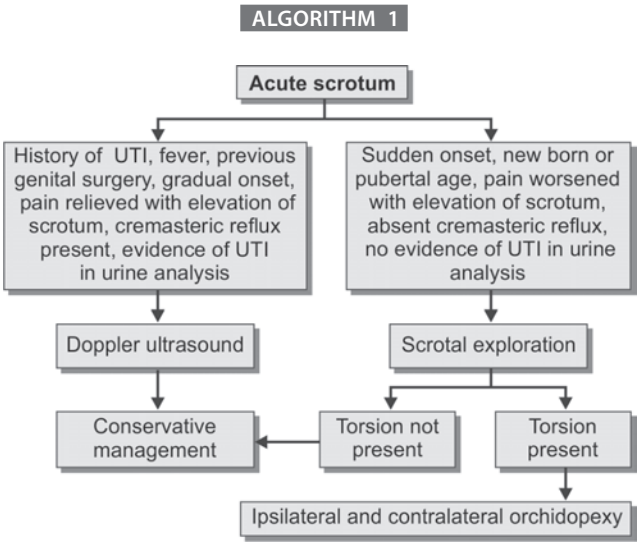


Fig. 2: Testis with torsion and gangrene



Perinatal Torsion

Management of perinatal torsion is controversial. One school of thought considers that salvage of a perinatally torted testis is very poor so that there is no need for emergency exploration. Other school of thought wants to give the benefit of the doubt and explore the testis since there is a possibility that torsion has occurred during or immediately after delivery and potential for salvage of the testis is higher.

Torsion of the Appendages of Testis

Torsion of the appendages of testis as evidenced by blue dot sign is conservatively managed with bed rest and anti-inflammatory drugs are justifiable. But, this is usually possible only in fair skinned children and that too if they present before scrotal edema develops. If doubt exists, exploration is the safer option. Exploration of contralateral side is not indicated (Fig. 3).

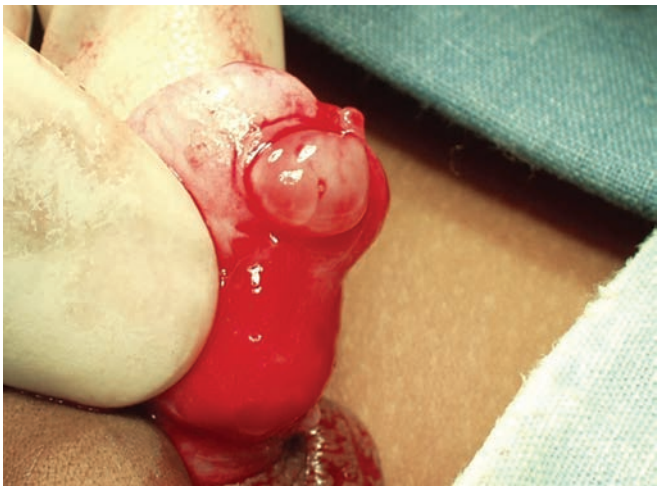


Fig. 3: Torsion of appendix of epididymis

Testicular Trauma

Testicular trauma occurs as a result of direct blow to the testis or straddle injury. Post-traumatic epididymo-orchitis occurs within a few days after trauma. This has noninfectious cause and can be managed with scrotal elevation and rest. Intratesticular hematoma can also be managed conservatively. However, rupture of the testis will require emergency surgery.

Clinical Pearl

- Epididymo-orchitis in childen should be a postoperative diagnosis.

KEY POINTS

- ☞ Torsion testis should be suspected in every case of acute scrotum
- ☞ It is better to explore the scrotum than wait when you are in doubt
- ☞ In the absence of predisposing causes for epidydimo-orchitis like urinary tract infections or genital abnormality, torsion testis should be the working diagnosis.

SUGGESTED READINGS

1. Boettcher M, Bergholz R, Krebs TF, Wenke K, Aronson DC. Clinical predictors of testicular torsion in children. Urology. 2012;79(3):670-4.
2. DAndrea A, Coppolino F, Cesarano E, Russo A, Cappabianca S, Genovese EA, et al. LUS in the assessment of acute scrotum. Crit Ultrasound J. 2013;5(Suppl 1):S8.
3. Kravchick S, Cytron S, Leibovici O, Linov L, London D, Altshuler A, et al. Color Doppler sonography: its real role in the evaluation of children with highly suspected testicular torsion. Eur Radiol. 2001;11(6):1000-5.
4. Nussbaum Blask AR, Rushton HG. Sonographic appearance of the epididymis in pediatric testicular torsion. AJR Am J Roentgenol. 2006; 187(6):1627-35.
5. Schoenfeld EM, Capraro GA, Blank FS, Coute RA, Visintainer PF. Near-infrared spectroscopy assessment of tissue saturation of oxygen in torsed and healthy testes. Acad Emerg Med. 2013;20(10):1080-3.
6. Tryfonas G, Violaki A, Tsikopoulos G, Avtzoglou P, Zioutis J, Limas C, et al. Late postoperative results in males treated for testicular torsion during childhood. J Pediatr Surg. 1994;29(4):553-6.

CHAPTER 129

Per-rectal Bleeding

Dasmit S Khokar

INTRODUCTION

Lower gastrointestinal (GI) bleeding is an alarming symptom of presentation. Among children of all ages, lower GI bleeding is the main symptom in 0.3% of patients presenting to the casualty; 50% are less than 1 year of age. Per-rectal bleeding accounts for 10–15% of referrals to a gastrointestinal service.

In most children, bleeding stops spontaneously but since the blood volume is small, resuscitation must begin early. Children can tolerate even massive blood loss surprisingly well, but sudden deterioration occurs when a critical point is reached.

At the outset, it is imperative to remember the thumb rule that age-appropriate tachycardia is the most sensitive indicator of critical blood loss in children. Any patient with an estimated blood loss more than 10% of the blood volume must be monitored in an intensive care unit.

Twenty percent patients in the neonatal intensive care unit are likely to experience stress gastritis with resultant coffee grounds in the nasogastric aspirate followed thereafter by malena.

CLINICAL CLASSIFICATION

- Hematochezia: fresh bleeding per rectum in large quantities. Clots plus fresh blood may be seen, hardly any stool matter
- Malena: usually a sign of bleeding that comes from a source proximal to the ligament of Treitz. However, massive upper GI bleeding can produce bright red blood per rectum if GI transit time is rapid
- Red currant jelly stools: blood mixed with mucus
- Maroon colored stool: occurs with distal small bowel bleeding, such as with Meckel's diverticulum.
- Blood mixed with loose stools: infective diarrhea, dysentery.

Painless bleeding in an otherwise healthy child will be construed differently from per-rectal bleeding in a sick child, irrespective of the quantity of bleeding.

ETIOLOGY

The most common causes of bleeding vary with the age at presentation, although almost all causes may be encountered at any age.

Neonates:

- Healthy baby: hemolytic disease of the newborn, fissure in ano, local trauma (as happens with an attempted forced catheter insertion into the rectum)
- Sick baby: necrotizing enterocolitis, bowel gangrene, sepsis, disseminated intravascular coagulation, Hirschsprung's disease with enterocolitis, complicated malrotation, milk or soya milk enterocolitis, or allergic colitis.
- Drugs causing GI bleeds include nonsteroidal anti-inflammatory drugs (NSAIDs), indomethacin, tolazoline, heparin, etc.
- Some maternal medications like cephalothin, aspirin, and phenobarbital can cross the placenta and cause per-rectal bleeding in the neonate after delivery
- Preemies and ventilated babies are prone to stress gastritis with resultant malena
- Idiopathic.

Up to 2 years of age:

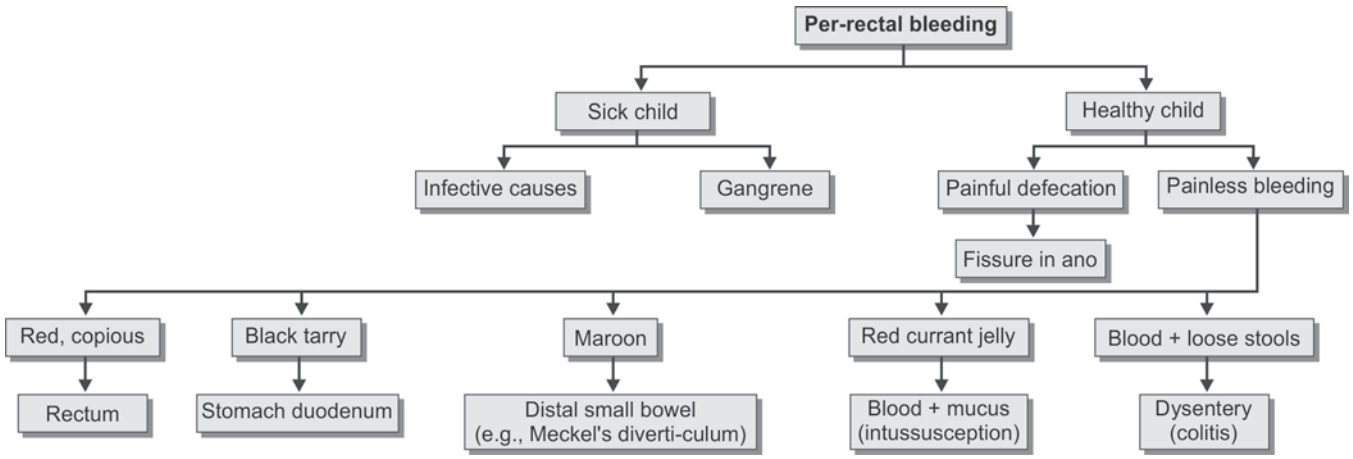
- Milk protein allergy
- Intussusception
- Fissure in ano
- Rectal polyps
- Malrotation
- Hemangioma and other vascular lesions of the gut
- Intestinal duplication
- Trauma due to foreign body or sexual assault
- Lymphonodular hyperplasia
- Eosinophilic gastroenteropathy
- Acquired thrombocytopenia
- Infectious diarrhea.

Elder than 2 years age:

- Infectious diarrhea

ALGORITHM 1

Basic algorithm of per-rectal bleeding



- Amoebic colitis
- Ulcerative colitis
- Crohn's disease
- Meckel's diverticulum
- Inflammatory bowel disease
- Bleeding dyscrasias
- Antibiotic-associated bleeding
- Food allergies
- Trauma
- Rectal polyp
- Juvenile polyposis coli
- Familial polyposis and colonic carcinoma or small bowel malignancy with/without intussusception
- Villous adenoma of the rectum
- Rectal prolapse
- Solitary ulcer of the rectum
- Henoch-Schonlein purpura
- Hemolytic uremic syndrome
- Lymphonodular hyperplasia
- Eosinophilic gastroenteropathy
- Vascular lesions of the gut.

ALGORITHM OF CLINICAL APPROACH TO THE DIAGNOSIS

- Bleeding related to defecation: anal or rectal lesion is likely
- Bleeding associated with pain: lesion is below the dentate line
- Blood mixed with stool matter: lesion is higher than the rectum
- Something coming out of the anus: rectal prolapse or rectal polyp, intussusception
- Bleeding associated with epigastric pain and heartburn: dyspepsia/gastritis
- Bleeding associated with high fever: enteric fever with terminal ileitis
- Bleeding associated with loss of weight, anorexia, night sweats, and fatigue: abdominal tuberculosis
- Colicky pain followed by red-currant jelly stools: intussusception
- Copious bleeding, usually painless or lower abdominal pain followed by hematochezia: meckel's diverticulum and duplication of the gut
- Abdominal pain, diarrhea, fever, prostration: infective ulceration
- Bleeding associated with abdominal distention in a septic child: intestinal gangrene, necrotizing enterocolitis.

In spite of extensive investigations, the cause may not be found in which case it is labeled as idiopathic. Munchausen syndrome by proxy should also be ruled out.

INVESTIGATIONS

- Digital rectal examination: it is the most essential primary investigation that is needed when a child presents with such a history. Hard fecalomas, anal stenosis, fissure in ano, rectal polyps, mass lesion prolapsed from above, etc. can be judged quite accurately. It is possible to differentiate between advanced colonic intussusception and rectal prolapse, judging by the depth to which the palpating finger can be inserted. In addition, rectal tone should always be assessed
- Ultrasonography abdomen: mass lesions can be detected as long as the bowel gas does not interfere with the medium of passage of the ultrasonic waves
- Barium enema: larger polyps and multiple polyps can be diagnosed quite easily with this investigation. However, smaller polyps are easier to see on endoscopy besides being amenable to biopsy also.
- Contrast enhanced computed tomography (CECT) abdomen: this is used judiciously so as to avoid radiation to the child. This is a highly sensitive and specific imaging technique for the abdomen. However, a trained pediatric radiologist is essential for interpreting the images accurately
- Magnetic resonance imaging abdomen: this is being tried as an alternative to CECT abdomen, but the resolution is often insufficient to accurately make a diagnosis

- Meckel's radionuclide scan with technetium 99 m pertechnetate: it can be used to detect the presence of a Meckel's diverticulum with ectopic gastric mucosa
- Red blood cell (RBC) labeled radionuclide scan: any bleeding which is more than 0.1 mL/min can be detected by this scan and the approximate location can be established. Newer RBC scans have an accuracy of nearly 90% in localizing the bleeding site
- Colonoscopy, gastroscopy, and capsule endoscopy: these are now being used with increasing frequency to try and establish a diagnosis and avoid a surgical exploration. The overall yield of colonoscopy is 64–80%. When rectal bleeding is associated with diarrhea, the yield is 97%. In children in the 0–12 years age group, colitis is the most common cause (36%), followed by polyps in (27%), whereas rectal ulcers, chronic anal fissures, and hemorrhoids account for 5% each
- Splanchnic angiography (superior mesenteric arteriography): it is sometimes resorted to for locating the bleeding vessel when the bleeding is massive. Even super-selective embolization has been successful in select cases although it can lead to bowel gangrene sometimes
- Laparoscopy: being minimally invasive, it is the last resort short of a laparotomy, in a case where all other investigations have been unable to come to a diagnosis
- Laparotomy: It is the last desperate attempt when a life-threatening bleeding event happens. It has the advantage of allowing palpation of the bowel wall, but one still cannot view the mucosal aspect unless opened. The limitation is that it is not possible to open and view the entire bowel. The yield is therefore increased further when laparotomy is coupled with transluminal endoscopy (enteroscopy). An endoscope is inserted either through a natural orifice or through an opening made in the bowel and guided by the operating surgeon.

In most of the cases, if the GI endoscopies are negative, then a period of observation is desirable. In case the patient bleeds significantly or repeatedly, then more invasive investigations become easier to justify. Many cases of idiopathic bleeding will not last beyond a few months.

Many of the causes of lower GI bleeding are medical causes and readers are directed to read appropriate source material for the same.

Some of the more common surgical causes have been discussed here in this chapter.

FISSURE IN ANO

This occurs due to trauma caused by passage of hard stools. This is the most common cause of per-rectal bleeding in India. Faulty diet is the usual cause of hard stools. Excessive milk and bakery products like biscuits and bread are the usual offenders. With increasing urbanization and break-down of the joint family system, it is not unusual to obtain a history where both parents are working, with lesser time at their disposal for spending with their children. This fact directs them to resort to appeasement methods to placate their demanding children, coupled with short cut alternatives to preparing wholesome food at home. Thus, children consume more fast foods, street foods, single-pot meals, and high calorie foods with low roughage value leading to constipation.

Another phenomenon seemingly on the rise is early, enforced toilet-training. The child is made to pass stools like an adult even before the sensation of passing stools or defecation reflexes are fully developed. This leads to acquired constipation with its ensuing complications one of which is fissure in ano.

Pathogenesis

The child strains and passes a hard stool. This hard bolus causes a laceration at the mucocutaneous junction which is extremely sensitive to pain. Any attempt by the child at passing stools would now be very painful, so the child holds back the stools. This leads to further water absorption from the stool matter causing it to harden further. This vicious cycle causes the fissure to become chronic. The aim of treatment is to break this vicious cycle so that the fissure can heal on its own.

It is important to differentiate between acute and chronic constipation when treating such children. Oral laxatives should be used for acute constipation only, along with advice on correction of diet. Oral laxatives are preferred for only acute constipation and should never be used for prolonged periods. Any patient, who needs an oral laxative for more than 7 days, needs to be investigated further for the cause of constipation and should be referred to a pediatric surgeon.

Patients with chronic constipation need prolonged bowel training and should be managed by a suppository bowel management program along with strict dietary correction. Suppositories having a local action are less habit-forming and are preferred over oral laxatives. Occasionally, soapy water enemas and mineral oil or olive oil instillation are needed for hard fecalomas. Phosphatic enemas can be used occasionally, but daily usage should be avoided to prevent electrolyte disturbances.

Clinical Presentation

The most common presentation is a painful passage of hard stool accompanied by straining. This is followed by a few drops of fresh blood. Passage of clots is unusual. Subsequent stools are painful, streaked with blood on one side and few drops of blood at the end of defecation.

The child might be habituated to passing stools in a standing position, pressing the buttocks together in an attempt to prevent the stools from exiting the painful anus. The face turns red as the child strains excessively and looks quite frightening to the parents. Finally, the child painfully passes a hard mass of stool with a streak of blood on it.

The fissure can be seen on careful examination of the perineum. The most common location is at the 6 o'clock position but can occur in any position. A recurrent fissure at 12 o'clock position or in an older child should alert the physician to the possibility of an inflammatory bowel disease.

Sometimes, a portion of the delicate anal valve can get avulsed and protrude from the anus. This is called an external

pile (although it is quite distinct from the usual piles). This can get infected leading to further worsening of the pain and tenderness.

Treatment

- The most important step is to treat the underlying cause of constipation as outlined above. Treating functional or habitual constipation (acquired megacolon) is quite difficult and the treatment may take anything from a few months to a few years
- Treatment of chronic constipation causing acquired megacolon starts only after a mechanical cause like an anorectal malformation has been ruled out. A bowel training program is started which includes a suppository or a nonelectrolytic enema regime with progressively reducing frequency, coupled with a strict high-roughage dietary program. This needs a very high degree of motivation of the parents to implement it appropriately
- Warm sitz bath twice a day
- Local anesthetic ointment: (lignocaine jelly/proctosedyl) application thrice a day
- NSAIDS when needed
- Antibiotics if an external pile shows evidence of infection
- Almost all fissures will heal with this treatment. Very rarely, if the fissure has become chronic and the conservative regime fails, a surgical option may need to be considered. Lord's dilatation or a lateral anal sphincterotomy may then be required under general anesthesia (GA).

INTUSSUSCEPTION

The most common age group of presentation of intussusception is 6–8 months, mean being around 10 months of age. The characteristic severe pain in abdomen accompanied by facial pallor soon followed by red currant jelly stools is pathognomonic of intussusception. The most common location is ileocecocolic with a hypertrophied Peyer's patch being the lead point. Sometimes, this episode may be preceded by an attack of acute gastroenteritis, so the clinician has to be very vigilant in treating such cases.

Diagnosis is quite easily possible by a typical target sign on an ultrasound examination of the abdomen in 97–100% of patients. Alternatively, barium enema can also be used with the additional advantage of being both diagnostic as well as therapeutic.

In patients more than 2 years of age or a small bowel intussusception, we have to bear in mind the possibility of a leading point being a bowel lesion, such as polyp, leiomyoma or a lymphoma, which may necessitate a bowel resection with anastomosis and the specimen being subjected to histopathological examination.

Treatment

Almost 95% of intussusceptions can be treated by hydrostatic reduction and surgery is not needed. This can be done by either using barium enema under an image intensifier fluoroscopy or normal saline enema under ultrasonography control or even gas reduction with air/oxygen depending on the facilities and expertise available. Although many centers prefer the safety-net of doing the procedure without any sedation, midazolam sedation (both intranasal as well as intravenous, 0.1 mg/kg) can be used in centers equipped with the requisite facilities and experience.

It must be remembered that intussusception recurs in 5–10% of children when reduced by nonoperative reduction and 1–4% after operative reduction.

Hydrostatic reduction treatment of intussusception is contraindicated in cases where peritonitis/gangrene has already developed as evidenced by severe rebound tenderness or rigidity of the abdomen.

Thus, early referral is crucial to a center equipped to handle such cases and most cases referred within 24 hours of the onset of symptoms will be successfully reduced by hydrostatic reduction.

It is imperative to remember that hydrostatic reduction is done on the threshold of the operation theatre and complete readiness for an emergency laparotomy is essential. This may be needed if the bowel ruptures during attempted reduction leading to fecal peritonitis and delay can be fatal.

In cases where reduction fails or gets complicated or the intussusception is already advanced, then the surgical options available are:

- Laparoscopic reduction or laparoscopic-assisted bowel resection and anastomosis
- Laparotomy with reduction or bowel resection.

RECTAL AND COLONIC POLYPS

Juvenile inflammatory polyps are the most common cause of bleeding in children older than 2 years of age. Most polyps are solitary juvenile polyps located in the rectum, hence are palpable during a digital rectal examination by an experienced pediatric surgeon. They present as painless, dropwise per-rectal bleeding after defecation. They may be pedunculated and can protrude from the anus. Occasionally, the connecting stalk may get broken leading to incessant bleeding, so even a per-rectal examination has to be done with great care.

If polyps are multiple, then a more sinister disease has to be explained to the relatives. The final diagnosis will of course be made after a histopathological confirmation of the type of polyp.

Juvenile polyps are the most common intestinal polyps in children, accounting for almost 90% of colonic polyps in children. Around 20–25% of patients with juvenile polyps present with occult blood loss and anemia rather than visible bleeding.

The majority of colonic polyps are sporadic and not associated with malignancy, but familial adenomatous polyposis and Peutz-Jeghers syndrome carry a risk of malignant transformation. When there are more than five polyps in the colon, multiple polyps throughout the GI tract or any number of juvenile polyps with a family history of juvenile polyps, it is known as juvenile polyposis syndrome, which carries a high malignant potential.

If the clinical history is strongly suggestive of the diagnosis of an intestinal polyp, but it is not felt on a per-rectal examination, then a colonoscopy under GA is essential.

Treatment

- Solitary rectal polyps are treated surgically by under-running the base and excising the polyp under GA, transrectally
- Proximally situated polyps or multiple polyps will need a pediatric colonoscopy with excision by electrocautery or argon plasma coagulation
- If multiple polyposis coli with adenomatous villous polyps are detected, then a laparoscopic or open total proctocolectomy with an endorectal ileoanal anastomosis procedure will be required. In addition, the patient will have to be kept on a strict follow-up colonoscopy regime to look for early malignancies.

RECTAL PROLAPSE

Diagnosis of rectal prolapse is quite easy with a good history taking and per-rectal digital examination. If there are hard fecal masses present on per-rectal examination, then the management shifts to management of chronic constipation as outlined above. If the anal sphincter tone is good, then again just softening of stools for a few months will cause the prolapse to disappear.

If conservative treatment fails, then a surgical intervention may need to be considered.

The various options available today are:

- Injection sclerotherapy for mild prolapse
- Laparoscopic mesh fixation of the rectum (may be done by laparotomy, if facilities for laparoscopy are not available)
- Posterior sagittal rectopexy
- Excision of a persistent rectal prolapse (stage IV, procedentia).

Clinical Pearls

Counseling points for parents

- Per-rectal bleeding has a wide variety of causes and needs a reliable history for the diagnosis
- It may need a battery of investigations to determine the cause and in spite of that a small percentage of cases may be idiopathic
- The commonest cause of per-rectal bleeding in India is caused by an anal fissure due to a faulty diet
- Avoid long-term oral laxatives
- Intussusception very rarely needs surgery
- Estimated blood loss more than 10% of the blood volume must be treated in the intensive care unit.

KEY POINTS

- ☞ Age-appropriate tachycardia is the most sensitive indicator of critical blood loss in children
- ☞ Clinical classification of bleeding is based on the gross stool characteristics
- ☞ Etiology varies with age
- ☞ A detailed history and careful clinical examination can usually elicit the cause in a majority of the cases
- ☞ The most common cause of per-rectal bleeding in India is fissure in ano caused by a faulty diet
- ☞ Oral laxatives are preferred only for acute constipation and should never be used for prolonged periods. Any patient, who needs an oral laxative for more than 7 days, needs to be investigated further and should be referred for a pediatric surgical consult
- ☞ Treating functional or habitual constipation (acquired megacolon) is quite difficult and the treatment may take anything from a few months to a few years
- ☞ Severe colicky pain in abdomen accompanied by facial pallor, soon followed by red currant jelly stools is pathognomonic of intussusception
- ☞ Almost 95% of intussusceptions can be treated by hydrostatic reduction and surgery is rarely needed
- ☞ Almost all cases of intussusception referred within 24 hours of the onset of symptoms will be successfully reduced by hydrostatic reduction
- ☞ Around 20–25% of patients with juvenile polyps present with occult blood loss and anemia rather than visible bleeding.

SUGGESTED READINGS

1. Arain Z, Rossi TM. Gastrointestinal bleeding in children: an overview of conditions requiring nonoperative management. Semin Pediatr Surg. 1999;8:172-80.
2. Bisset GS III, Kirks DR. Intussusception in infants and children: diagnosis and therapy. Radilogy. 1988;168:141-5.
3. Clarke G. et al. Investigating painless rectal bleeding—Is there scope for improvement? J Pediatr Surg. 2005;40:1920-2.
4. Cynamon H A, Milov DE, Andres JM. Diagnosis and management of colonic polyps in children. J Pediatr. 1989;114:593-5.
5. de Ridder L, van Lingen AV, Taminiau JA, Benninga MA. Rectal bleeding in children: endoscopic evaluation revisited. Eur J Gastroenterol Hepatol. 2007;19:317-20.
6. Durno CA. Colonic polyps in children and adolescents. Can J Gastroenterol. 2007;21(4):233-9.
7. El-Mouzan MI, Abdullah AM. Yield of colonoscopy in children with rectal bleeding: Saudi Medical Journal. 2004;8:998-1001.
8. Friedman CJ, Fechner RE. A solitary juvenile polyp with hyperplastic and adenomatous glands. Dig Dis Sci. 1982;27:946-8.
9. Rozen P, Baratz M. Familial juvenile colonic polyposis with associated colon cancer. Cancer. 1982;49:1500-3.
10. Teach SJ, Fleicher GR. Rectal bleeding in pediatric emergency department. Ann Emerg Med. 1994;23:1252-8.

CHAPTER 130

Inguinal Hernia

Satish K Aggarwal, Nitin Pant

INTRODUCTION

Inguinoscrotal swellings in children are a common reason for pediatric consultation. Some of them may resolve spontaneously (e.g., hydroceles) while others (e.g., hernia) almost always require surgery. Obstructed hernia may require emergency operation to prevent bowel strangulation. The aim of this chapter is to enable a pediatrician to understand the anatomy and pathology of processus vaginalis, its association with testicular decent, and its role in manifestations of hydrocele and hernia. The reader should be able to make a correct diagnosis and counsel parents about need for surgery, or watchful waiting in hydroceles, and make timely surgical referral to avoid complications of obstruction and strangulation in hernia. A brief description of available surgical techniques is also given.

The testis descends into the scrotum during the seventh month of gestation pushing a diverticulum of peritoneum (processus vaginalis) ahead of it. This processus begins to obliterate in a caudal-cranial fashion once the testis descends to the scrotal base. The closure starts shortly before birth and normally completed during the first year of life, leaving only the tunica vaginalis surrounding the testis. The obliterated processus vaginalis lies alongside the vas and vessels within the spermatic cord. Failure of obliteration results in patent processus vaginalis—the underlying abnormality in all hernias, hydroceles, and encysted hydrocele of the cord.

INGUINAL HERNIA

Definition

By definition, a hernia is the protrusion of the contents of a cavity along with its membrane through any normal or abnormal opening. If the processus is wide enough, it allows intestinal contents (bowel, omentum) to herniate through it. This processus vaginalis forms the hernia sac which can extend from the internal inguinal ring to the tunica vaginalis (the inguinoscrotal hernia). More commonly, the sac is incomplete, lying proximal to an obliterated segment that intervenes between the sac and the tunica vaginalis (bubonocele). This accounts for the vast majority of inguinal hernia in children. If the processus is narrow allowing only peritoneal fluid to pass through, a hydrocele results. If the hydrocele extends up to the base of scrotum, it is called a vaginal hydrocele. If the peritoneal fluid collects in a loculus of the processus at some point along its course in the spermatic cord, it is called encysted hydrocele. This loculus usually communicates with the peritoneal cavity proximally, but the distal part remains obliterated.

Types

Nearly all inguinal hernias in children are indirect, with patent processus vaginalis being the underlying abnormality. It travels from the deep inguinal ring across the inguinal canal, comes out of the superficial ring and travels along the spermatic cord to the scrotum. Incidence is 0.8–4.4% with male to female ratio between 3–10:1. The incidence is higher in infants—keeping with higher rates of patent processus vaginalis in infancy. Preterm babies accordingly have highest incidence varying from 16–25%. Right-sided hernias are more common (60%), attributable to the late descent of the right testis as compared to the left, hence a higher probability of patent processus vaginalis on the right. In girls, the canal of Nuck undergoes the same obliteration as the processus vaginalis in boys. The obliteration is more likely to be complete, hence a lower overall incidence of hernias, but there is a higher incidence of bilateral hernias. The incidence of bilateral hernia is higher if the first presentation is on the left side.

Direct inguinal hernia results from a weakness in the posterior wall of the inguinal canal. They are rare in children.

Clinical Presentation and Examination

The typical presentation of inguinal hernia in boys is a smooth painless swelling in the groin, which bulges on crying or

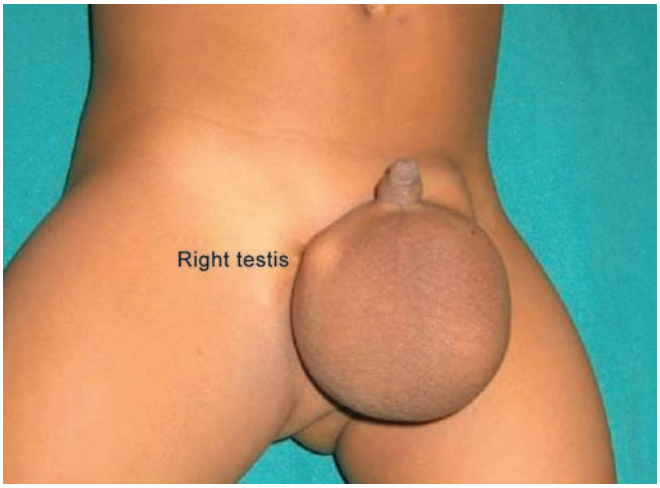


Fig. 1: Left-sided hernia in a boy. Note the left inguinoscrotal swelling. The right testis has been pushed due to the large hernia

straining. The swelling may extend to the scrotum as seen in figure 1. It disappears either spontaneously when the child is quiet and relaxed, or by gentle manual pressure—a maneuver to elicit "reducibility" of a hernia. Older children often complain of groin or inguinal pain during exercise. To elicit hernia in the clinic, a young child can be made to strain or cry while older children can be asked to stand and perform valsalva maneuver or blow a balloon. Clinically, one can elicit the characteristic cough/strain impulse over the swelling. The swelling extends in the inguinal canal deep to the external oblique aponeurosis and emerges from the superficial inguinal ring. Therefore, the upper margin is not well defined (one cannot get above the swelling), hence it is called an inguinoscrotal swelling. When the history is suggestive but the typical hernia swelling is not elicitable during examination, the index finger should be rolled transversely across the spermatic cord over the pubic bone; if there is a hernial sac, the "rustle" of contiguous layers of peritoneum represents the empty hernial sac—referred to as a "silken sleeve" or "silk glove sign". Even if it is not present, it may be appropriate to assume the diagnosis of hernia on the basis of intelligent history. Another source of confusion arises when the parents mistake a testis in the superficial inguinal pouch for a hernia. In these cases, the site of the swelling should be precisely indicated and the presence of a testis in the scrotum documented. If doubt still exists, the parents can be advised to photograph the swelling as it appears and examination can be repeated later. The opposite side should always be examined, and both testes confirmed to be in the scrotum. Certain conditions are associated with an increased incidence of inguinal hernia including prematurity, cryptorchidism, connective tissue disorders, mucopolysaccharidoses, congenital hip dislocation, cystic fibrosis, ascites, ventriculoperitoneal shunt, peritoneal dialysis, abdominal wall defects, meningomyelocele, and exstrophy bladder.

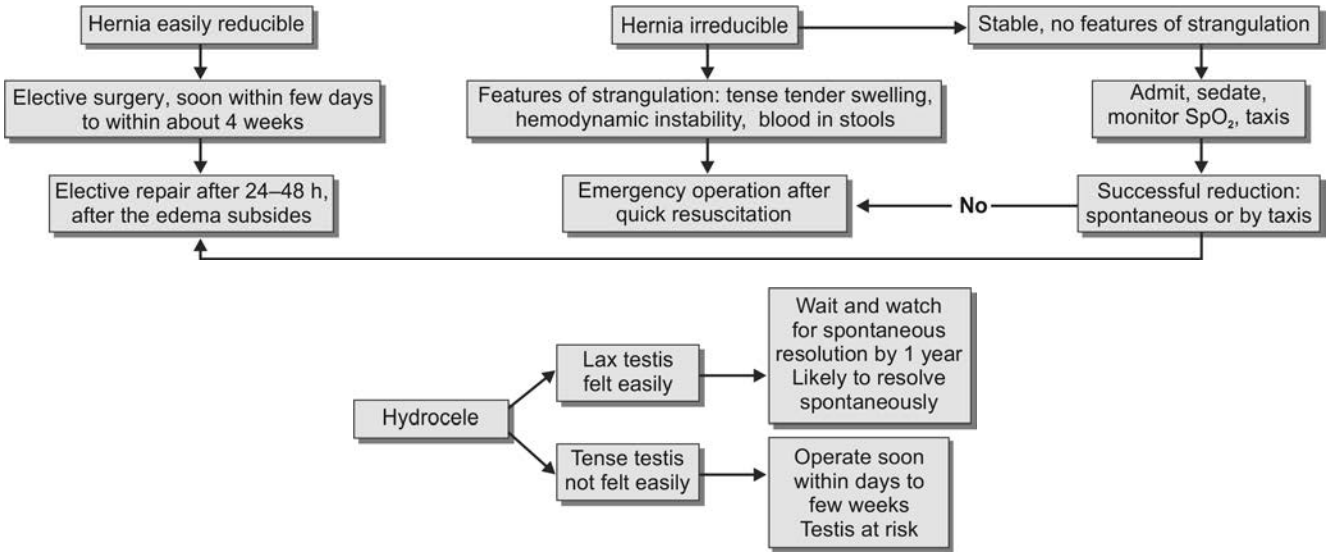
Management

Algorithm 1 shows a suggested approach to the management of hernia and hydrocele.

An inguinal hernia will not resolve spontaneously, so surgery is always indicated. Most full-term infants and older children undergo an elective herniotomy soon after diagnosis. It is a day care operation performed under general anesthesia through a small skin crease incision in the groin. The hernia sac is gently dissected from the cord structures (vas and vessels) and transected and ligated at the deep inguinal ring. The distal sac is left *in situ* but opened widely. The testis is confirmed in the scrotum before closing. No repair of the inguinal floor (herniorrhaphy) is needed unless special situations exist.

ALGORITHM 1

Algorithm for management of hernia/hydrocele in an infant



Timing of Surgery

Infants

Elective surgery within days to few weeks from diagnosis. It is not a dire emergency but waiting longer may invite complications like obstruction—requiring emergency surgery with possibility of bowel resection. Obstructed hernia is a common complication during infancy.

Older children

Elective operation within few weeks.

Preterm babies

Low birth weight babies, who are admitted to neonatal units with prematurity related issues, often develop a hernias. The author's practice is to operate on them once the medical issues are over and the child is otherwise ready to be sent home. However, there is an increased risk of anesthesia and postoperative apnea risk. They may require postoperative monitoring and ventilation for about 24 hours.

INCARCERATED HERNIA

An incarcerated hernia is one which does not reduce spontaneously and is not reducible by gentle pressure. If left untreated, it soon becomes obstructed, causing symptoms of intestinal obstruction which may progress quite rapidly to strangulation. Strangulation may cause intestinal and testicular ischemia—the swelling becomes tense and tender and there are features of intestinal obstruction. Strangulated hernia requires emergency surgery to relieve intestinal obstruction and save the gut and the testis. If the hernia is incarcerated but not strangulated, the child may be mildly irritable with groin pain but there is no abdominal distension and no features of intestinal obstruction or hemodynamic instability. Such a child should be admitted for monitoring and sedated. Often the hernia will reduce spontaneously within about 30 minutes of the child becoming quiet. If not, "taxis" is applied—the surgeon stands on the side of hernia and pushes the contents toward the inguinal canal across the superficial ring with fingers of the right hand, simultaneously aligning the sac to the superficial ring by the fingers of the left hand on the top of the sac. Simply pushing the contents are not successful because the sac turns on itself as it comes out of the superficial ring. If taxis is successful, the hernia should be repaired in 24–48 hours after the tissue edema subsides. If taxis is unsuccessful, another attempt may be made about an hour later (provided the patient is stable). If it still fails, urgent operation should be carried out.

Risk of incarceration is highest in infancy reaching an incidence of up to 30%. Therefore, surgery should be performed soon after the diagnosis in this subset of patients so as to avoid the risk of incarceration and strangulation.

An obstructed or strangulated hernia needs urgent exploration after adequate resuscitation.

HYDROCELE

When the processus vaginalis is patent with a small lumen it allows some peritoneal fluid to seep down along the cord producing a soft, fluid-filled swelling (Fig. 2). This collection of fluid between the layers of the tunica vaginalis is referred to as hydrocele. Unilateral or bilateral congenital hydroceles are common in the first few months of life. The swelling usually is very mild in the morning when the child wakes up; it gradually fills up during the day as the child remains active. When sleeping, some fluid recedes back gradually making the swelling smaller. But this swelling is not reducible manually because of very small size of patent processus (ink well effect). Table 1 shows how to differentiate between a hernia and a hydrocele. The child is unaffected by the presence of the swelling. Clinically, there is no impulse on crying or straining as in hernia. The swelling is painless; it is situated around the testis, is brightly translucent and cannot be emptied by pressure. The underlying testis may be palpable when the hydrocele is lax, and when it is tense, the testis shadow can be demonstrated by transillumination. The upper limit of the hydrocele is clearly defined—the palpating finger "can get above it", except

Fig. 2: Right hydrocele. It was a lax hydrocele. The testis could be felt easily through the hydrocele

TABLE 1: Differentiating between hernia and hydrocele

Hernia	Hydrocele
Inguinoscrotal swelling. One cannot get above the swelling	Scrotal swelling. One can get above*
Not transilluminant**	Transilluminant
Can feel testis separately below the sac	Cannot feel testis separately except in very lax hydroceles, when one can palpate testis within the hydrocele sac

*Large abdominoscrotal communicating hydroceles can be inguinoscrotal, but they are rare. Also, they are brilliantly transilluminant.

**In an infant, a bowel loops in a hernia sac may become transilluminant.

in unusual varieties (abdominoscrotal hydroceles). Most hydroceles resolve spontaneously as the processus obliterates by the age of 1 year and surgery is only required if the hydrocele persists beyond 2 years. Unusual situation that may warrant an early surgery are: very tense hydrocele causing discomfort to the child and possible compression of testicular vessels, abdominoscrotal hydroceles, hydroceles associated with ventriculoperitoneal (VP) shunts, and when a hernia cannot be excluded with certainty. An encysted hydrocele of the cord is a loculus of fluid located above and separate from the tunica vaginalis. Clinically, the swelling is separate from the testis and one can get both above and below the swelling. As it is in line with the processus, it moves when the testis is pulled down. Uncommonly, an acute hydrocele develops secondary to epididymo-orchitis, torsion, trauma or tumor—these hydroceles resolve spontaneously. The operation for hydrocele is the same as that for hernia.

SPECIAL CONSIDERATIONS

Preterm Babies

They have high incidence of hernia but, owing to a wider neck, the rate of incarceration is comparatively lower than in term babies. When diagnosed in the neonatal unit they should be repaired just before sending them home from medical point of view. Bilateral operation is often necessary.

Hernia with Undescended Testis

Undescended testis is always accompanied by a hernial sac, but is at low risk of incarceration. They can be safely repaired at the time of orchidopexy (generally at 6 months). However, the parents are warned about the danger signs of obstruction. If symptomatic hernia develops, an early repair of hernia and undescended testis is performed.

Hernia with Ventriculoperitoneal Shunts

These hernias tend to be bilateral and have about 20% risk of incarceration. Bilateral early repair is in order.

Hernia in a Female Child

The incidence of bilaterality is high in females. The ovary may be a content and it is difficult to reduce. Often, there is a fallopian tube also herniating out. If there is no pain or tenderness in the ovary, an elective operation may be done within a few days to weeks, but if there is pain or tenderness, it may indicate torsion and requires urgent operation. Rarely, androgen insensitivity syndrome (AIS) in a phenotypic female may present with a hernia with a testis in the sac. The authors advocate a preoperative ultrasound in females with hernia to confirm presence of uterus and tubes. If a suspicious gonad is found in the sac on the table, gonad is not removed; parents are counseled, hernia repaired, and the child investigated further with karyotype. Laparoscopy is a good tool to confirm internal genital anatomy and repair hernia, which are often bilateral. The author favors laparoscopic approach in all female hernias. Routine use of karyotype to pick up a rare case of AIS is not warranted. AIS requires removal of both testes and life-long replacement of estrogens.

Bilateral Hernia

Twenty percent hernias are bilateral. Contralateral hernia may also develop later after repair of ipsilateral hernia. It is more common in infancy and girls, and when the presenting hernia is on the left. Bilateral repair should be performed for clinically present bilateral hernias. But, routine contralateral exploration for a unilaterally presenting hernia is controversial. Some surgeons follow the practice of bilateral exploration in selected situations like preterm babies, presenting hernia on left side, and infants and female hernia. With advent of laparoscopic hernia repair, this issue is largely resolved as both the deep rings are clearly visible and without any additional ports, bilateral repair can be performed laparoscopically.

LAPAROSCOPIC VERSUS OPEN REPAIR OF HERNIA

Open repair of hernia through a skin crease incision is a standard time tested operation with universally good results. However, laparoscopic repair has also made inroads during the last decade with improved techniques largely resembling open hernia repair. The advantages of laparoscopic repair are: clear magnified view of vas and vessels (Fig. 3), therefore, less chances of damaging them, no stretching of cord structures, no disturbance to the testis, hence, less complication of testicular fixation in the wound, and ability to do simultaneous bilateral repair, if necessary. The disadvantages are: need to go transperitoneally, more cost, and a higher incidence of postoperative hydrocele. Most surgeons agree on its use for female hernia. For males, the debate continues (Table 1).

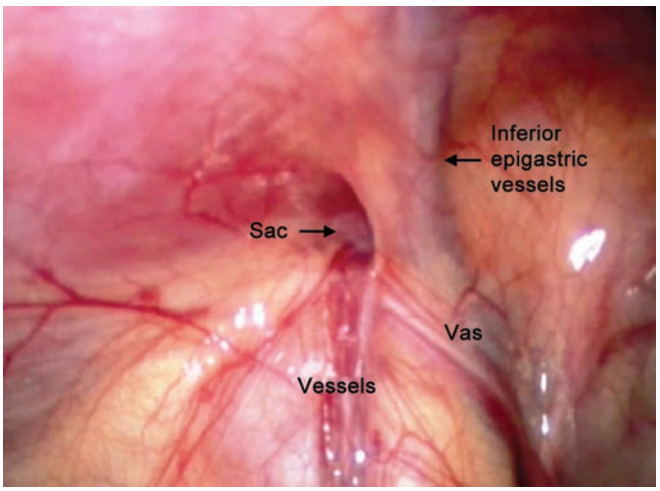


Fig. 3: Laparoscopic view of left hernia in a boy. The vas and vessels are clearly visible in the magnified view, hence less likely to be injured during repair

Clinical Pearls

Indications of surgery in hydrocele

- Persistent hydrocele beyond 2 years
- Tense hydrocele threatening testicular vessels at any age
- Hydrocele developing de novo after 2 years
- Hydrocele with ventriculoperitoneal shunt
- Abdominoscrotal hydrocele.

KEY POINTS

- ☞ Congenital hernia and hydroceles develop from patent processus vaginalis
- ☞ Hydrocele contains fluid and hernia contains bowel or omentum
- ☞ Hernia is inguinoscrotal while hydrocele is scrotal
- ☞ Incidence of hernia is high in infants. Probability of complications—obstruction and strangulation, is also higher in them
- ☞ Surgery should be performed soon after diagnosis to prevent complications
- ☞ Obstructed or strangulated hernia requires emergency operation
- ☞ Hydroceles usually resolve spontaneously in the first year of life
- ☞ Tense hydroceles may cause compression of testicular vessels, hence require surgery.

SUGGESTED READINGS

1. Barthold JS. Abnormalities of the testis and scrotum and their surgical management. In: Wein AJ, Kavoussi LR, Partin AW (Eds). Campbell Walsh Urology. 10th ed. Elsevier-Saunders; 2012. pp. 3556-96.
2. Borkar NB, Pant N, Ratan SK, Aggarwal SK. Laparoscopic repair of indirect inguinal hernia in children: does partial resection of sac make any impact on outcome? J Laparoendosc Adv Surg Tech. 2012;22(3):290-4.
3. Chan KL, Tam PK. Technical refinements in laparoscopic repair of childhood inguinal hernias. Surg Endosc. 2004;18:957-60.
4. Glick PL, Boulanger SC. Inguinal hernias and hydroceles. In: Coran G, Adzick NS, Krummel TM (Eds). Pediatric Surgery, 7th ed. Elsevier-Saunders; 2012. pp. 985-1001.
5. Inguinal Region and Acute Scrotum in Hutson JM, Brien MO, Woodward AA (Eds). Jones Clinical Paediatric Surgery Diagnosis and Management, 6th ed. Blackwell Publishing; 2008. pp. 168-71.
6. Lloyd DA. Inguinal and femoral hernia. In: Zeigler MM, Azizkhan RG, Weber Thomas R (Eds). Operative Pediatric Surgery, International edition. Mc Graw Hill Professional; 2003. pp. 543-54.
7. Saranga BR, Arora M, Baskaran V. Minimal access surgery of pediatric inguinal hernias: a review. Surg Endosc. 2008;22:1751-62.

CHAPTER 131

Antenatal Hydronephrosis

Anurag Krishna

INTRODUCTION

Routine antenatal ultrasonography has focused our attention to urological abnormalities that occur in babies. Ultrasonologists routinely use terms such as pelvicaliectasis, caliectasis, and hydronephrosis, leading to confusion in the minds of the obstetrician, the neonatologist, and the pediatric surgeon as to the precise significance of this finding. This review aims to outline a logical approach to this problem through the gestational period into the neonatal period emphasizing what needs to be done and when, and more importantly, what need not be done.

MAGNITUDE OF THE PROBLEM

It is estimated that some degree of dilatation of the fetal renal collecting system is identified in 1–5% of all pregnancies, but in only one-fifth of these, dilatation is significant. The term hydronephrosis simply denotes dilatation of the upper urinary tract and does not necessarily imply the presence of an obstruction or a significant functional abnormality of any kind. In fact, only 3% of babies with a renal pelvis diameter less than 10 mm had a significant abnormality needing surgery. Antenatal hydronephrosis (ANH) could occur because of:

- Functional dilatation: minor degree of dilatation that usually spontaneously resolves or stabilizes later in gestation or early infancy
- Obstruction: usually at the pelvi-ureteric junction, at the ureterovesical junction, or in the urethra [as in posterior urethral valves (PUV)]
- Vesicoureteral reflux (VUR)
- Renal dysplasia including multicystic dysplastic kidneys
- Uncommon conditions like duplex collecting system or prune belly syndrome, etc.

What Is Significant Dilatation?

The Society of Fetal Urology (SFU) has recommended a grading system for hydronephrosis (Table 1). An alternate method is to measure the renal pelvis anteroposterior diameter.

A renal pelvis anteroposterior diameter of more than 10 mm after 24–26 weeks of gestation is generally accepted as a reasonable criterion to denote significant dilatation. The presence of caliectasis or calyceal dilatation is considered an additional factor indicative of significant hydronephrosis. More recently, there is evidence to suggest that milder degrees of dilatation may also be significant in such babies, who may have VUR rather than obstruction. Currently, a renal pelvis diameter of at least 4 mm before 33 weeks and 7 mm after 33 weeks is considered significant. ANH can be classified as mild, moderate, or severe for prognostic purposes (Table 2). A large systematic review suggests that the risk of significant postnatal pathology is 11.9% for mild, 45.1% for moderate, and 88.3% for severe hydronephrosis.

TABLE 1: Grading of hydronephrosis

Grade	Pattern of renal sinus splitting
0	No splitting
1	Urine in pelvis barely splits sinus
2	Urine fills intrarenal pelvis
2	Urine fills extrarenal pelvis, major calyces dilated
3	SFU grade 2 and minor calyces dilated and parenchyma preserved
4	SFU grade 3 and parenchyma thin

SFU, Socity of Fetal Urology.

TABLE 2: Definition of antenatal hydronephrosis by anteroposterior diameter

Degree of ANH	Second trimester	Third trimester
Mild	4 to <7 mm	7 to <9 mm
Moderate	7 to ≤10 mm	9 to ≤15 mm
Severe	>10 mm	>15 mm

ANH, antenatal hydronephrosis

Information from a Good Antenatal Ultrasound Scan

While assessing the significance of the antenatal renal dilatation, particularly with a view to identify a possible cause and whether it is worth continuing pregnancy, the ultrasound must be done carefully and must give the following information:

- Estimated fetal size and weight, and its comparison with normal for that gestational age
- Amniotic fluid volume (AFV)
- Whether dilatation is unilateral or bilateral, and whether ureters are dilated or not
- Degree of dilatation (SFU grading) and dilatation of calyces
- Bladder fullness, thickness, and emptying
- Appearance of external genitalia
- Any other associated malformation.

The initial study is usually done at 16–20 weeks of gestation using an appropriate transducer. There are no specific guidelines on how frequently to image the fetus. It would be reasonable to do the ultrasound every 4 weeks till 32 weeks and two weekly thereafter, mainly to assess the AFV.

Current Status of Fetal Intervention

The rationale for fetal urinary decompression is that those with severe obstruction early in gestation have significant impairment of both renal and pulmonary development. It has been recognized that if the AFV is adequate up to 27 weeks of gestation, then severe pulmonary hypoplasia is unlikely to occur. Percutaneous shunting of the bladder into the amniotic space is technically feasible with some morbidity. However, its role is extremely limited.

There is no place for any fetal intervention in unilateral hydronephrosis. Even with bilateral pelviureteric junction obstruction (PUJO), if the AFV is normal, percutaneous drainage of the fetal kidneys or early delivery are not warranted.

Natural History of Antenatal Hydronephrosis

Spontaneous resolution of prenatally detected hydronephrosis occurs in 50–70% of all fetuses. This regression may be noted on serial antenatal ultrasound scans or in the postnatal life up to 3 years. Furthermore, in a substantial number, even if the hydronephrosis does not resolve completely, the renal function does not deteriorate despite persistence of pelvic dilatation. On the other hand, 15–33% of patients show progressive renal deterioration during observation. It has been noted that increasing degrees of hydronephrosis correlated with increased risk of urological pathologies that may need surgical intervention.

POSTNATAL EVALUATION OF ANTENATAL HYDRONEPHROSIS

Immediately after birth, the following must be recorded:

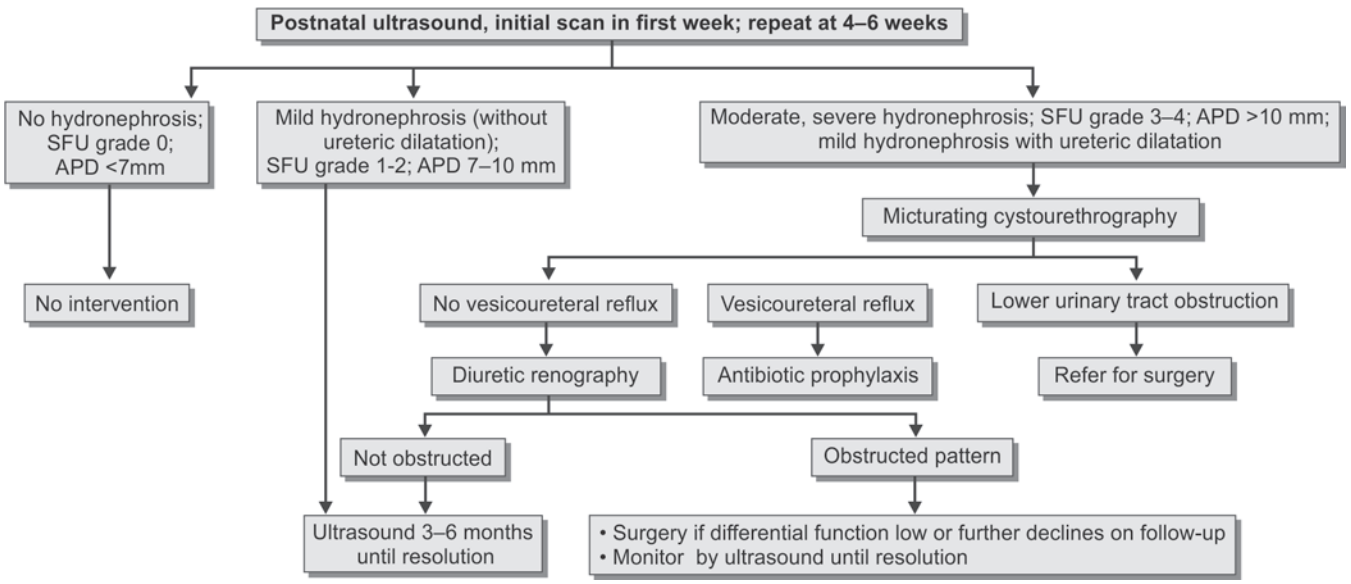
- Sex of the baby: in males, PUV is an important diagnosis to be ruled out as it requires early surgical intervention
- Palpable kidney: common causes are PUJO (more commonly unilateral), multicystic dysplastic kidney (unilateral), and PUV (unilateral or bilateral)
- Palpable bladder: indicative of PUV in boys.

If the diagnosis of PUV is suspected, all further investigations need to be done urgently as the baby requires early surgical intervention. These babies need renal function tests, ultrasound scan, voiding cystourethrogram (VCUG) within a day or two after birth so that surgical ablation of the valves may be done at the earliest.

In all other situations, there is no great haste to perform investigations (Algortihm 1). The initial study to be done is the ultrasound scan that must preferably not be done in the first 2–3 days. However, if the mother is being discharged earlier, it is practical to send the baby with the ultrasound scan results.

ALGORITHM 1

Scheme for postnatal evaluation in patients with antenatal hydronephrosis



SFU, Society of Fetal Urology; APD, anteroposterior dianeter.

Following the ultrasound scan, a VCUG is done. There is no doubt that the conventional VCUG is preferred to a direct radionuclide cystogram (DRCG) because the latter does not give a good delineation of the bladder and urethral anatomy and that reflux, if present, cannot be accurately graded. Controversy surrounds two aspects of VCUG:

- Should VCUG be done in all babies?
- When should it be done?

Should VCUG be done in all babies?

Voiding cystourethrogram is an invasive procedure, and some studies have quoted a 6% rate of urinary tract infection (UTI) following VCUG. This has made most clinicians reluctant to ask for a VCUG in newborn babies. However, if properly performed under antibiotic cover, the procedure is safe with no risk of UTI (personal experience). There are some recent reports that claim that routine VCUGs may not be indicated in all babies with antenatally detected hydronephrosis. These studies recommend VCUG for those babies with:

- bilateral hydronephrosis
- dilated ureters
- presence of UTI.

This literature against routine use of VCUG is far from convincing. Most large centers recommend that this test must be done in all babies with ANH even if the postnatal ultrasound scan is normal. VUR has been recorded in 15–30% babies born with an antenatal diagnosis of hydronephrosis. Tibballs reported that among 255 renal units with reflux, the postnatal ultrasound was normal in 177 (70%). Furthermore, some studies have shown that the postnatal ultrasound may be normal even with the higher grades of VUR (12% of grade V and 31% with grade IV). The Indian Society of Pediatric Nephrology has recommended a middle path for performing VCUG if there is moderate-to-severe hydronephrosis, dilated ureters, or bladder or urethral abnormalities.

When should it be done?

Some authors recommend that a VCUG should be done at 4–6 weeks postnatal age. Though, again, it would be more practical to do it before the baby leaves hospital. Either way, till the VCUG has been done and VUR excluded the baby needs to be on low dose antibiotics using amoxicillin (15 mg/kg/day) or cephalexin (50 mg/kg/day). Trimethoprim (2 mg/kg/day) may be used safely in babies after 4–6 weeks of age. Neonates who do not have VUR do not need further antibiotic chemoprophylaxis.

Role of Radionuclide Imaging Studies

In most babies, the ultrasound scan is repeated at 4–6 weeks of age. In most situations, a diuretic renogram is done at about 4 weeks of age to evaluate renal functional status and presence of obstruction. Renograms performed immediately after birth may be difficult to interpret due to the immature function of the kidneys and their handling of the radioisotope. Diuretic renogram is indicated in all kidneys with grade 3 or 4, and occasionally grade 2 hydronephrosis; there is bilateral PUJO or ureterovesical junction obstruction; if there is a solitary kidney; or, the kidney is palpable and tense.

The renal scan is superior to the introvenous pyelogram for many reasons. It is safer (contrast reactions and radiation are less), there is better visualization of the collecting system, and objective and quantitative assessment of relative function of each kidney is possible. The ideal radionuclide is mercaptoacetyltriglycine, but a cheaper, though less accurate option is the diethylenetriamine pentaacetate acid (not dimercaptosuccinic acid) scan. In lower grades of hydronephrosis, if VUR has been excluded, no further workup with renal scans may be necessary. These babies need observation with 3-monthly ultrasound to ensure that the degree of hydronephrosis is static and not worsening.

Follow-up Evaluation

Currently, no single test can reliably predict whether a hydronephrotic kidney will improve or deteriorate. Most people agree that nearly all infants with unilateral PUJO are initially managed conservatively if the diuretic renogram shows at least 35–40% differential renal function. Exception are infants with renal infection, tense renal lump or pelvis anteroposterior diameter more than 50 mm. Follow-up ultrasound scan and diuretic renography is repeated at 3–6 months and if there is a deterioration in differential renal function, pyeloplasty is indicated. Nearly 20% infants will show deterioration on follow-up requiring pyeloplasty. This usually happens in the first year of life.

Children with lesser degree of hydronephrosis (up to pelvis anteroposterior diameter of <20 mm) need to be followed up with a ultrasound scan at 3 months, 1 year, then 2, 5, and 10 years. Radionuclide study is done at 3 months, 1 year, and if required at 2, 5, and 10 years. If the renal function or degree of dilatation improves, there is no further need for the isotope study.

Clinical Pearls

- Hydronephrosis >7 mm after 33 weeks is significant
- Look for bladder emptying in fetuses with hydronephrosis, particularly bilateral
- First postnatal ultrasound may be done 48–72 hours after birth
- In male babies, always exclude possibility of posterior urethral valves by looking for bladder emptying
- Till a voiding cystourethrogram is done, it may be safer to give low dose antibiotic prophylaxis
- Diethylenetriamine pentaacetate acid renogram should be done if obstruction is suspected. Dimercaptosuccinic acid renal scan is to be done in cases with vesicoureteral reflux.

KEY POINTS

- ☞ Antenatal hydronephrosis does not necessarily mean obstruction
- ☞ Most such pregnancies can be carried to term
- ☞ Fetal intervention is not required in majority of cases
- ☞ Postnatal evaluation must be done in all such babies and must include a surgical opinion
- ☞ A majority do not need surgical intervention, but those that do need, requires an early surgical evaluation.

SUGGESTED READINGS

1. Ansari MS, Ayyildiz HS, Jayanthi VR. Is voiding cystourethrogram necessary in all cases of antenatal hydronephrosis? Indian J Urol. 2009;25(4):545-6.
2. Becker AM. Postnatal evaluation of infants with an abnormal antenatal renal sonogram. Curr Opin Pediatr. 2009;21(2):207-13.
3. Blane CE, DiPietro MA, Zerin JM, et al. Renal sonography is not a reliable screening examination for vesicoureteral reflux. J Urol. 1993;150:752.
4. Coret A, Morag B, Katz M, Lotan D, Heyman Z, Hertz M. The impact of fetal screening on indications for cystourethrography in infants. Pediatr Radiol. 1994;24:516-8.
5. Corteville JE, Gray DL, Crane JP. Congenital hydronephrosis: correlation of fetal ultrasonographic findings with infant outcome. Am J Obstet Gynecol. 1991;165:384.
6. De Kort EHM, Bambang Oetomo S, Zegers SH. The long term outcome of antenatal hydronephrosis up to 15 millimeters justifies a noninvasive postnatal follow-up. Acta Paediatrica. 2008;97;708-13.
7. Dhillon HK. Prenatally diagnosed hydronephrosis: the Great Ormond Street experience. Br J Urol. 1998;81(Suppl 2):39-44.
8. DiSandro MJ, Kogan BA. Neonatal management. Role for early intervention. Urol Clin North Am. 1998;25(2):187-97.
9. Dudley JA, Haworth JM, McGraw ME, Frank JD, Tizard EJ. Clinical relevance and implications of antenatal hydronephrosis. Arch Dis Child. 1997;76:F31.
10. Elder JS. Antenatal hydronephrosis. Fetal and neonatal management. Pediatr Clin North Am. 1997;44(5):1299-321.
11. Freedman ER, Rickwood AMK. Prenatally diagnosed pelviureteric junction obstruction: a benign condition? J Pediatr Surg. 1994;29:769-72.
12. Gloor JM, Ramsey PS, Ogburn Jr PL, Danilenko-Dixon DR, DiMarco CS, Ramin KD. The association of isolated mild fetal hydronephrosis with postnatal vesicoureteral reflux. J Matern Fetal Neonatal Med. 2002;12:196-200.
13. Grignon A, Filion R, Filiatrault D. Urinary dilatation in utero: classification and clinical applications. Radiology. 1986;160:645.
14. Herndon C, McKenna P, Kolon T, Gonzales ET, Baker LA, Docimo SG. A multicenter outcomes analysis of patients with neonatal reflux presenting with prenatal hydronephrosis. J Urol. 1999;162(3 Pt 2):1203-8.
15. Herndon CD. Antenatal hydronephrosis: differential diagnosis, evaluation, and treatment options. Scientific World Journal. 2006;6:2345-65.
16. Homsy YL, Williot P, Danais S. Transitional neonatal hydronephrosis: fact or fantasy? J Urol. 1986;136:339.
17. Kitagawa H, Pringle KC, Stone P, Flower J, Murakami N, Robinson R. Postnatal follow-up of hydronephrosis detected by prenatal ultrasound: the natural history. Fetal Diagn Ther. 1998;13(1):19-25.
18. Kleiner B, Callen PW, Filly RA. Sonographic analysis of the fetus with ureteropelvic junction obstruction. AJR. 1987;148:359-63.
19. Koff SA, Campbell KD. The nonoperative management of unilateral neonatal hydronephrosis: natural history of poorly functioning kidneys. J Urol. 1994;152:593.
20. Koff SA, McDowell GC, Byard M. Diuretic radionuclide assessment of obstruction in infant: guidelines for successful interpretation. J Urol. 1988;140:1167-8.
21. Koff SA. Postnatal management of antenatal hydronephrosis using an observational approach. Urology. 2000;55:609-11.
22. Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. Pediatrics. 2006;118:586.
23. Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a metaanalysis. Pediatrics. 2006;118: 586-93.
24. Longpre M, Nguan A, Macneily AE, Afshar K. Prediction of the outcome of antenatally diagnosed hydronephrosis: a multivariate analysis. J Pediatr Urol. 2012;8(2):135-9.
25. Mandell J, Blyth BR, Peters CA, Retik AB, Estroff JA, Benacerraf BR. Structural genitourinary defects detected in utero. Radiology. 1991;178:193-6.
26. Mandell J, Lebowitz RL, Peters CA, Estroff JA, Retik AB, Benacerraf BR. Prenatal diagnosis of the megacystis-megaureter association. J Urol. 1992;148:1487-9.
27. Mandell J, Peters CA, Estroff JA, Benacerraf BR. Late onset severe oligohydramnios associated with genitourinary abnormalities. J Urol. 1992;148:515.
28. Marra G, Barbieri G, Moioli C, Assael BM, Grumieri G, Caccamo ML. Mild fetal hydronephrosis indicating vesicoureteric reflux. Arch Dis Child. 1994;70: F147-9.
29. Mears AL, Raza SA, Sinha AK, Misra D. Micturating cystourethrograms are not necessary for all cases of antenatally diagnosed hydronephrosis. J Pediatr Urol. 2007;3(4):264-7.
30. Moorthy I, Joshi N, Cook JV, Warren M. Antenatal hydronephrosis: negative predictive value of normal postnatal ultrasound—a 5-year study. Clin Radiol. 2003;58:964-70.
31. Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, et al. The Society of Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol. 2010;6(3):212-31.
32. Ouzounian JG, Castro MA, Fresquez M, al-Sulyman OM, Kovacs BW. Prognostic significance of antenatally detected fetal pyelectasis. Ultrasound Obstet Gynecol. 1996;7(6):424-8.
33. Palmer LS, Maizels M, Cartwright PC, Fernbach SK, Conway JJ. Surgery versus observation for managing obstructive grade 3 to 4 unilateral hydronephrosis: a report from the Society for Fetal Urology. J Urol. 1998;159:222.
34. Passerotti CC, Kalish LA, Chow J, Passerotti AM, Recabal P, Cendron M, et al. The predictive value of the first postnatal ultrasound in children with antenatal hydronephrosis. J Pediatr Urol. 2011;7:128-36.
35. Persutte WH, Koyle M, Lenke RR, Klas J, Ryan C, Hobbins JC. Mild pyelectasis ascertained with prenatal ultrasonography is pediatrically significant. Ultrasound Obstet Gynecol. 1997;10(1):12-8.
36. Phan VR, Traubici J, Hershenfield B, Stephens D, Rosenblum ND, Geary DF. Vesicoureteral reflux in infants with isolated antenatal hydronephrosis. Pediatr Nephrol. 2003;18:1224-8.
37. Ransley PG, Dhillon HK, Gordon I, Duffy PG, Dillon MJ, Barratt TM. The postnatal management of hydronephrosis diagnosed by prenatal ultrasound. J Urol. 1990;144:584-7.
38. Reddy PP, Mandell J. Ureteropelvic junction obstruction: prenatal diagnosis, therapeutic implications. Urol Clin N Am. 1998;25(2):171-80.
39. Sairam S, Al-Habib A, Sasson S, Thilaganathan B. Natural history of fetal hydronephrosis diagnosed on mid-trimester ultrasound. Ultrasound Obstet. Gynecol. 2001;17(3):191-6.
40. Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, et al. Revised guidelines on management of antenatl hydronephrosis. Indian Pediatr. 2013; 50(2):215-31.
41. Thomas DFM, Madden NP, Irving HC, Arthur RJ, Smith SE. Mild dilatation of the fetal kidney: a follow-up study. Br J Urol. 1994;74:236-9.
42. Tibballs JM, De Bruyn R. Primary vesicoureteral reflux—how useful is postnatal ultrasound? Arch Dis Child. 1996;75:444.
43. Vates TS, Shull MJ, Underberg-Davis SJ, Fleisher MH. Complications of voiding cystourethrography in the evaluation of infants with prenatally detected hydronephrosis. J Urol. 1999;162(3 Pt 2):1221-3.
44. Yerkes E, Adams M, Pope JC 4th, Brock JW 3rd. Does every patient with prenatal hydronephrosis need voiding cystourethrography? J Urol. 1999;162: 1218-23.
45. Zerin JM, Ritchey ML, Chang AC. Incidental vesicoureteral reflux in neonates with antenatally detected hydronephrosis and other renal abnormalities. Radiology. 1993;187:157-60.

CHAPTER 132

Management of Vesicoureteric Reflux

Minu Bajpai, Aparajita Mitra, Manisha Jana, Rakesh Kumar, Chandra S Bal

Primary vesicoureteric reflux (VUR) is seen in 1% of the general population. It is seen in 37% of children and up to 50% of neonates who present with urinary tract infection (UTI). The association of the triad of UTI-VUR-nephropathy forms the basis of treatment of VUR. However, lack of application of appropriate tools in the studies has led to inconsistencies in management protocols. In VUR, some urine flows back into the ureters during the act of micturation depending upon the grade of reflux. VUR may resolve spontaneously with increasing age, albeit slowly. At the end of 5 years, grades I and II reflux persist in 37% of children and at 10 years in 25%. During the corresponding periods, grades III–V reflux persist in 48 and 23%, respectively. Negative prognostic factors for resolution are recurrent UTIs and bladder dysfunction. Bilateral reflux resolved more slowly than unilateral reflux and it resolved more rapidly in boys than in girls. Antibiotic prophylaxis has been widely employed in the hope of prevention of pyelonephritis. However, pyelonephritis occurs despite antibiotics.

MAINSTAY OF MODERN MANAGEMENT OF VESICOURETERIC REFLUX

- Continuing VUR has the potential to cause long-term renal damage, therefore, early diagnosis and prevention of pyelonephritis are very important
- UTI may occur even in nondilating VUR (grades I and II). In a follow-up study in children with VUR, who were evaluated using criteria specified in the American Academy of Pediatrics (AAP) guidelines, 17.2% of children with normal ultrasound had renal injury identified on renal scanning, and 62.1% had grade III or higher VUR
- The Subcommittee on UTI of the AAP acknowledges that it is important to detect urinary tract anomalies, such as VUR, at the outset, once UTI is confirmed. Children with VUR are believed to be at risk for ongoing renal damage with subsequent infections, resulting in hypertension and renal failure. Therefore, identifying urinary abnormalities [by ultrasonography and micturating cystourethrogram (MCU)] may offer the benefit of preventing hypertension and renal failure
- It has been recognized that, the diagnosis of UTI in young children is often delayed as the clinical presentation is often with vague general symptoms
- Any antenatally diagnosed and postnatally confirmed dilated ureter or hydronephrosis or diagnosis of conditions like duplication anomalies or pelvic kidneys have a risk of ipsilateral VUR, whereas, multicystic dysplastic kidney and renal agenesis has an increased incidence of contralateral VUR. Therefore, MCU/voiding cystourethrogram (VCUG) should be carried out after confirmed, UTI even in presence of mild hydronephrosis. Once VUR is confirmed, a full workup is carried out, which includes dimercaptosuccinic acid (DMSA) scans and glomerular filtration rate (GFR) estimation
- Long-term antibiotic use may increase the severity of otitis media in children. In some studies, including the National Institute for Clinical Excellence (NICE) guidelines, prophylactic antibiotics have been found neither to be effective in reducing the risk of recurrent pyelonephritis nor incidence of renal scarring in children less than 30 months of age who have grade II–IV VUR
- It should be recognized that infants often have non-specific symptoms of UTI which may remain unnoticed
- Renin angiotensin system has been shown to be activated even in the presence of sterile reflux. The upper tracts are, therefore, at risk in presence of VUR even between the episodes of UTI
- Endoscopic treatment is viewed as preferable to open surgery by 60% of parents even for grades I–II reflux and 80% of those with grade III reflux over long-term antibiotic prophylaxis (Figs 1A and B)
- Presently, the endoscopic treatment of VUR by dextranomer/hyaluronic acid (DXHA) is increasingly viewed as first line therapy for reflux (Figs 2A and B)

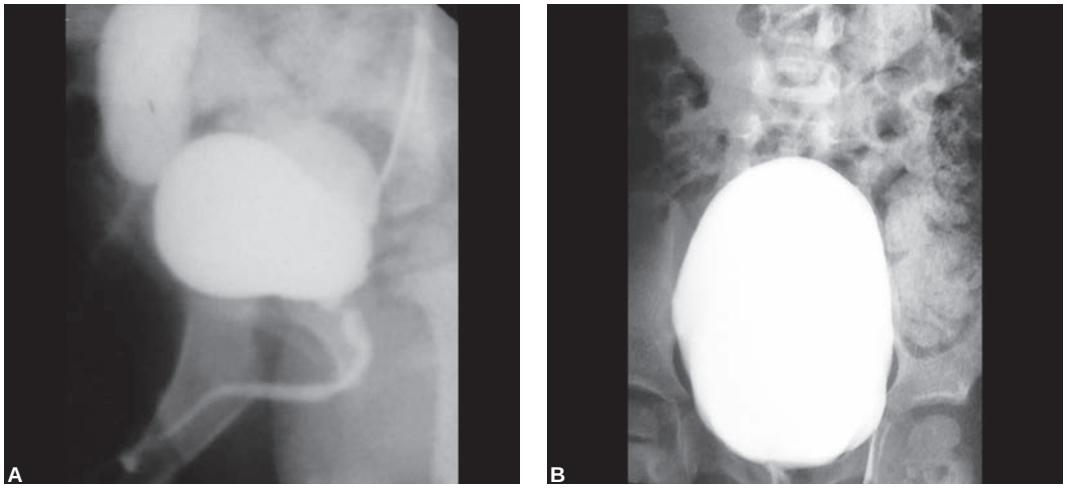


Fig. 1: Micturating cystourethrogram showing high grade reflux: **A,** before and **B,** after endoscopic injuction

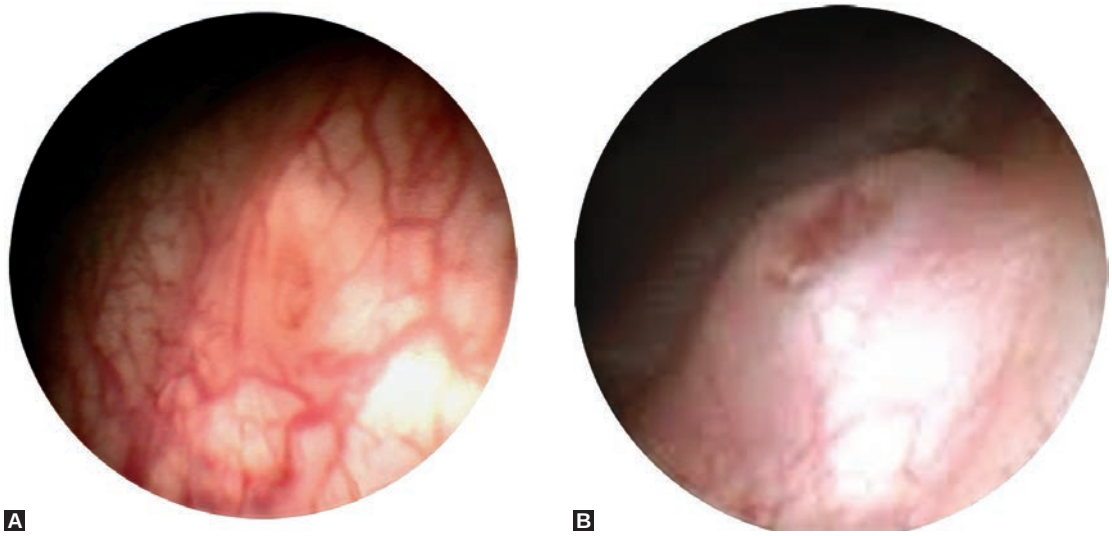


Fig. 2: Cystoscopic view of the ureteric orifice: **A,** before and **B,** after injection of dextranomer/hyaluronic acid copolymer (deflux)

- Parental preference for choice of therapy is honored and they should be offered information on the three options of therapy:

Option A (Antibiotic Prophylaxis)

Continuous antibiotic prophylaxis (CAP) does not require any procedure, as compared to the other two options. However, it does not cure reflux and only reduces the incidence of UTI. Pyelonephritis may continue to occur. It also requires long-term treatment, with a low success rate after 1 year (33% in grades II–IV reflux) is a major disadvantage. It has been recognized that after 2 years of age, chances of spontaneous resolution of VUR are low, while prolonged antibiotic use leads to side effects. CAP is still being recommended until more definitive studies suggest otherwise.

Option B (Endoscopic Injection)

Endoscopic injection recreates the antireflux mechanism by injecting an inert material into the bladder wall at the ureteric orifice. While general anesthesia is required, it is generally a day care procedure. Its success rates range from 70 to 83%. Success for even grades IV and V reflux reaches above 90% after two or more injections.

Option C (Open Surgery)

The aim of open surgery is to prevent reflux by reimplantation of ureter and restoring the antireflux mechanism. Success rates for open surgery are 98%, with few complications. However, the higher success rates for open surgery necessitate greater expense and the need for in-patient hospitalization.

- Grade V VUR should be offered open/laparoscopic surgery. Depending upon the availability and affordability, endoscopic injection may be offered as an option while explaining the need for two or more injections. When treated by surgery, ureteric reimplantation should be performed after 18 months of age. Till this age, CAP should be given. If recurrent infections continue to occur before this period, either endoscopic injection or surgery may be offered even earlier by creating a pop-off mechanism
- Grades III and IV VUR as well as associated cortical abnormalities delay reflux resolution. Considerations should be given to treat these by intention to cure, such as endoscopic injection (option 2) or open surgery (option 3)
- If CAP is used, reassessment of VUR by cystogram between 12 and 24 months after the prior cystogram is recommended to determine when therapy can be stopped
- Open or endoscopic surgery shall be offered in the presence of UTI, new scars in DMSA scanning, and parental preference. If decision to intervene is postponed even after frequent UTIs, there is a higher risk of continuing postoperative UTIs
- After open surgery, ultrasonography should be performed to rule out obstruction. Follow-up monitoring should be carried out for infections, new scarring, and somatic growth through adolescence.

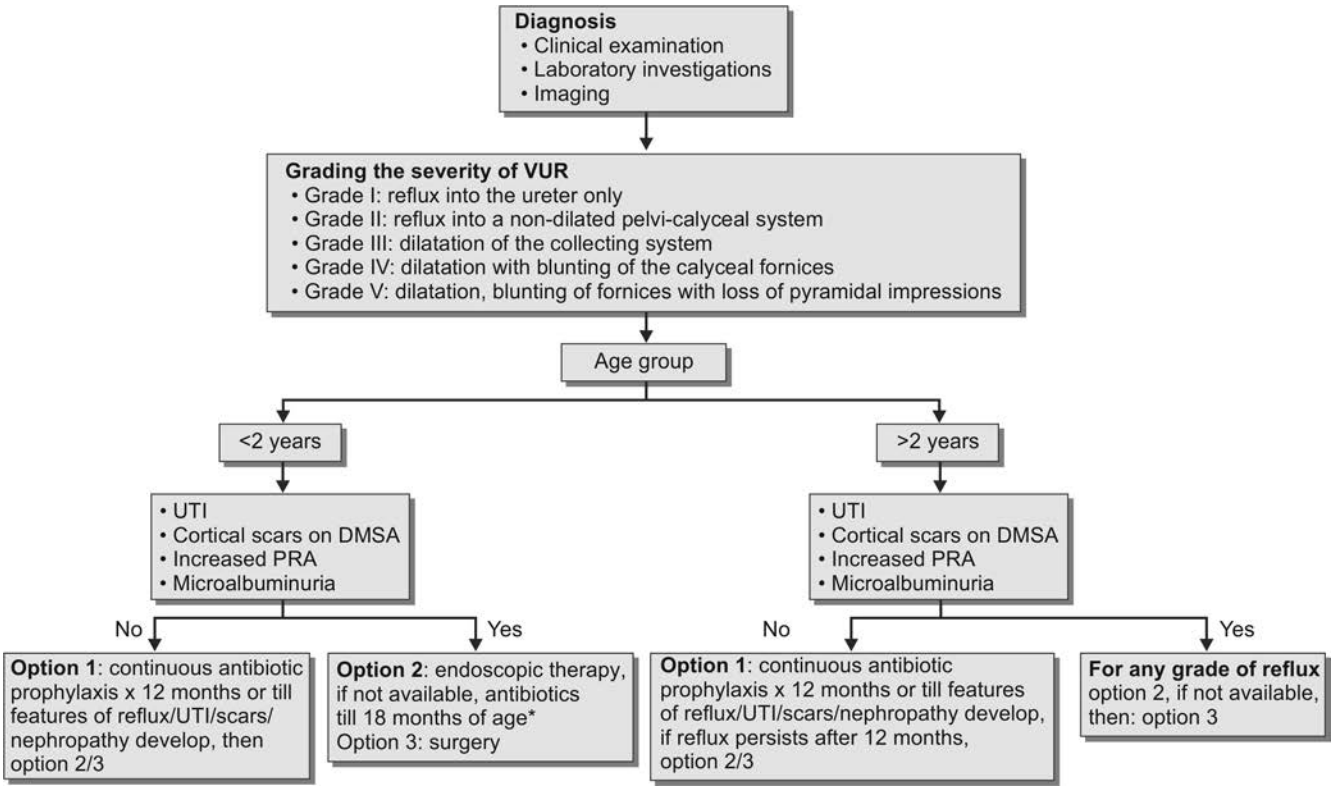
MANAGEMENT OF VESICOURETERIC REFLUX

Following considerations should be given while outlining choice of therapy:

- Reflux diagnosed in infancy resolves in about 50% within 24 months
- According to NICE guidelines, as well as other studies, prophylactic antibiotics are not effective in reducing the risk of recurrent pyelonephritis or renal scarring in children less than 30 months of age who have grade II–IV VUR. However, antibiotics seem to be better than placebo in preventing infection if given for short periods, but, have side effects with prolonged use
- Infants often have nonspecific symptoms of UTI which may remain unnoticed. They also have a greater risk of morbidity related to infection
- Continuing VUR has the potential to cause long-term renal damage; therefore, early diagnosis and prevention of pyelonephritis are very important
- Renal injury/scars are mediated through the activation of renin angiotensin system:
    - Microalbuminuria indicates that renal tubular injury has already begun as this is an early marker of inception of renal damage

ALGORITHM 1

Management of vesicoureteric reflux



VUR, vesicoureteric reflux; UTI, urinary tract infections; DMSA, dimercaptosuccinic acid; PRA, plasma renin activity.

*If recurrent UTIs develop during the waiting period, then some other temporizing surgery, such as lower ureteric pop-off mechanism, should be offered to the patient.

  - Raised plasma renin activity (PRA) indicates that activation of renin angiotensin system has already begun
- Renin angiotensin system has been shown to be activated even in the presence of sterile reflux. Therefore, the upper tracts are at risk in presence of VUR even between the episodes of UTI
- It has been recognized that after 2 years of age, chances of spontaneous resolution of VUR are low
- Ureteric reimplantation should be avoided before 18 months of age.

Management of Vesicoureteric Reflux in the Child under 2 Years of Age

Children under 2 years of age should be assessed for renal abnormalities and bladder bowel dysfunction. When present, treatment for the latter is initiated.

- Children with grades I, II, and III VUR who do not have either UTI, cortical scarring, raised PRA, or microalbuminuria form a special group: they should be offered option 1 (CAP) for a period of 12 months or till the time any of the above features develop, whichever is earlier. In the absence of UTIs, MCU should be done between 12 and 24 months. If there is persistence of reflux or any of the above features develop, they should be offered option 2 or 3, as follows
- Children with any grade of reflux who have either UTI, cortical defects/scarring, raised PRA, or microalbuminuria: they should be offered option 2 (endoscopic treatment). In the event of nonavailability or, nonaffordability due to cost of injection, option 3 should be offered. In the case of decision on the latter case (option 3), antibiotics should be continued till 18 months of age ("waiting period" during which open surgery by ureteric reimplantation is best avoided). During this "waiting period" if adverse circumstances appear, such as recurrent UTI, cortical defects, rise in PRA or microalbuminuria, surgical options other than ureteric reimplantation may be considered. These are temporizing procedures such as creating a pop-off mechanism.

Management of Vesicoureteric Reflux in the Child Over 2 Years of Age

Children over 2 years of age should be assessed for renal abnormalities and bladder bowel dysfunction. When present, treatment for the latter is initiated.

- Children with grades I, II and III VUR over 24 months of age and who do not have either UTI, cortical scarring, raised PRA, or microalbuminuria form a special group: they should be offered option 1 for a period of 12 months or till the time any of the above features develop, whichever is earlier. If there is persistence of reflux or any of the above features develop, they should be offered option 2 or 3
- Children with any grade of reflux who have either UTI, cortical defects/scarring, raised PRA, or microalbuminuria: they should be offered option 2 (endoscopic treatment). In the event of nonavailability or, nonaffordability due to cost of injection, option 3 should be offered.

Additional Information

- Endoscopic treatment can be offered concomitant with management of bladder and bowel dysfunction. It has been found to be safe and effective in resolving VUR in children with associated lower urinary tract (LUT) dysfunction, even before their LUT condition has fully resolved. However, bladder bowel dysfunction should definitely be under control before surgical intervention
- Reflux in solitary kidney and bilateral reflux:
  - Any grade of reflux with either UTI, cortical defects/scarring, raised PRA, or microalbuminuria should be offered endoscopic injection/surgery
  - Grades I and II reflux without UTI, cortical defects/scarring, raised PRA, or microalbuminuria: antibiotics for a period of 12 months. If there is persistence of reflux or any of the above features develop they should be offered option 2 or 3.

Clinical Pearls

- Antibiotics seem to be better than placebo in preventing infection if given for short periods, but have side effects with prolonged use
- Infants often have nonspecific symptoms of urinary tract infection (UTI) which may remain unnoticed. They also have a greater risk of morbidity related to infection
- Continuing vesicoureteric reflux (VUR) has the potential to cause long-term renal damage. Therefore, early diagnosis and prevention of pyelonephritis are very important
- Renin angiotensin system has been shown to be activated even in the presence of sterile reflux. Therefore, the upper tracts are at risk in presence of VUR even between the episodes of UTI
- It has been recognized that after 2 years of age, chances of spontaneous resolution of VUR are low
- Ureteric reimplantation should be avoided before 18 months of age.

CONCLUSION

- While managing VUR, it is important to take into account individual risk factors in each child. These are: age, sex, grade of reflux, bilaterality, bladder dysfunction, and bowel function
- It has been recognized that, while antibiotics have some role for short periods of time, endoscopic injection and surgery are offered with intention to "cure" to stop reflux and are more effective in long-term renal outcomes
- Parental preference should be honored and details of the three options of management of VUR should be explained to them.

KEY POINTS

- ☞ Children with vesicoureteric reflux (VUR) are believed to be at risk for ongoing renal damage
- ☞ Urinary tract infection (UTI) may occur even in nondilating VUR (grades I and II)

- ☞ Therefore, identifying urinary abnormalities [by ultrasonography and micturating cystourethrogram (MCU)], at the outset—once UTI is confirmed—may offer the benefit of preventing hypertension and renal failure
- ☞ Micturating cystourethrogram/voiding cystourethrogram should be carried out after confirmed UTI even in presence of mild hydronephrosis
- ☞ Pyelonephritis occurs despite antibiotics
- ☞ Long-term antibiotic use may increase the severity of otitis media in children. In some studies, including the National Institute for Clinical Excellence guidelines, prophylactic antibiotics have been found neither to be effective in reducing the risk of recurrent pyelonephritis nor incidence of renal scarring in children less than 30 months of age who have grade II–IV VUR
- ☞ Endoscopic treatment is viewed as preferable to open surgery by 60% of parents even for grades I–II reflux and 80% of those with grade III reflux over long-term antibiotic prophylaxis
- ☞ Presently, the endoscopic treatment of VUR by dextranomer/hyaluronic acid is increasingly viewed as first line therapy for reflux
- ☞ Parental preference for choice of therapy is honored and they should be offered information on all the three options of therapy: CAP, endoscopic injection treatment, and open/laparoscopic surgery.

SUGGESTED READINGS

1. American Academy of Pediatrics. Practice parameter: the diagnosis, treatment & evaluation of the initial urinary tract infection in febrile infants & young child. Committee on Quality Improvement Subcommittee on Urinary Tract Infection. Pediatrics. 1999;103:843-52.
2. Bajpai M, Bal CS, Kalaivani M, Gupta AK. Plasma renin activity for monitoring vesicoureteric reflux therapy: mid-term observations. J Pediatr Urol. 2008;4(1):60-4.
3. Bajpai M, Bal CS, Kumar R, Chaturvedi PK, Kalaivani M, Gupta AK. Persistent renin-angiotensin system activation after anti-reflux surgery and its management. J Pediatr Urol. 2011;7(6):616-22. doi: 10.1016/j.jpurol.2011.06.012. Epub 2011 Jul 31.
4. Bajpai M, Mitra A, Bal CS, Kumar R, Jana M. Journal of Progress in Paediatric Urology. July-September, 2014 (in press).
5. Bajpai M, Pal K, Bal CS, Gupta AK, Pandey RM. Role of plasma renin activity in the management of primary vesicoureteric reflux: a preliminary report. Kidney Int. 2003;64(5):1643-7.
6. Bajpai M, Verma A, Panda SS. Endoscopic treatment of vesico-ureteral reflux: experience of 99 ureteric moieties. J Indian Assoc Pediatr Surg. 2013;18(4):133-5. doi: 10.4103/0971-9261.121112.
7. Capozza N, Lais A, Matarazzo E, Nappo S, Patricolo M, Caione P. Treatment of vesico-ureteric reflux: a new algorithm based on parental preference. BJU Int. 2003;92(3):285-8.
8. Elder JS, Peters CA, Arant BSJ, Ewalt DH, Hawtrey CE, Hurwitz RS, et al. Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol. 1997;157:1846-51.
9. Froom J, Culpepper L, Green LA, de Melker RA, Grob P, Heeren T, et al. A cross-national study of acute otitis media: risk factors, severity and treatment at initial visit: Report from the International Primary Care Network (IPCN) and the Ambulatory Sentinel Practice Network (ASPN). J Am Board Fam Pract. 2001;14:406-17.
10. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics. 2006;117:626-32.
11. Management and screening of primary vesicoureteral reflux in children: AUA guideline (2010). Panel Members: Craig A. Peters, MD, Chair; Steven J. Skoog, MD, Vice-Chair; Billy S. Arant, Jr., MD; Hillary L. Copp, MD; Jack S. Elder, MD, Facilitator; R. Guy Hudson, MD; Antoine E. Khoury, MD; Armando J. Lorenzo, MD; Hans G. Pohl, MD; Ellen Shapiro, MD; Warren T. Snodgrass, MD.
12. Margolis DJ, Bowe WP, Hoffstad O, Berlin JA. Antibiotic treatment of acne may be associated with upper respiratory tract infection. Arch Dermatol. 2005;141:1132-6.
13. Matouschek E. Die behandlung des vesikorenalen refluxes durch transurethrale einspritzung von Teflon paste. Urologe A. 1981;20:263-4.
14. Mentzel HJ, Vogt S, Patzer L, Schubert R, John U, Misselwitz J, et al. Contrast-enhanced sonography of vesicoureterorenal reflux in children: preliminary results. AJR Am J Roentgenol. 1999;173:737-40.
15. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, et al. Prophylaxis after first febrile urinary tract infection in children? A Multicenter, Randomized, Controlled, Noninferiority Trial. Pediatrics. 2008;122:1064-71.
16. Mori R, Lakhanpaul M, Verrier-Jones K. Diagnosis and management of urinary tract infection in children: summary of NICE guidance. BMJ. 2007;335:395-7.
17. Nelson CP, Copp HL, Lai J, Saigal CS; the Urologic Diseases in America Project. Is Availability of Endoscopy Changing Initial Management of Vesicoureteral Reflux? J Urol. 2009;182:1152-7.
18. Noe HN, Wyatt RJ, Peeden JN Jr, Rivas ML. The transmission of vesicoureteral reflux from parent to child. J Urol. 1992;148:1869-71.
19. Ogan K, Pohl HG, Carlson D, Belman AB, Rushton HG. Parental preferences in the management of vesicoureteral reflux. J Urol. 2001;166:240-3.
20. Pennesi M, Travan L, Peratoner L, et al. North East Italy Prophylaxis in VUR study group. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatr. 2008;121:e1489-94.
21. Riccabona M. Management of recurrent urinary tract infection and vesicoureteral reflux in children. Curr Opin Urol. 2000;10:25-8.
22. RIVUR Trial Investigators, Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med. 2014;370(25):2367-76.
23. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol. 2008;179:674.
24. Savage DC, Howie G, Adler K, Wilson MI. Controlled trial of therapy in covert bacteriuria of childhood. Lancet. 1975;1:358-61.
25. Schwab CW Jr, Wu HY, Selman H, Smith GH, Snyder HM 3rd, Canning DA. Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. J Urol. 2002;168(6):2594-9.
26. Sencan A, Carvas F, Hekimoglu IC, Caf N, Sencan A, Chow J, et al. Urinary tract infection and vesicoureteral reflux in children with mild antenatal hydronephrosis. J Pediatr Urol. 2014;10(6):1008-13.
27. Sj str m S1, Sill n U, Bachelard M, Hansson S, Stokland E. Spontaneous resolution of high grade infantile vesicoureteral reflux. J Urol. 2004;172(2):694-8; discussion 699.
28. Smellie JM, Prescod NP, Shaw PJ, Risdon RA, Bryant TN. Childhood reflux and urinary infection: a follow-up of 1041 years in 226 adults. Pediatr Nephrol. 1998;12:727-36.
29. Suson KD, Mathews R. Evaluation of children with urinary tract infection impact of the 2011 AAP guidelines on the diagnosis of vesicoureteral reflux using a historical series. J Pediatr Urol. 2014;10(1):182-5. doi: 10.1016/j.jpurol.2013.07.025. Epub 2013 Sep 8.
30. Tanagho EA, Hutch JA, Meyers FH, Rambo ON Jr. Primary vesicoureteral reflux: experimental studies of its etiology. J Urol. 1965;93:165-76.
31. Van Batavia JP, Nees SN, Fast AM, Combs AJ, Glassberg KI. Outcomes of vesicoureteral reflux in children with non-neurogenic lower urinary tract dysfunction treated with dextranomer/hyaluronic acid copolymer (Deflux). J Pediatr Urol. 2014;10(3):482-7. doi: 10.1016/j.jpurol.2013.10.017. Epub 2013 Nov 12.
32. Verma A, Panda SS, Bajpai M. Role of endoscopic treatment of vesicoureteric reflux in downgrading renin angiotensin system activation. J Pediatr Urol. 2014;10(2):386-90. doi: 10.1016/j.jpurol.2013.10.015. Epub 2013 Nov 8.

CHAPTER 133

Intussusception

Gautam S Agarwal, Anurag Krishna

INTRODUCTION

Intussusception is an acquired invagination of the bowel into itself, usually involving both small and large bowel (Figs 1 and 2). Ileocolic intussusception is the most common cause of small bowel obstruction in children. Intussusception is an emergent condition where delay in diagnosis is not rare, and may result in bowel obstruction, venous congestion, subsequent bowel necrosis, and perforation.

INCIDENCE AND CLINCAL FEATURES

The peak age for idiopathic intussusception is 5–10 months and typically ranges up to 3 years. The most common clinical presentation is of an infant with crampy abdominal pain and irritability, vomiting, and bloody stools, although signs and symptoms vary considerably and overlap with other abdominal conditions. The clinical features of intussusception are given in table 1.

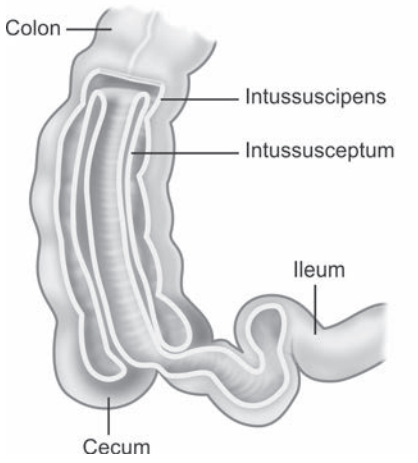


Fig. 1: Diagramatic representation of intussusception

DIAGNOSIS

Radiographs typically are ordered by the clinician to exclude other diagnoses (Fig. 3). Even in experienced hands, abdominal radiographs have poor sensitivity (45%) for the detection of intussusception but may serve to screen for other diagnoses in the differential diagnosis, such as constipation, and for free peritoneal air.

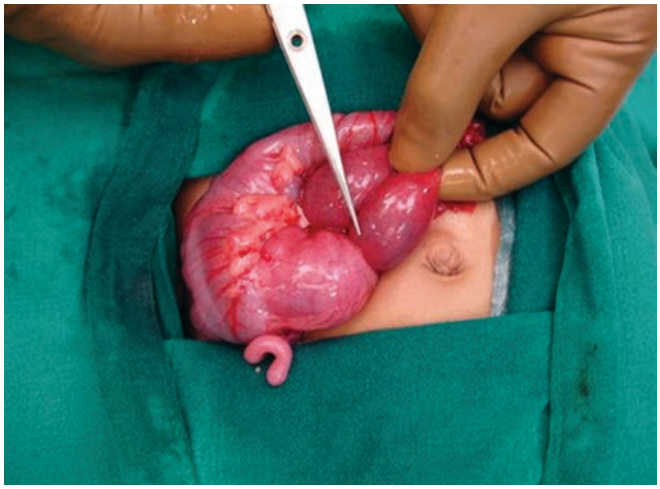


Fig. 2: Operative photograph showing the intussusception

TABLE 1: Clinical features of intussusception

Abdominal colic	65%
Lump	35–70%
Rectal bleeding	50–80%
Triad	7.5–50%
Vomiting	75–85%
Preceding respiratory/gastrointestinal symptoms	<25%

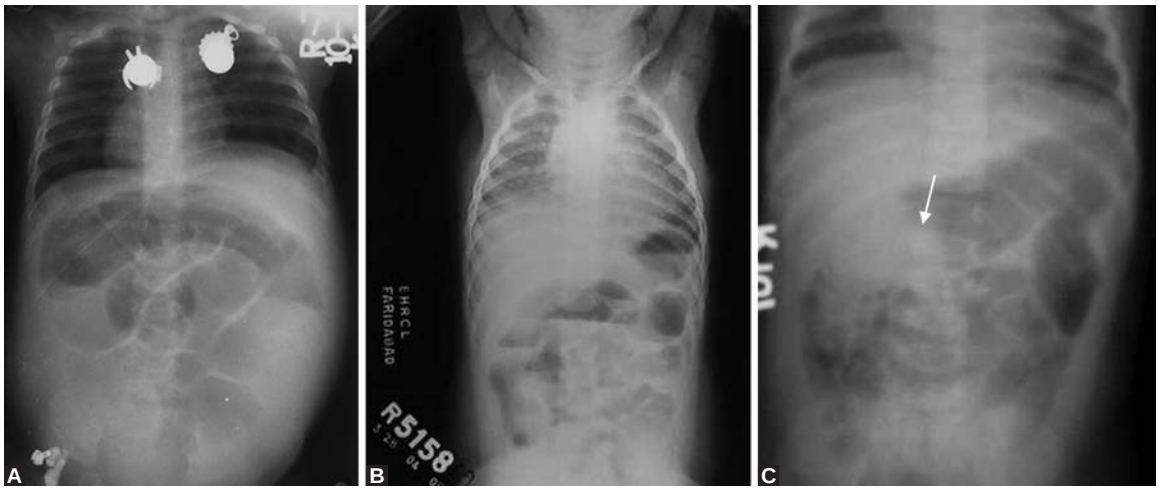


Fig. 3: X-rays of abdomen: **A,** right iliac fossa empty; **B,** signs of intestinal obstruction; **C,** soft tissue mass (arrow). Normal X-ray does not rule out intussusception

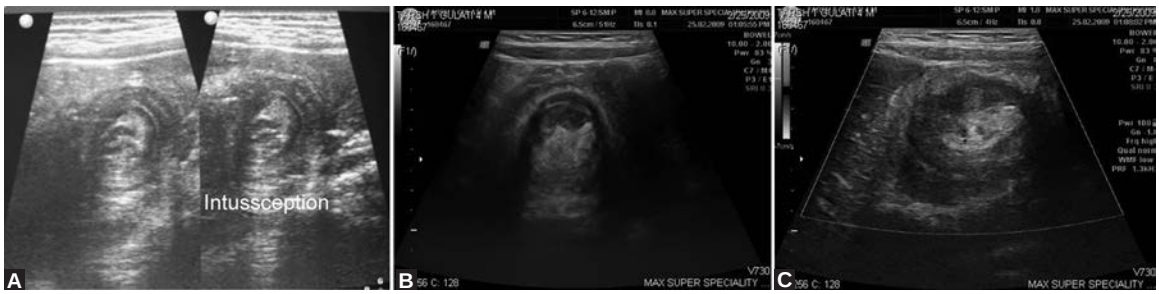


Fig. 4: Ultrasound showing whorled appearance of intussusception

The presence of a curvilinear mass within the course of the colon (the crescent sign), particularly in the transverse colon just beyond the hepatic flexure, is a nearly pathognomonic sign of intussusception.

The absence of bowel gas in the ascending colon is one of the most specific signs of intussusception on radiographs. However, small-bowel gas located in the right abdomen on radiographs may mimic ascending colon or cecal gas.

Sonography increasingly is used to diagnose either intussusception or alternative causes for a child's abdominal symptoms.

Sonography also plays a role in the evaluation of reducibility of intussusception, the presence of a lead point mass, the potential incomplete reduction after enema (vs. edema of the ileocecal valve), and of intussusception limited to small bowel.

At this point in time, there are no reliable clinical prediction models that accurately can identify all patients with intussusception. The clinical triad of colicky abdominal pain, palpable abdominal mass, and current jelly stools is present in less than 50% of cases.

There is no doubt that a computed tomography scan of the abdomen may diagnose intussusception. However, the cost, radiation dose, and risk of sedation in these young children make it far less practical than sonography. Published sonography studies from single institutions suggest high accuracy, approaching 100% in experienced hands, with a sensitivity of 98–100% and specificity of 88–100% (Fig. 4).

TREATMENT

For the treatment of intussuception, follow the following steps:

- Resuscitate first
- Nonoperative reduction contraindicated if
  - Long-standing—usually v>36–48 h
  - Gross abdominal distension
  - Hemodynamic instabillity. Intussuception

Treatment options:

- Nonsurgical perferred, except in few cases
- Surgery is absolutely indicated in
  - Shock, sepsis
  - Perforation peritonitis
  - Failed reduction
- Nonsurgical
  - "Pushing" agent
    - Air
    - Fluid—water, saline, barium
  - Imaging modality
    - Ultrasound
      - Pros: avoids radiation
      - Cons: operator dependent

- Fluoroscopy
  - Pros: Confidence
  - Cons: Radiation.

Barium is no longer the liquid contrast medium of choice for reduction of intussusception due to risk of barium peritonitis, infection, and adhesions if perforation occurs during the enema. While iodinated contrast is considered a safer agent than barium, one should be aware that it may produce fluid and electrolyte shifts if perforation occurs because contrast is absorbed from the peritoneum.

An intussusception encountered in the rectum has only a 25% reduction rate, but intussusceptions encountered elsewhere in the colon, including the hepatic flexure, can be expected to have a successful reduction rate of approximately 80%. The most common location to encounter idiopathic intussusception is at the hepatic flexure.

Before enema reduction, dehydration should be treated with intravenous fluid resuscitation. If the child is clinically unstable, he or she should not undergo enema. Children with evidence of peritonitis, shock, sepsis, or free air on abdominal radiographs are not candidates for enema. These children should be stabilized and treated surgically.

The presence of small-bowel obstruction reduces the probability of successful enema reduction but it is not a contraindication to performing the enema.

The most important factor that decreases the reduction rate of enema is the duration of symptoms. The longer the duration of symptoms beyond 24 hours, the lower the likelihood of successful contrast enema reduction. Most literature suggests a significant delay is typically 48 hours of symptoms but some reports suggest 24 or 72 hours.

Age less than 3 months is associated with both a higher perforation rate and a lower rate of successful reduction, as is dehydration and small-bowel obstruction. These situations are less common. The lethargy, as seen in this child, is not rare when they become dehydrated. It is important to correct the child's dehydration to improve the enema intussusception reduction rate.

The most important potential complication of enema is bowel perforation. The most common site is at or just proximal to the intussusception in the transverse colon. Perforations with air tend to be smaller than those with liquid enema although the overall perforation rates are similar.

The air enema is considered superior at reduction, cleaner (based on appearance of peritoneal cavity at surgery when perforation occurs), safer, and faster with less radiation when compared with liquid enema. In a summary of the literature, there were 32 studies using air reduction and 39 using liquid (barium, iodinated contrast, saline, or water) reduction techniques. Air enema studies had significantly higher mean reduction rates compared with liquid enema studies (82% vs. 68%).

The air enema technique is well described in the literature. Briefly, the enema tip should be placed within the child's rectum and taped in place with abundant tape. The child is placed in a prone position to allow the radiologist or assistant to squeeze the buttocks closed and prevent air from leaking. Air is rapidly insufflated into the colon under fluoroscopic observation.

Once the intussusception is encountered, its reduction is followed fluoroscopically until it is completely reduced. Air should flow freely from the cecum into the distal small bowel loops to signify complete reduction. One critical safety issue is to keep air pressure below a maximum limit of 120 mmHg to avoid the risk of perforation.

There is no direct evidence supporting the commonly taught "rule of threes" regarding the liquid enema technique, particularly the appropriate height of the enema bag.

The superior air enema reduction rate may be due to the presence of higher intraluminal pressure for air compared with standard hydrostatic reduction.

In case of failure of reduction and above mentioned absolute indications, sometimes an operative reduction is required. At laparotomy, the mass is delivered and gentle manual reduction is done. The key to reduction is slow, constant milking and squeezing in a retrograde manner.The intussusceptum is pushed rather than pulled. Infrequently when the maneuver fails, or if the bowel is gangrenous, resection of the intestine with end-to-end anastomosis may be required.

RECURRENCE

Fifty percent of children who develop recurrent intussusception will present within 48 hours, although recurrences have been reported up to 18 months later. If the clinical concern is for recurrent intussusception, there is little added information gained by abdominal radiography. Radiographs may show alternative diagnoses or obstruction but if the clinical concern is for recurrent intussusception, sonography is the most reliable test.

There is no question that sonography to screen for intussusception is a valid imaging test. However, in this situation, the pretest probability is high for the diagnosis of intussusception and, therefore, enema would be the reasonable next step. Repeat enema is both safe and effective in recurrent intussusception, as long as the child remains clinically stable. If the patient is not clinically stable, or has signs of peritonitis, then the patient should undergo surgical reduction.

Intussusception recurrence rates average 10% in large series, with a range of 5.4–15.4%, regardless of air versus liquid enema technique. The recurrence rates are less than or equal to 5% when surgical reduction is performed, presumably due to the development of adhesions.

The risk of a pathologic lead point (Fig. 5) in children with recurrent intussusception is low. No predictive clinical factors have been identified for pathologic lead point in these children with recurrent intussusception. No clear risk factors are known for why some children have recurrences although some do have a focal pathologic lead point. Those with diffuse bowel abnormalities (diffuse pathologic lead points) and ileocolic intussusception, such as children with cystic fibrosis, Henoch-Schönlein purpura, or celiac disease, may be treated with enema reduction more aggressively than those with focal pathologic lead points to avoid surgery. Repeat enema is both

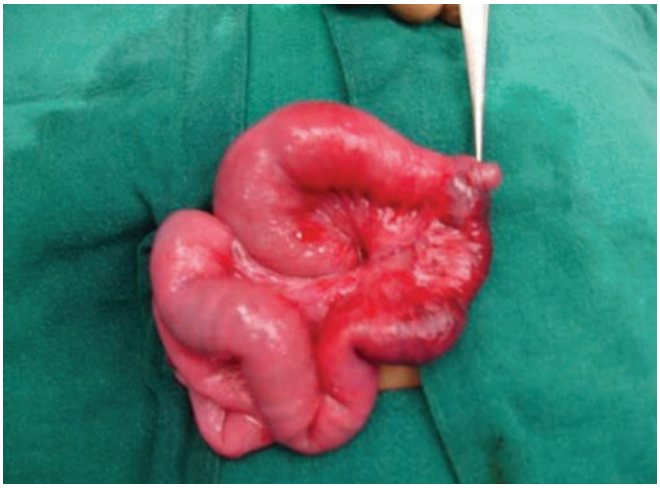
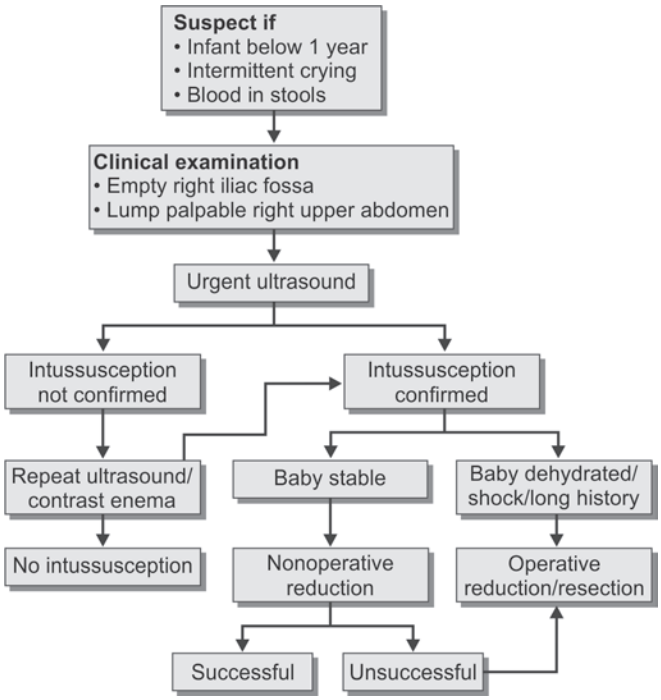


Fig. 5: Operative photograph showing a small Meckel's diverticulum as the lead point

ALGORITHM 1

Algorithm for management of intussusception



safe and effective in recurrent intussusception as long as the child remains clinically stable.

Some articles have reported associations between intussusception and viral infection, particularly adenovirus, although the lack of seasonality suggests more than one pathogen. Approximately 5–6% of intussusceptions in children are caused by pathologic lead points that are due to either focal masses or diffuse bowel wall abnormality. The most common focal pathologic lead points are (in decreasing order of incidence) Meckel's diverticulum, duplication cyst, polyp, and lymphoma.

Problems:

- Delayed presentation (meain 48 h)
  - Rectal bleeding, vomiting, dehydration
- Abdominal distension
  - Difficulty in feeling lump
  - Difficulty in using ultrasound for dx/dt
- Will a radiologist come at night?

KEY POINTS

- ☞ High index of suspicion
- ☞ Rapid initial resuscitation
- ☞ Attempt "safe" and "sure" reduction
- ☞ Operate if doubtful.

SUGGESTED READINGS

1. Beasley SW, Glover J. Intussusception: prediction of outcome of gas enema. J Pediatr Surgery. 1992;27:474-5.
2. Bratton SL, Haberkern CM, Waldhausen JH, Sawin RS, Allison JW. Intussusception: hospital size and risk of surgery. Pediatrics. 2001;107:299-303.
3. Daneman A, Alton DJ, Ein S, Wesson D, Superina R, Thorner P. Perforation during attempted intussusception reduction in children: a comparison of perforation with barium and air. Pediatr Radiol. 1995;25:81-8.
4. Daneman A, Navarro O. Intussusception part 1: a review of diagnostic approaches. Pediatr Radiol. 2003;33:79-85.
5. Daneman A, Navarro O. Intussusception part 2: an update on the evolution of management. Pediatr Radiol. 2004;34:97-108.
6. Del-Pozo G, Gonzalez-Spinola J, Gomez-Anson B, Serrano C, Miralles M, Gonz lez-deOrbe G, et al. Intussusception: trapped peritoneal fluid detected with US: relationship to reducibility and ischemia. Radiology. 1996;201:379-83.
7. Ein SH. Leading points in childhood intussusception. J Pediatr Surgery. 1976;11:209-11.
8. Ein SH. Recurrent intussusception in children. J Pediatr Surgery. 1975;10:751-5.
9. Gu L, Alton D, Daneman A, Stringer DA, Liu P, Wilmot DM, et al. John Caffey award. Intussusception reduction in children by rectal insufflation of air. AJR. 1988;150:1345-8.
10. Guo JZ, Ma XY, Zhou QH. Results of air pressure enema reduction of intussusception: 6396 cases in 13 years. J Pediatr Surgery. 1986;21:1201-3.
11. Hernanz-Schulman M, Foster C, Maxa R, Battles G, Dutt P, Stratton C, et al. Experimental study of mortality and morbidity of contrast media and standardized fecal dose in the peritoneal cavity. Pediatr Radiol. 2000; 30:369-78.
12. Katz M, Phelan E, Carlin JB, Beasley SW. Gas enema for the reduction of intussusception: relationship between clinical signs and symptoms and outcome. AJR. 1993;160:363-6.
13. Kirks DR. Diagnosis and treatment of pediatric intussusception: how far should we push our radiologic techniques? Radiology. 1994;191:622-3.
14. Mercer S, Carpenter B. Mechanism of perforation occurring in the intussuscipiens during hydrostatic reduction of intussusception. Can J Surgery. 1982;25:481-3.
15. Navarro O, Daneman A. Intussusception part 3: diagnosis and management of those with an identifiable or predisposing cause and those that reduce spontaneously. Pediatr Radiol. 2004;34:305-12.
16. Parashar UD, Holman RC, Cummings KC, Staggs NW, Curns AT, Zimmerman CM, et al. Trends in intussusception-associated hospitalizations and deaths among US infants. Pediatrics. 2000;106:1413-21.
17. Shiels WE II, Kirks DR, Keller GL, Ryckman FR, Daugherty CC, Specker BL, et al. John Caffey award. Colonic perforation by air and liquid enemas: comparison study in young pigs. AJR. 1993;160:931-5.
18. Shiels WE II, Maves CK, Hedlund GL, Kirks DR. Air enema for diagnosis and reduction of intussusception: clinical experience and pressure correlates. Radiology. 1991;181:169-72.
19. Stringer MD, Pablot SM, Brereton RJ. Paediatric intussusception. BR J Surg. 1992;79:867-76.
20. West KW, Stephens B, Vane DW, Grosfeld JL. Intussusception: current management in infants and children. Surgery. 1987;102:704-10.

CHAPTER 134

Neonatal Jaundice: Surgical Perspective

Nidhi Sugandhi, Veereshwar Bhatnagar

INTRODUCTION

Jaundice in a neonate can have varied connotations. Its spectrum ranges from physiological jaundice on one hand to obstructive jaundice requiring urgent surgical correction on the other hand.

Structural anomalies in the biliary tract causing direct hyperbilirubinemia due to obstruction to bile outflow are amenable to surgical correction. Box 1 lists the structural anomalies presenting with neonatal hyperbilirubinemia. These anomalies may be intrahepatic or extrahepatic; of these, extrahepatic biliary atresia (EHBA) is the most common. While extrahepatic obstructions have high likelihood to be surgically correctable, others with diffuse intrahepatic structural anomalies, such as Caroli's disease and Alagille syndrome may be cured only with radical surgery like segmental hepatectomy or liver transplantation.

Though they constitute only 0.2–0.4% of total cases of neonatal hyperbilirubinemia, the urgency to diagnose and treat the surgical causes of neonatal jaundice stems from two facts: (i) most of the surgical causes of neonatal jaundice are correctable if operated upon early and (ii) if left untreated they progress rapidly to cause irreversible liver damage, cirrhosis, portal hypertension, liver failure, and eventually death. Thus it is important to diagnose the group of jaundiced neonates likely to have surgically correctable causes of jaundice and initiate appropriate treatment.

Box 1: Causes of neonatal surgical jaundice

- Extrahepatic biliary atresia
- Choledochal cyst:
  - Caroli's disease
- Inspissated bile syndrome
- Gallstones or biliary sludge
- Biliary hypoplasia and Alagille syndrome
- Neonatal sclerosing cholangitis

PHYSIOLOGICAL VERSUS PATHOLOGICAL JAUNDICE

Confusion with the physiological jaundice normally present in the early neonatal period can lead to delay in identification of neonates requiring further investigations and treatment. Specific parameters indicate pathological jaundice. These are enumerated in table 1.

A noteworthy point is that even minimal rise of direct or conjugated bilirubin is pathological and needs to be investigated. Thus the most important initial test is measurement of the serum conjugated bilirubin concentration to establish the presence of cholestasis.

Cholestatic jaundice or direct hyperbilirubinemia is the hallmark of surgically correctable biliary tract anomalies. However, it is also a component of mixed hyperbilirubinemia in another group of disorders with intrahepatic cholestasis including idiopathic neonatal hepatitis (INH). Box 2 lists the causes of direct hyperbilirubinemia including the structural anomalies and causes of neonatal cholestasis. Thus, once cholestatic liver disease has been established, the next challenge is to differentiate the structural anomalies from INH which can be treated medically in most cases. The clinical features and investigations needed to differentiate between the two groups of disorders are discussed in subsequent sections.

TABLE 1: Indicators of pathological jaundice

Onset	<24 h
Rate of progression	>0.5 mg/dL/h or >5 mg/dL/24 h
Total bilirubin	>15 mg/dL
Direct bilirubin	>2 mg/dL or >20% total bilirubin
Duration	Any jaundice lasting beyond 3 weeks
Associated symptoms	Clay colored stools/dark colored urine/ sepsis/poor feeding

Box 2: Causes of conjugated hyperbilirubinemia cholestasis

Obstructive cholestasis

- Biliary atresia
- Choledochal cysts
- Bile duct paucity
- Inspissated bile syndrome
- Gallstones/biliary sludge
- Caroli disease
- Neonatal sclerosing cholangitis

Intrahepatic cholestasis and neonatal hepatitis

- Viral infection:
  - Herpes simplex
  - Cytomegalovirus
  - Human immunodeficiency virus
  - Parvovirus B19
  - Other
- Bacterial infection:
  - Sepsis
  - Urinary tract infection
  - Syphilis
- Genetic/metabolic disorders:
  - Alpha1-antitrypsin deficiency
  - Tyrosinemia
  - Galactosemia
  - Progressive familial intrahepatic cholestasis
  - Alagille syndrome
  - Other
- Endocrine disorders:
  - Hypothyroidism
  - Hypopituitarism
- Toxic:
  - Drugs
  - Parenteral nutrition
- Systemic:
  - Shock
  - Heart failure
  - Neonatal lupus
- Neonatal cholestasis
- Obstructive cholestasis

CLINICAL FEATURES

Surgical jaundice is not evident immediately after birth and appears after 5–7 days. Usually, it merges with the physiological jaundice and is suspected due to unusual prolongation of the physiological jaundice. Sometimes, it may also appear 2–3 weeks after birth, subsequent to clearing of the physiological jaundice. Typically, the first stools of the neonate are normal and cholic. Differentiating features need to be looked for. Characteristically, history of clay colored stools and dark colored urine indicates direct hyperbilirubinemia. It should be noted that intermittent passage of cholic stools, though more frequent in intrahepatic cholestasis, does not rule out extrahepatic obstruction. Children are initially active with normal growth during the first few weeks. Neonatal choledochal cyst can closely resemble EHBA clinically with a fulminant course including pancreatitis and cholangitis in contrast to intermittent symptoms as seen in older children. The classic triad of pain, mass, and jaundice is typically not seen.

Infants whose cholestasis is caused by bacterial sepsis, hypopituitarism, or metabolic disorders such as galactosemia may be acutely ill. Infants who have metabolic liver disease may have poor feeding, inadequate weight gain, hypoglycemia, and hypotonia. Hepatitis due to TORCH (Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, HErpes simplex, and Syphilis) agents may be associated with dysmorphic facies, microcephaly, and low birth weight, prematurity, and other congenital anomalies.

Physical examination reveals firm to hard hepatomegaly. Late stages may reveal cirrhotic liver and splenomegaly indicating development of portal hypertension. Signs of liver failure appear later and include ascites, spider nevi and coagulopathy.

However, no details in the history or physical examination are capable of differentiating all infants with neonatal hepatitis from those who have biliary atresia. Many infants who have intrahepatic cholestasis (10–15%) have cholestasis so severe that they mimic biliary obstruction.

EVALUATION OF THE CHOLESTATIC NEONATE

Pathological jaundice with conjugated bilirubin fraction above 20% establishes the diagnosis of cholestasis. Further investigations are aimed at differentiating between neonatal hepatitis and extrahepatic obstruction and assessing the severity of liver derangement.

Initial Investigations

Conventional serologic liver function tests are often nonspecific but discrimination between extrahepatic ductal disease and neonatal hepatitis is sometimes possible. Hyperbilirubinemia secondary to neonatal hepatitis is characterized by elevation of both the direct and indirect component whereas rise in indirect bilirubin in extrahepatic obstruction is a late event after the onset of liver failure. Similarly, synthetic function of the liver as assessed by coagulation profile and serum proteins is impaired only in later stages in extrahepatic obstruction. Gamma-glutamyl transferase may be elevated in both the conditions but is usually higher in extrahepatic obstruction. Box 3 enumerates the basic serologic tests for patients suspected with jaundice due to a surgical cause.

Specific Investigations

A battery of tests is required to establish the presence and cause of extrahepatic obstruction. Despite these the definitive

Box 3: Initial investigations in neonatal direct hyperbilirubinemia

- Fractionated serum bilirubin concentration
- Liver enzymes:
  - Alanine aminotransferase
  - Aspartate aminotransferase
  - Alkaline phosphatase
  - Gamma-glutamyl transferase
- Tests of liver function:
  - Blood glucose
  - Serum albumin
  - Coagulation studies (prothrombin time, partial thromboplastin time, coagulation factor levels)
- Complete blood count
- Urinary bilirubin and urobilinogen levels
- Bacterial cultures of blood, urine, others as indicated

diagnosis may be established only on the operating table with the help of intraoperative cholangiogram (IOC).

Ultrasonography

A quick, noninvasive, and cheap initial investigation, an ultrasonography is very useful to indicate extrahepatic obstructive lesions. It can definitively diagnose or rule out choledochal cyst which is visible as a cystic subhepatic mass. Gall bladder stone and biliary sludge are also easily visible. Certain features, viz., absence of gall bladder or a gall bladder less than 1.5 cm in size with no contractility in response to feeding, triangular cord sign due to hyperechoic portal plate, and fibrous cord remnant raise suspicion of EHBA. In particular, the triangular cord sign has 100% specificity but only 73% sensitivity to diagnose EHBA. Preduodenal portal vein, asplenia, or polysplenia are further supportive of a diagnosis of EHBA. Dilated proximal biliary radicles rule out EHBA and favor inspissated bile duct syndrome. However, this is an operator dependent investigation and can, therefore, only guide further investigations rather than definitively diagnose all extrahepatic obstructions.

Tc99m-hepatobiliary Iminodiacetic Acid Scintigraphy

Failure to excrete this technetium labeled isotope into the duodenum even after 24 hours is diagnostic of EHBA. Infants who have biliary atresia do not excrete isotope into the gut, making the test 100% sensitive for this disorder. Unfortunately, specificity is not satisfactory as severe neonatal hepatitis cases may also not excrete the isotope. Pretreatment with phenobarbitone (5 mg/kg/day) for 3–5 days preceding imaging enhances excretion and increases discrimination between EHBA and neonatal hepatitis, and therefore, should always be followed.

Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) is being increasingly used to evaluate extrahepatic obstruction and in one small series has shown 100% diagnostic accuracy in the evaluation of biliary atresia (Figs 1 and 2). However, further evaluation is required in larger series before establishing its role in diagnostic evaluation. The usefulness is also limited due to high cost and difficulty in performing this investigation in neonates.

Liver Biopsy

Liver biopsy was earlier considered a definitive investigation for differentiating neonatal hepatitis and biliary obstruction. However, characteristics thought to suggest EHBA (including bile ductular proliferation, bile plugs in small bile ducts, portal tract fibrosis and edema, swelling, vacuolization, sloughing of biliary epithelium, inflammatory cell infiltration, and giant cell transformation) may also be present in advanced stages of severe neonatal hepatitis. Moreover it is an invasive investigation and may require some time for analysis. In approximately one-third of the specimens, the histological findings are not clear-cut, so further evaluation becomes necessary. A combination of open biopsy (with a guaranteed adequacy of size of specimen) and operative cholangiography is recommended as the ideal approach to the obstructed child.

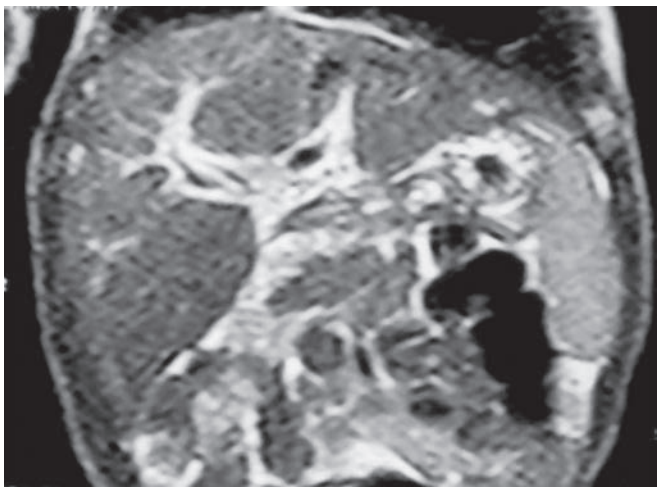


Fig. 1: Magnetic resonance cholangiopancreatography in a patient with extrahepatic biliary atresia demonstrating absence of gall bladder and intrahepatic ducts

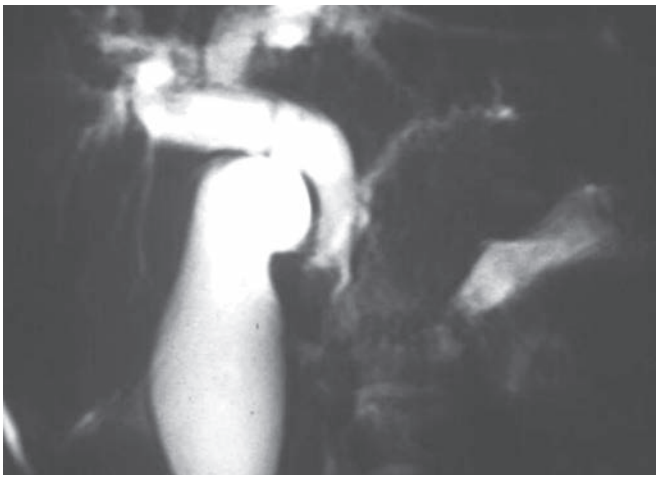


Fig. 2: Magnetic resonance cholangiopancreatography showing a cystic dilatation of the common bile duct suggestive of choledochal cyst

Intraoperative Cholangiogram

The gold standard for the diagnosis of EHBA with highest sensitivity and specificity and widely employed as an effective practical tool is operative cholangiography. The liver and extrahepatic biliary atresia ducts are inspected by a minilaparotomy incision and, if present, gall bladder is cannulated and injected with radiopaque dye (Fig. 3). Failure of the dye to reach the duodenum and/or nonopacification of the proximal biliary ducts, confirm the diagnosis of EHBA (Fig. 4). Additionally, flushing of bile ducts may prove to be therapeutic in cases of inspissated bile ducts and some cases of neonatal hepatitis with secondary bile duct obstruction. Liver biopsy can be taken at the same time. Details of intrahepatic ductal anatomy are also clearly seen with an IOC (Fig. 5).

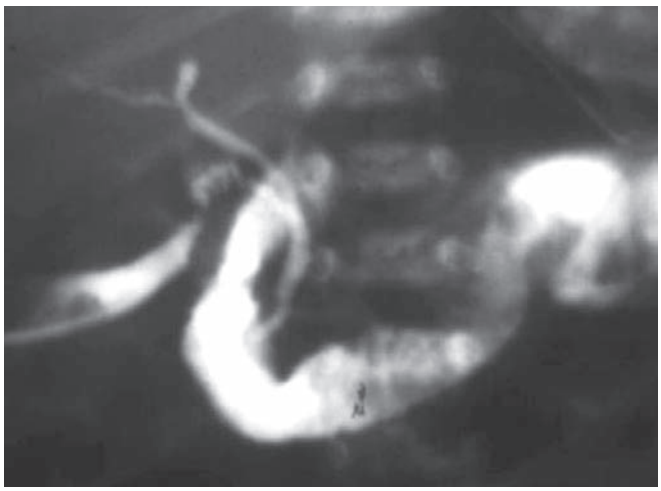


Fig. 3: Intraoperative cholangiogram demonstrating normal opacification of proximal and distal bile ducts and dye entering the duodenum

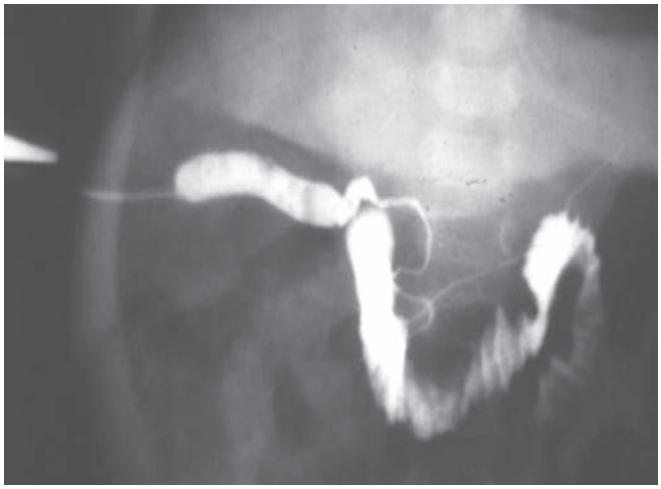


Fig. 4: No opacification of the proximal bile ducts on intraoperative cholangiogram suggestive of extrahepatic biliary atresia

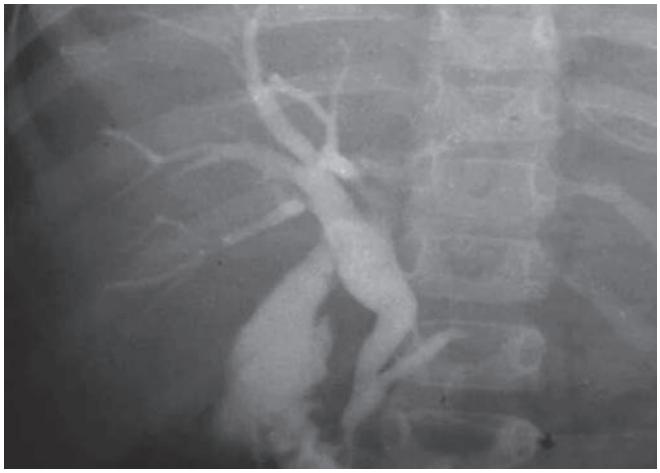


Fig. 5: Intraoperative cholangiogram showing a fusiform dilatation along the course of common bile duct and common hepatic duct suggesting a choledochal cyst. The intrahepatic ductal anatomy and the pancreatico-choledocal junction are also visualized

Box 4: Additional tests for neonatal hepatitis/cholestasis

- Serum α1-antitrypsin level and phenotype
- Serologies and cultures for viruses (TORCH agents, parvovirus B19, human herpes virus type 6, human immunodeficiency virus, others)
- Sweat chloride analysis for cystic fibrosis
- Metabolic screen (urine and serum, amino and organic acids)
- Endocrine studies (thyroxine, thyroid-stimulating hormone, evaluation for hypopituitarism as indicated)
- Specific enzyme assays on liver tissue, fibroblasts, others such as red blood cells (e.g., red cell galactose-1-phosphate uridylyltransferase activity)
- Genetic testing as indicated:
  - Cystic fibrosis
  - Alagille syndrome
  - Three forms of progressive familial intrahepatic cholestasis

Additional Tests

Additional serological tests may be done simultaneously with above investigations to negate the possibility of neonatal hepatitis. It is important to perform the above mentioned investigations like ultrasound and cholangiography simultaneously along with the following serological tests rather than wait for the results of serological tests as timing of intervention in cases of extrahepatic obstruction is of utmost importance in determining the long-term prognosis. The serological tests for neonatal hepatitis are listed in box 4.

MANAGEMENT (ALGORITHM 1)

Direct hyperbilirubinemia with non-excretion of radionuclide in Tc99m-hepatobiliary iminodiacetic acid (HIDA) scans even after 24 hours mandate a minilaparotomy with cholangiography and liver biopsy. It cannot be emphasized enough that the surgery should never be delayed to wait for results of the serological tests. The timing of the surgery to restore the bile flow is crucial. Best immediate and long-term results are obtained when surgery is performed at less than 60 days of age. Delay leads to proportionally more liver damage and poorer outcome. Studies have demonstrated 10-year survival rate of patients undergoing surgery before 60 days to be 68–80% compared to 15% survival in those undergoing surgery after 90 days.

The infant should be stabilized preoperatively with special attention to correction of any coagulopathy and antibiotics to prevent or treat cholangitis.

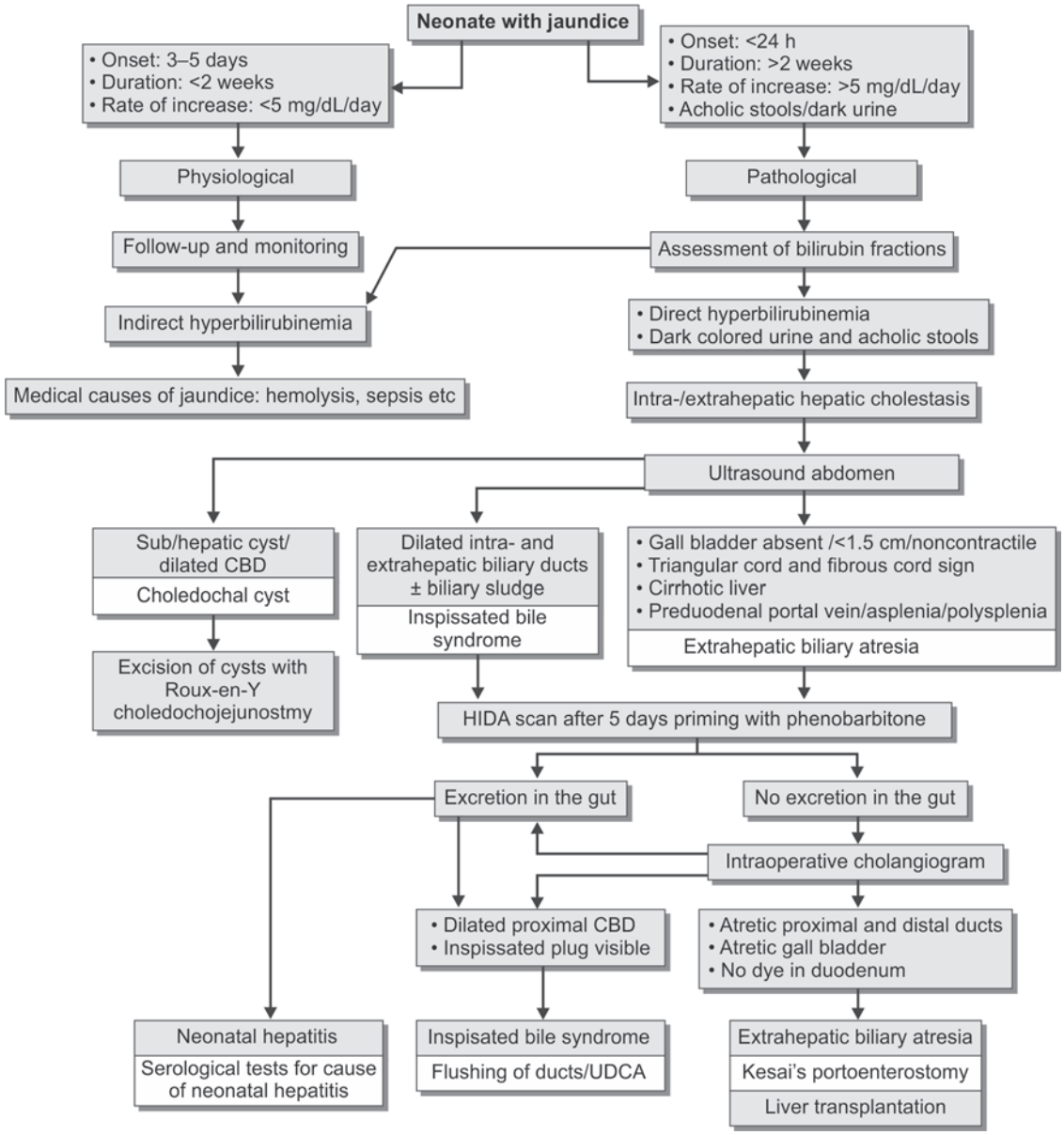
Infants with preoperative diagnosis of choledochal cyst undergo a straightforward excision of cyst with Roux-en-Y hepaticojejunostomy. For others, findings on IOC determine the further procedure.

Nonexcretion or minimal excretion of dye with proximal dilatation of biliary radicles indicate inspissated bile syndrome which responds to thorough flushing of the ducts. Clearing of the ducts may be confirmed by repeating the IOC at the end of the procedure.

Absence of gall bladder with atretic common bile duct, nonexcretion of dye with no proximal visible biliary radicles along with a firm or hard, cirrhotic enlarged liver confirms

ALGORITHM 1

Management of neonate with jaundice



CBD, common bile duct; HIDA, Tc99m-hepatobiliary iminodiacetic acid; UDCA, ursodeoxycholic acid.

the diagnosis of EHBA and the surgeon proceeds with Kasai portoenterostomy (KPE). This entails resecting the fibrous tissue at the area of porta hepatis, with subsequent apposition of a Roux-en-Y loop of intestine to act as a conduit for biliary drainage. The resection at the area of the porta hepatis is believed to expose small but patent bile ducts that can directly drain into the jejunal loop and restore the bile flow.

COMPLICATIONS

Cholangitis is the most common and serious complication with an incidence of 33–60%. It is more common in the first few years after surgery and contributes to progressive liver dysfunction and cirrhosis, thus being responsible for delayed failure of KPE. The incidence can be reduced with a longer Roux loop (>50–70 cm), construction of an intussuscepted valve at the jejunojejunostomy site, postoperative prophylactic antibiotics [recommended trimethoprim (4 mg/kg/day)—sulfamethoxazole (20 mg/kg/day or neomycin 25 mg/kg/day)] and use of oral steroids [prednisone (2 mg/kg/day)] for at least 3 months postsurgery.

Poor weight gain and malnutrition with poor absorption of fat soluble vitamins may persist even after surgery. Portal hypertension may progressively worsen due to initial liver

damage and can cause life threatening variceal bleeding and hypersplenism.

POSTOPERATIVE MANAGEMENT

Prophylactic antibiotics and steroids are continued for 3 months after surgery to prevent cholangitis. Steroids are known to have additional anti-inflammatory and immunosuppressive effects, thus decreasing edema, collagen deposition, and scarring. They are also thought to have choleretic effect by stimulation of Na^+/K^+-ATPase.

Ursodeoxycholic acid is administered for its choleretic effect and is specially indicated after flushing in inspissated bile syndrome. Additionally, Vitamin A, D, E, and K supplements are recommended to prevent malnutrition. Box 5 surmises post-KPE treatment.

OUTCOME

If the Kasai operation succeeds in restoring bile flow, the evolution of biliary cirrhosis is prevented or at least delayed; 10-year survival rate for patients who have their native livers is approximately 30% in reports from multiple centers. As a general observation, out of all the infants diagnosed with EHBA undergoing KPE, in one-third bile flow is never restored despite anatomically patent hepaticojejunostomy, possibly due to irreversibly fibrosed biliary ductules at the porta hepatis. Two-thirds achieve bile flow after KPE; half of these (30–35% of total) will have sustained bile flow and remain free of long-term sequelae. However, in the other half of those achieving initial bile drainage (35% of total), progressive liver insufficiency insidiously develops with return of jaundice, cirrhosis, and portal hypertension. Thus, despite initial palliation, these children eventually require liver transplantation. Factors influencing prognosis are the patient's age at the time of surgery, extension of liver fibrosis at surgery, degree of intrahepatic bile duct injury, number of episodes of ascending cholangitis, the surgeon's expertise, and the site of bile duct obstruction.

LIVER TRANSPLANTATION

Extrahepatic biliary atresia accounts for nearly half of all pediatric liver transplants. It is considered for patients in whom there is delayed presentation with established liver failure, bile outflow cannot be established even after KPE, or there is progressive decrease in biliary outflow and worsening of the liver damage with uncontrollable sequelae. Primary transplant instead of KPE has been suggested as an alternative but not recommended. Apart from shortage of donor organs, KPE restores bile flow in at least one-third of the patients and delays the onset of end stage liver disease in another third. Thus liver transplantation is an important but only a salvage procedure in the management of EHBA.

Box 5: Postoperative medical treatment in extrahepatic biliary atresia

- Ursodeoxycholic acid: 10–15 mg/kg/day
- Trimethoprim (4 mg/kg/day): sulfamethoxazole (20 mg/kg/day) or neomycin (25 mg/kg/day)
- Vitamin A, D, E, and K drops
- Prednisone (2 mg/kg/day)

CONCLUSION

Conjugated hyperbilirubinemia in a neonate presents a surgical challenge and indicates intrahepatic or extrahepatic bile flow obstruction. EHBA, choledochal cysts, biliary sludge/gall stones, and inspissated bile are the common causes of surgically correctable neonatal jaundice, of which EHBA is the most common. USG, HIDA, and IOC should be undertaken early in the workup of direct hyperbilirubinemia to differentiate surgically correctable lesions from neonatal hepatitis. Surgical correction should be done by the age of 2 months for best outcomes. The pediatrician has an important role in identification and early referral of infants with surgically correctable causes of neonatal jaundice.

KEY POINTS

- ☞ Direct hyperbilirubinemia is always pathological
- ☞ Intrahepatic or extrahepatic cholestasis causes direct hyperbilirubinemia
- ☞ Extrahepatic cholestasis is amenable to surgical correction
- ☞ Jaundice due to extrahepatic obstruction appears 5–7 days postnatally and may be waxing and waning
- ☞ Infants with extrahepatic obstruction are better preserved than those with neonatal hepatitis
- ☞ Intraoperative cholangiogram is the gold standard for diagnosing extrahepatic biliary obstruction
- ☞ A non-excretory Tc99m-hepatobiliary iminodiacetic acid scan with suggestive ultrasonography mandate an intraoperative cholangiogram.

SUGGESTED READINGS

1. Davenport M, Betalli P, D'Antiga L, Cheeseman P, Mieli-Vergani G, Howard ER. The spectrum of surgical jaundice in infancy. Pediatr Surg. 2003;38(10):1471-9.
2. Grosfeld JL, O'Neill JA, Coran AG, Fonkalsrud EW. Pediatric surgery. 6th ed. Mosby Elsevier; 2006.
3. Edward R Howard ER, Mark D Stringer MD, Paul M Colombani PM. Surgery of the liver, bile ducts and pancreas in children. 2nd ed. Arnold Publishers;2002.
4. Kliegman RM, Stanton BMD, St. Geme J, Schor N, Behrman RE. Nelson's textbook of pediatrics. 19th ed. Elsevier; 2011.
5. Moyer V, Freese DK, Whitington PF, Olson AD, Brewer F, Colletti RB, et al.; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2004;39(2):115-28.
6. Sherlock S, Dooley J. Diseases of the liver and biliary system. 11th ed. Blackwell Publishing; 2008..
7. Suchy JF. Neonatal cholestasis. Pediatr Rev. 2004;25:388-95.
8. Wani BN, Jajoo SN. Obstructive jaundice in neonates. Trop Gastroenterol. 2009;30(4):195-200.

CHAPTER 135

Atopic Dermatitis

Vibhu Mendiratta, Nikita, Sarita Sanke

INTRODUCTION

Atopic eczema is a chronic relapsing pruritic, non-contagious endogenous eczema. It begins in infancy and continues up to adulthood. It occurs in individuals who have atopic tendency. These individuals may develop any or all of the three closely linked conditions: atopic eczema, asthma, or allergic rhinitis. The hallmark of the disease is pruritic dermatitis that localizes in different areas depending on age. It is a familial and chronic disease and its symptoms can increase or disappear over time.

EPIDEMIOLOGY

Atopic dermatitis (AD) most often begins in childhood before age 5 and may persist into adulthood. For some, it flares periodically and then subsides for a time, even up to several years. Atopic dermatitis can affect almost 20% of children. It affects between 1 and 3% of adults. It is estimated that 75% of the cases of AD improve by the time children reach adolescence, whereas 25% continue to have difficulties with the condition through adulthood. The prevalence of AD is however quite difficult to establish since the diagnostic criteria are not applied universally and are not standard, but it is thought to vary roughly between 10 and 30%.

ETIOLOGY

Four main factors interact closely in the etiology and pathogenesis of this condition:

- Genetic predisposition
- Impaired immunity
- Epidermal barrier dysfunction
- Environmental factors.

APPROACH TO THE PATIENT (ALGORITHM 1)

Atopic dermatitis looks different in infants, children, and adults.

In infants, an erythematous oozy rash may develop by 2 or 3 months of age. It develops suddenly, predominantly affecting the scalp and face, especially on the cheeks. The extensors of the limbs like elbows, knees, and ankles are more commonly involved. It is intensely itchy and interferes with the sleep of the child. The skin of the child in general is dry and xerotic. The diaper area being constantly moist is never involved in AD. Atopic dermatitis has to be differentiated from seborrheic dermatitis (SD) where in there are greasy scales over scalp (cradle cap), and face mostly over eyebrows, nasolabial folds, retroauricular grooves and neck. Diaper area is classically involved unlike in AD. The rash in SD is nonpruritic, and the infants are totally undisturbed by it. Hair loss is rare in SD, but common in AD probably due to itching and rubbing.

Clinical Pearls

- Pruritic exudative plaques over face and scalp: suspect atopic dermatitis
- Diaper area is never involved in atopic dermatitis.

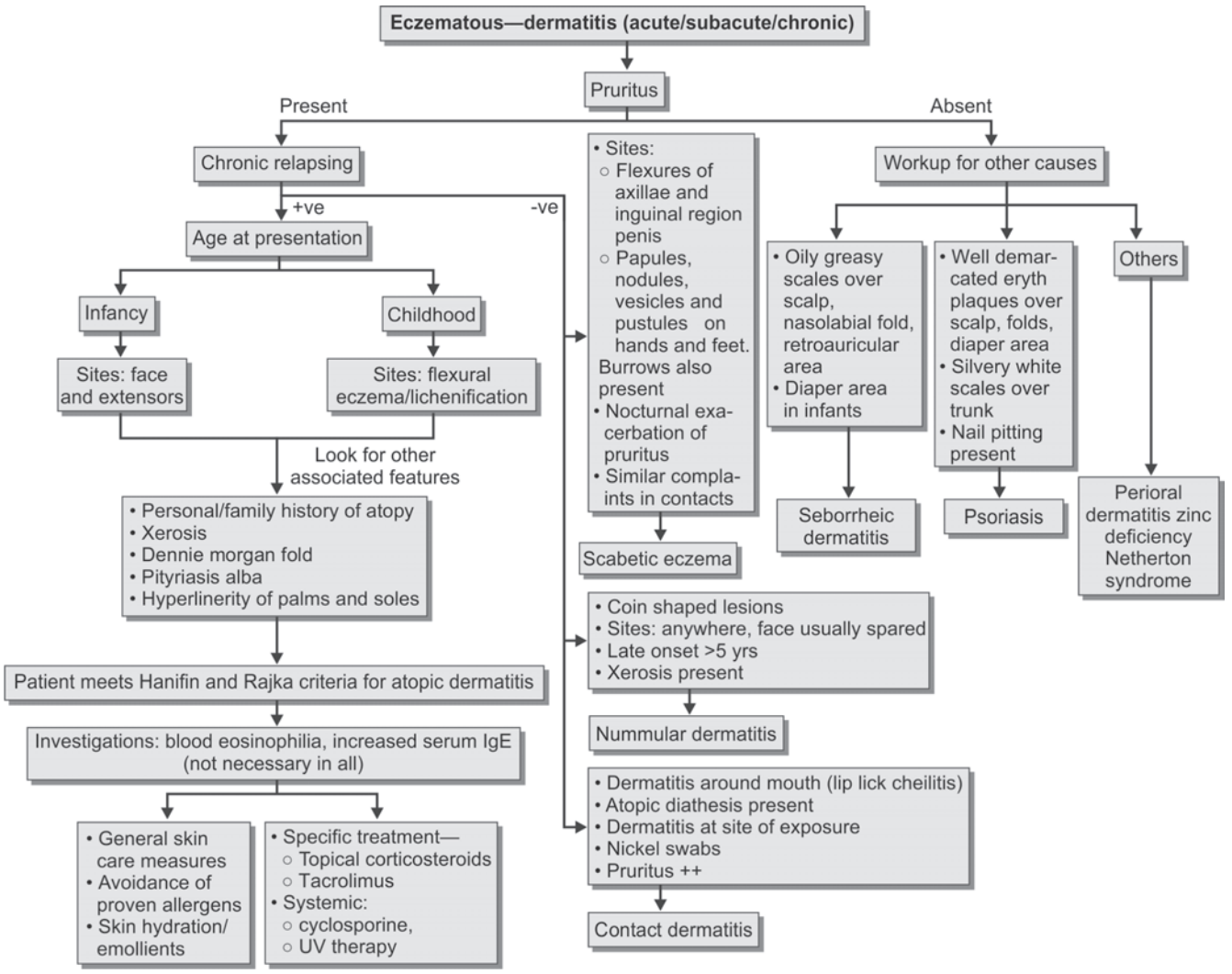
Psoriasis in infants is not uncommon and is often mistaken with AD. It often affects the scalp, folds and diaper area. Lesions over trunk (if present) are well demarcated erythematous plaques surmounted by a thin white scale.

Atopic dermatitis in children beyond 2 years of age involves the flexures like the cubital fossa, popliteal fossa, neck, groins, wrists, and ankles. The involved skin is erythematous and oozy, at places lichenification develops due to constant itching. Scabietic eczema should be ruled out where in lesions of varied morphology like papules, pustules and nodules along with burrows can be seen especially over hands and feet with relative sparing of face. History of nocturnal itching can be elicited in family members.

Flexural erythematous rash along with dry xerotic skin elsewhere is seen in Netherton syndrome, which makes it essential to differentiate it from AD. Here, examination

ALGORITHM 1

Approach to a patient with eczematous dermatitis



of the hair will reveal trichorrhexis invaginata, with raised immunoglobulin E.

Zinc and biotin deficiency can present as an eczematous eruption or an erythroderma, and are often misdiagnosed as AD before other symptoms and signs become evident. The skin eruption consists of dermatitis on the face that has a typical horseshoe appearance on the cheeks and around the chin, with perianal involvement. However, there is no xerosis or pruritus. In older children the lesions are seen on the elbows and knees, whereas in AD the flexures are usually involved.

Other dermatitis like nummular dermatitis, allergic or irritant dermatitis can resemble AD and should be ruled out.

It is rare for adults to get AD. About half (50%) of people who get AD during childhood continue to have milder signs and symptoms of AD as an adult. When an adult has AD, it often looks different from the AD of childhood. They may continue to have a diffuse pattern of eczema but the skin is often more dry and lichenified than in children. Commonly, adults have persistent localized eczema, possibly confined to the hands, eyelids, flexures, nipples, or all of these areas. The skin is prone to secondary bacterial infections.

Clinical Pearl

- Always look for hyperlinerity of palms, Dennie morgan fold and other features of atopy when suspecting atopic dermatitis.

Individuals with AD may show other associated features of atopy like generalized xerosis, Dennie morgan fold, hyperlinearity of palms, pityriasis alba, keratosis pilaris, allergic shiners, and ichthyosis vulgaris.

MANAGEMENT

Treatment of atopic eczema may be required for many months and possibly years. It nearly always requires:

- Reduction of exposure to trigger factors (where possible)
- Antihistamines: both first and second generation can be used to control pruritus. Regular application of emollients, multiple times per day is very important
- Topical steroids (current mainstay of treatment; commonly used in conjunction with moisturizers): Hydrocortisone, triamcinolone, or betamethasone; ointment bases are generally preferred, particularly in dry environments
- Immunomodulators: tacrolimus and pimecrolimus (calcineurin inhibitors) are considered second-line therapy.

Other treatments options available include the following:

- Systemic therapy: systemic corticosteroids, methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil
- Phototherapy: ultraviolet A for acute exacerbations, narrowband ultraviolet B for chronic disease
- Biological: omalizumab
- Others: probiotics, antibiotics for clinical infections.

Clinical Pearl

What to tell parents?

- Keep child in humid environment
- Avoid pets, dust
- Use lukewarm water for bathing
- Apply adequate emollients immediately after bath.

KEY POINTS

- ☞ Atopic dermatitis is always itchy
- ☞ It remits and relapses
- ☞ It effects extensors and face in less than 2 years children, and flexures in children elder than 2 years and adults
- ☞ Seborrheic dermatitis, flexural psoriasis, and zinc deficiency are great mimickers and should be excluded.

SUGGESTED READINGS

1. Arnacho-Saucedo G, et al. Actualización en dermatitis atópica. Propuesta de algoritmo de actuación. Actas Dermosifiliogr. 2013;104:4-16.
2. Bhavani MN, Vandergriff T, Rasmussen H, Jacobe H. Phototherapy in the management of atopic dermatitis: a systematic review. Photodermatology, Photoimmunology & Photomedicine. 2007;23(4):106-12.
3. De Benedetto A, Agnihothri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects? The Journal of Investigative Dermatology. 2009;129(1):14-30.
4. McCollum AD, Paik A, Eichenfield LF. The safety and efficacy of tacrolimus ointment in pediatric patients with atopic dermatitis. Pediatr Dermatol. 2010;27:425-36.
5. Morris A, Rogers M, Fischer G, Williams K. Childhood psoriasis: a clinical review of 1262 cases. Pediatr Dermatol. 2001;18:188-98.
6. Torrelo A. Tacrolimus tópico en el tratamiento de la dermatitis atópica en niños. Actas Dermosifiliogr. 2008;99(Suppl 2):1428-9.

CHAPTER 136

Approach to a Child with Hypopigmented Macules

Vibhu Mendiratta, Pravesh Yadav

INTRODUCTION

Hypopigmented macules in a child can be a cause of worry for the parents and physician alike. Hypopigmented macules may be present since birth or may appear later in childhood. This chapter briefly outlines the approach to such presentation (Algorithm 1).

Various genetic, autoimmune, and infective diseases may manifest as hypopigmented lesions in children. Hypopigmented macules may present at birth or later in childhood. Localized hypopigmented lesions with forelocks may present at birth in patients with piebaldism or Waardenburg syndrome. Piebaldism presents as depigmented patches on the ventral or lateral trunk and/or the mid-extremities with the sparing of hand and feet. Poliosis is a common feature. It is not associated with systemic features. Waardenburg syndrome is associated with dystopia canthorum, broadening of the nasal root, presence of hypoplastic alae nasi, synophrys, poliosis, heterochromia iridis, congenital sensorineural hearing loss, musculoskeletal abnormalities like limb contractures and hypoplasia of the limb musculature, and Hirschsprung disease.

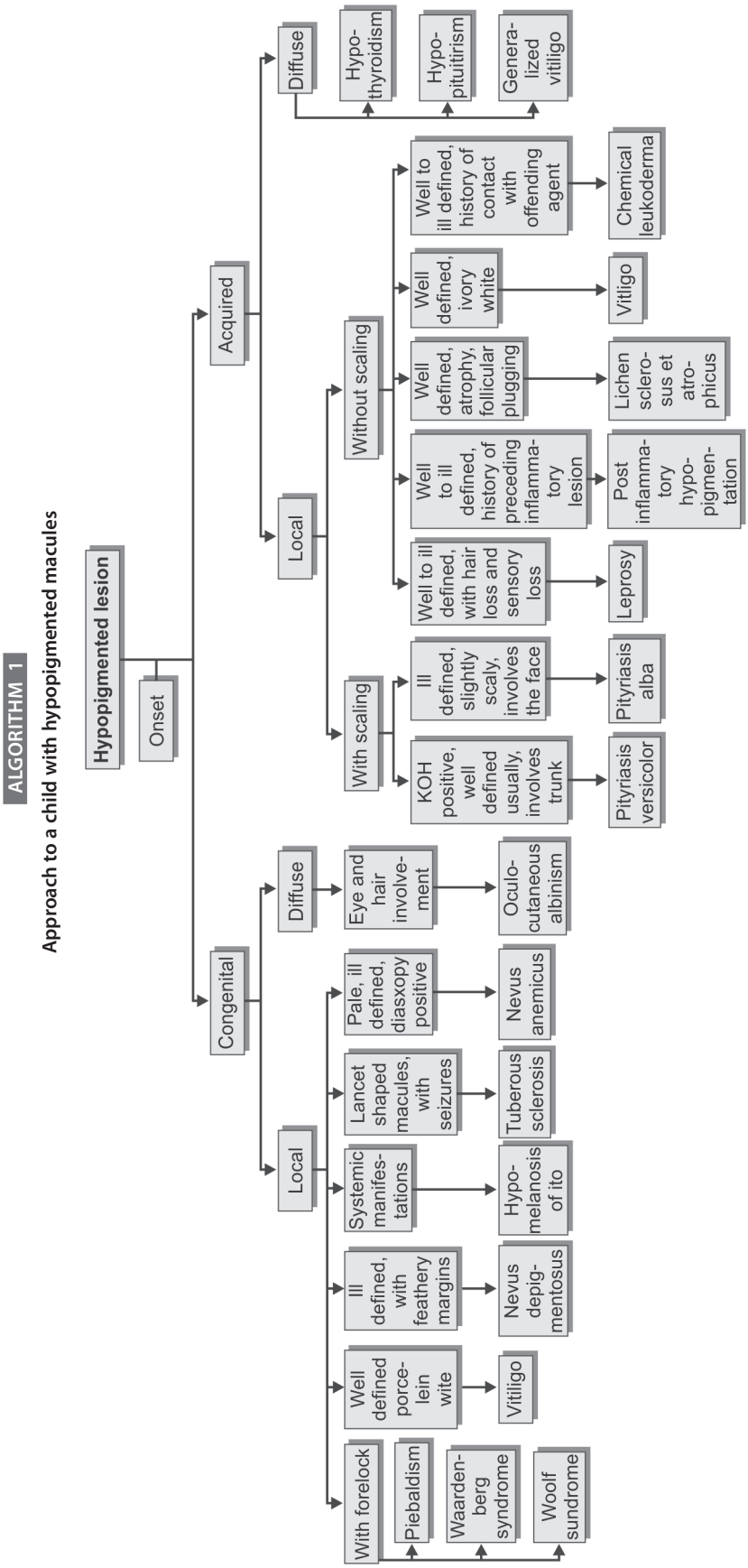
Nevus depigmentosus presents as ill-defined hypopigmented macules with feathery margins. Similar cutaneous lesions along lines of blaschko with or without extracutaneous manifestations occur in hypomelanosis of Ito. Localized hypopigmented lesions without forelock may occur in vitiligo. Nevus anemicus presents as pale, ill defined hypopigmented macules, which merges with surrounding skin on diascopy. Tuberous sclerosis may present as off white macules, which are oval at one end and taper to the other end, resembling ash leaf called as ash-leaf macules. They are often present at birth or appear within the first few years of life commonly over trunk and buttocks. Wood's lamp may be used to improve detection especially in light pigmented individuals. Three or more hypopigmented macules constitute a major feature for the diagnosis of tuberous sclerosis. A less common type of hypopigmentation is the "confetti" skin lesions involving the legs or forearms which are considered a minor feature for tuberous sclerosis.

Generalized hypopigmentation with hair and eye involvement occurs in albinism. It results either from enzymatic defects in the biosynthesis of melanin, from melanosomal defects that interfere with melanin formation, or from problems in the intracellular transport and localization of proteins essential for melanin biosynthesis. In oculocutaneous albinism (OCA) type 1A, or the classic tyrosinase negative OCA, there is a complete inability to synthesize melanin in skin, hair, and eyes, which results in the characteristic "albino phenotype". Affected individuals are born with white hair and skin. The phenotype OCA type 1B can range from minimal hair pigment to near normal skin and hair pigment. They have very little or no pigment at birth and develop varying amounts of melanin in the hair and skin in the first or second decade of life.

Localized well defined, slightly, scaly, hypopigmented macules involving the trunk, chest, back, and shoulders occurs in pityriasis versicolor. It is caused by Malassezia species, which on potassium hydroxide microscopy show hyphae and blastospores in the typical "spaghetti and meatballs" appearance. A yellow-green fluorescence is visible using Wood's lamp examination. Pityriasis alba typically presents as ill defined localized powdery white scaly lesions involving the head and neck region, which may progress to non-scaly hypopigmented macules. It is commonly seen in atopic individuals. Leprosy presents as well to ill defined hypopigmented macules with loss of sweating, hair loss, and loss of sensation. Lesions in tuberculoid pole presents as single to a few xerotic hypopigmented macules with hair loss. Lesions in lepromatous pole present as multiple ill defined, infiltrated hypopigmented macules and hair loss may occur later on. Diagnosis of leprosy may be confirmed by slit skin smear or histopathological examination. Inflammatory lesions may lead to post-inflammatory hypopigmentation which presents as well to ill defined hypopigmented macules. Lichen sclerosus et atrophicus presents as a pruritic erythematous patch in the early stage, evolving into a well defined porcelain hypopigmented plaques with epidermal

ALGORITHM 1

Approach to a child with hypopigmented macules



atrophy and follicular atrophy. Vitiligo is a common disorder of depigmentation occurring in approximately 1% of the world's population. Various hypotheses have been proposed including autoimmune, neurogenic, etc. Vitiligo may be associated with diabetes mellitus, thyroid diseases, etc. Histopathology shows absence of melanocytes and melanin in epidermis. Hypomelanotic macules present in a localized form or generalized form. Various morphological forms have been described like acrofacial, segmental, etc. Hairs over the lesion may also turn gray. Spontaneous repigmentation may occur in some lesions. Exposure to chemicals may lead to ill defined hypopigmented macules of chemical leukoderma.

Diffuse acquired hypopigmentation may occur in patients with hypothyroidism and hypopituitarism.

Clinical Pearls

- Localized hypopigmented lesions with forelocks may present at birth in patients with piebaldism (without systemic features) or Waardenburg syndrome (with systemic features)
- Generalized congenital hypopigmentation with hair and eye involvement occurs in albinisim
- Vitiligo may present in a localized form or generalized form at birth or later in life.

KEY POINTS

- ☞ Localized hypopigmentation without scaling at birth may be seen in nevus depigmentosus, nevus anemicus, vitiligo, piebaldism or Waardenburg syndrome
- ☞ Generalized hypopigmentation may be seen in albinism or vitiligo
- ☞ Localized scaly acquired hypopigmentation may be seen in pityriasis versicolor, and pityriasis alba
- ☞ Vitiligo presents as acquired depigmented, and non-scaly macules
- ☞ Leprosy may present with hypopigmented lesions with loss of sensation.

SUGGESTED READINGS

1. Anstey AV. Disorders of skin colour. In: Burns T, Breathnach S, Griffiths C, Cox N (Eds). Rook's Textbook of Dermatology, 8th edition. India: Wiley-Blackwell; 2010. pp. 58.1-58.59.
2. Lapeere H, Boone B, Schepper SD, Verhaeghe E, Ongenae K, Geel NV, et al. Hypomelanoses and hypermelanoses. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Pallar AS, Leffell DJ (Eds). Fitzpatrick's Dermatology in General Medicine, 7th edition. New Delhi: McGraw Hill; 2008. p. 622.

CHAPTER 137

Pediatric Acne

Vibhu Mendiratta, Niti Gaur, Aashim Singh

INTRODUCTION

Acne vulgaris is a common inflammatory condition of the pilosebaceous unit with a peak incidence during adolescence. However, it may be found in all age groups including neonates and infants (Algorithm 1).

NEONATAL ACNE

The onset of neonatal acne is usually before the first 6 weeks of life. It affects about 20% of the newborns. The papules typically occur across nasal bridge and cheeks. There are no comedones. This benign condition is hormonally mediated. Neonatal acne may be hard to distinguish from heterogeneous papulopustular acneiform conditions typically without comedones, such as neonatal cephalic pustulosis or transient neonatal pustular melanosis. Neonatal cephalic pustulosis pustules are usually confined to the cheeks, chin, eyelids, and forehead, but the scalp, neck, upper chest, and back may be involved. It has been attributed to overgrowth of Malassezia species. Newborns may present with or develop transient neonatal pustular melanosis, with pustules on the chin, neck or trunk. Within 24 hours, these pustules rupture, leaving hyperpigmented macules with a rim of faint white scale. Most cases of neonatal acne resolve by 3 months of age but severe cases can be treated topically with 2% ketoconazole cream, benzoyl peroxide or erythromycin.

INFANTILE ACNE

Infantile acne may begin approximately at 6 weeks of age and last for 6–12 months. It is more common in boys and presents with comedones as well as inflammatory lesions, which can include papules, pustules, or occasionally nodular lesions. Physical examination should include assessment of growth including height, weight, and growth curve; testicular growth and breast development; presence of hirsutism or pubic hair; clitoromegaly; and increased muscle mass. The etiology is postulated to be transient rise in dehydroepiandrosterone sulfate and luteinizing hormone levels. Most infantile acne is self-limited and not associated with underlying endocrine pathology. There is some evidence that infantile acne predisposes to more severe adolescent acne. Infantile acne may be treated with topical antimicrobial agents; topical retinoids; non-cycline antibiotics, such as erythromycin; and, occasionally, isotretinoin.

Clinical Pearl

- Acne not responding to treatment or with unusual presentation should be further evaluated to look for underlying endocrine pathology.

MID-CHILDHOOD ACNE

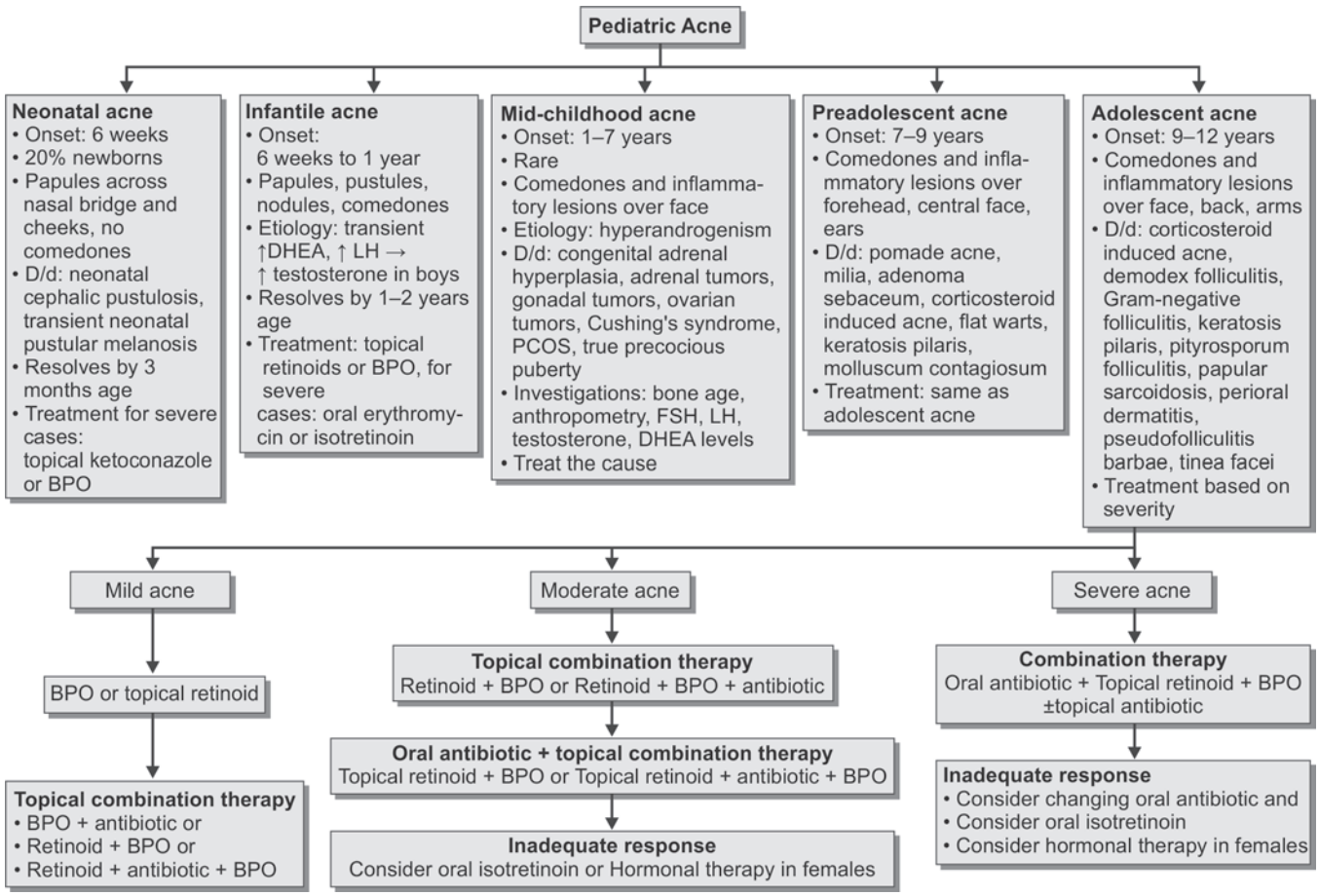
Mid-childhood acne presents primarily on the face with a mixture of comedones and inflammatory lesions. Children between the ages of 1 and 7 years, however, do not normally produce significant levels of adrenal or gonadal androgens; hence, acne in this age group is rare. When it does occur, an endocrine abnormality should be suspected. In addition to treatments to address androgen-secreting tumors or congenital adrenal hyperplasia, the treatment of mid-childhood acne is similar to that of adolescent acne except that oral tetracyclines are usually not an option in children younger than 8 years of age because of the risk of damage to developing bones and tooth enamel. Hormonal therapy could be used if warranted by endocrinologic pathology.

Clinical Pearl

- Tetracyclines are contraindicated in children <8 years and oral isotretinoin is not recommended in children <12 years according to the food and Drug Administration.

ALGORITHM 1

Approach to pediatric acne depending on age of onset



PREADOLESCENT ACNE

Preadolescent (7–12 years) acne is common and may precede other signs of pubertal maturation. It is characterized by a predominance of comedones on the forehead and central face (the so-called "T-zone") with relatively few inflammatory lesions. Further workup is generally unnecessary unless there are signs of excess androgens. Treatment of uncomplicated preadolescent acne is comparable to that of acne in older age groups, as discussed later.

ADOLESCENT ACNE

Adolescent acne (12–19 years) is common and characterized by comedones and inflammatory lesions over face, back, arms. Acne can be categorized as predominately comedonal, inflammatory and/or mixed. Presence or absence of scarring, post-inflammatory hyperpigmentation or erythema should be assessed. Severity may be broadly categorized as mild, moderate or severe. The pathogenesis of acne involves the interplay of four factors: sebaceous hyperplasia under the influence of increased androgen levels, alterations in follicular growth and differentiation, colonization of the follicle by Propionibacterium acnes, and consequent immune response and inflammation.

TREATMENT OF MILD ACNE

Topical therapy alone or in combination is recommended as initial treatment of mild acne. Benzoyl peroxide (BPO) as a single agent, topical retinoids, or combinations of topical retinoids, antibiotics and BPO as individual agents or fixed-dose combinations may be used. If the response is inadequate then a topical retinoid or BPO may be added to monotherapy with either agent.

TREATMENT OF MODERATE ACNE

Moderate acne may be initially treated with topical combinations including a retinoid and BPO and/or antibiotics, or with oral antibiotics in addition to a topical retinoid and BP and/or topical antibiotics. Optimally, the topical regimen would include a retinoid and a benzyl peroxide-containing formulation, either separately or as a combination product. In addition, use of an oral antibiotic may be especially prudent if there is evidence of acne scarring, even if the current severity

of inflammatory acne is more modest. Typically, 4–8 weeks of compliant oral antibiotic use are needed before the clinical effects of an oral antibiotic are visible, whereas maximal response may require 3–6 months of administration.

TREATMENT OF SEVERE ACNE

Patients with severe acne are at significant risk for scarring. Severe acne should be treated with oral antibiotics and topical retinoids with BPO, with or without topical antibiotics, with consideration of hormonal therapy in pubertal females or oral isotretinoin. Patients unresponsive to these topical and oral therapies will benefit with oral isotretinoin.

Clinical Pearl

- Childhood acne may persist and raises the risk of development of severe scarring acne in adulthood.

KEY POINTS

- ☞ Acne may present in all age groups. It may be physiological or pathological in pediatric age groups
- ☞ Mild to moderate forms are usually self-limited but severe forms of acne require topical or oral treatment to prevent scarring
- ☞ Pediatric acne may be a pointer toward virilization, especially if unresponsive to conventional treatment.

SUGGESTED READINGS

1. Cantatore-Francis JL, Glick SA. Childhood acne: evaluation and management. Dermatol Ther. 2006;19(4):202-9.
2. Cunliffe WJ, Baron SE, Coulson IH. A clinical and therapeutic study of 29 patients with infantile acne. Br J Dermatol. 2001;145(3):463-6.
3. Del Rosso JQ, Kim G. Optimizing use of oral antibiotics in acne vulgaris. Dermatol Clin. 2009;27(1):33-42.
4. Niamba P, Weill FX, Sarlangue J, Labrèze C, Couprie B, Taïeh A. Is common neonatal cephalic pustulosis (neonatal acne) triggered by Malassezia sympodialis? Arch Dermatol. 1998;134(8):995-8.
5. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Global alliance to improve outcomes in acne. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol. 2003;49(Suppl 1):S1-37.
6. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Global alliance to improve outcomes in acne. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol. 2003;49(Suppl 1):S1-37.
7. Herane MI, Ando I. Acne in infancy and acne genetics. Dermatology. 2003;206(1):24-8.
8. Jansen T, Burgdorf WH, Plewig G. Pathogenesis and treatment of acne in childhood. Pediatr Dermatol. 1997;14(1):17-21.
9. Krakowski AC, Eichenfield LF. Pediatric acne: clinical presentations, evaluation, and management. J Drugs Dermatol. 2007;6(6):589-93.
10. Poli F. Acne on pigmented skin. Int J Dermatol. 2007;46(Suppl 1):39-41.

CHAPTER 138

Approach to Congenital Melanocytic Nevus

Vibhu Mendiratta, Pravesh Yadav

INTRODUCTION

Congenital melanocytic nevus (CMN) represent a developmental abnormality of normal melanocytic development. This is probably due to mutation that occurs in a progenitor cell that results in the abnormal extensive accumulation of melanocytic cells along migration pathways during normal development. The events leading to the nevomelanocyte accumulation may also have effects on the surrounding tissue probably due to a change in the local cytokine environment of the nevomelanocytic cells. According to American National Institutes of Health consensus definition, CMN have been categorized according to size into small, under 1.5 cm in diameter, large as having a diameter between 1.5 and 20 cm and giant nevi as having a diameter of 20 cm or more (Algorithm 1).

Congenital melanocytic nevi are usually obvious and deeply pigmented at birth. Majority of these nevi are macular at birth with smooth, regular and sharply demarcated contour and distortion of the skin markings. As the child grows, the nevus usually grows in proportion. At some sites, such as the scalp, there is commonly a considerable increase in terminal hair. In other sites, an increase in terminal hair tends to occur more subtly over time and may be accompanied by the development of rugosity. As the infant grows, the surface of the nevus may become rugose or warty and nodules can develop within a large nevus. Congenital melanocytic nevi may develop a halo of depigmentation, heralding a potential spontaneous resolution. Loss of pigmentation has been associated with regression of underlying melanocytes. Dermatoscopy can sometime prove to be helpful in the diagnosis showing a characteristic reticular or globular pattern. A significant proportion of nevi may become paler in the first 1–2 years of life, and at sites such as the scalp may fade to cosmetic insignificance.

There may be associated abnormalities such as meningeal involvement, spina bifida, or meningocele when the nevus is located over the vertebral column, or club-foot and hypertrophy or atrophy of the deeper structures of a limb. Absence of subcutaneous fat is the most common associated anomaly and may be symptomatic in sites such as over the sacrum. Neurocutaneous melanosis may rarely produce raised intracranial pressure, hydrocephalus or space-occupying spinal lesions. A variety of proliferative neoplasms may develop in CMN. Superficial spreading melanoma is the most significant complication of CMN but the level of risk is reasonably low. In giant nevi, there is a definite risk, with the age of onset of the melanoma being earlier than in the general population. A magnetic resonance imaging scan should be considered in babies with nevi over the cranium or spine to exclude significant leptomeningeal melanocytosis. Regular neurological examination, however, is clearly important.

Histopathology shows presence of nevomelanocytes in the epidermis as well ordered theques and/or nevomelanocytes in the dermis in the form of sheets, nests, cords and/or single cells. Presence of nevomelanocytes in the lower two-thirds of the reticular dermis and association with appendageal and neurovascular structures is more commonly seen with CMN than acquired nevi. Nevomelanocytes may be prominent within and around the blood vessels showing an inflammatory appearance. Hair follicles are often quite large and associated with abundant melanin in the hair bulb.

Differentials of CMN include CALM (café au lait macules), nevus spilus, Becker's nevus, lentigo simplex, nevus sebaceous, smooth muscle hamartoma, epidermal nevi, dermal melanocytosis, and solitary mastocytoma.

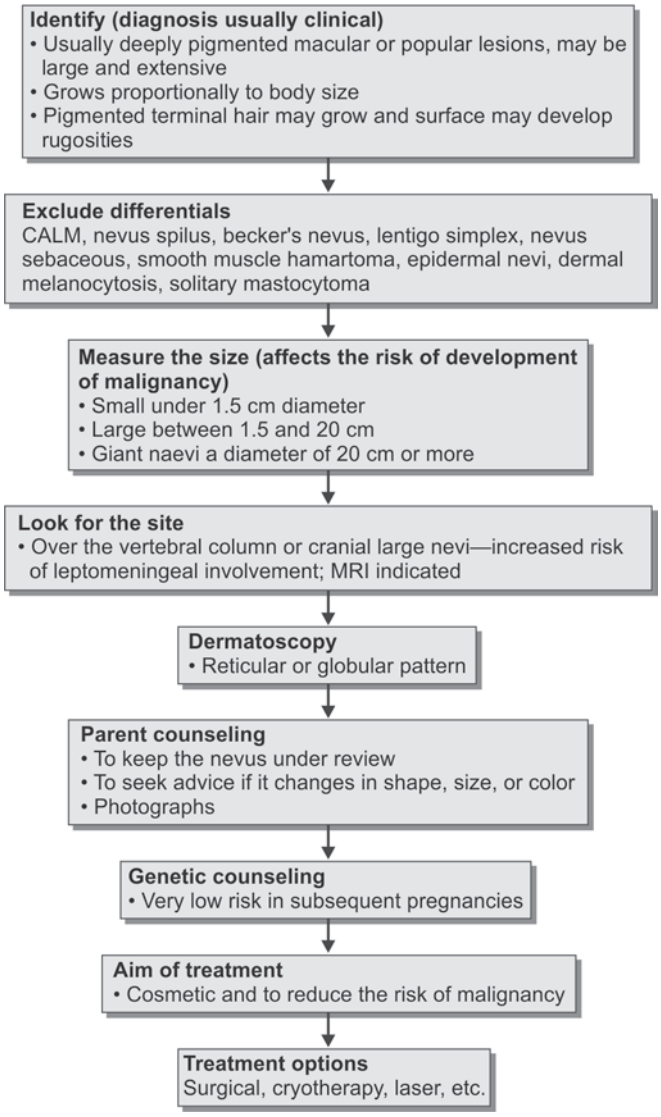
Congenital melanocytic nevi are essentially considered to be developmental abnormalities of the skin, with a very low risk of recurrence in subsequent pregnancies, which is particularly important when reassuring parents who have a child with a giant melanocytic nevus. The aims of treatment are to improve the cosmetic effect of nevi and to reduce the risk of malignant transformation. The most common treatment is surgical, using a variety of plastic surgical techniques such as multistep surgery, the use of tissue expanders and grafting. Tissue expansion is usually used for the head and neck, but in other sites excision and grafting are more usual, with consequently poorer cosmetic results. Other ablative techniques have been

tried such as cryotherapy and, more recently, the Q-switched ruby laser.

Parents of children with CMN left *in situ* should be advised to keep the nevus under review and to seek advice if it changes in shape, size, or color. Photographs of the child's nevus and images of melanomas may be useful tools. Even small nevi that are difficult to keep under review, such as those in the scalp or in the middle of the back may be prophylactically excised, particularly if they have any atypical features such as intense or irregular pigmentation which persists beyond infancy.

ALGORITHM 1

Approach to congenital melanocytic nevus



CALM, café au lait macules; MRI, magnetic resonance imaging

Clinical Pearls

- Nevus located over the vertebral column: rule out abnormalities such as meningeal involvement, spina bifida, or meningocele
- Giant nevi (diameter of 20 cm or more): higher risk.

KEY POINTS

- ☞ Congenital melanocytic nevus (CMN) is a developmental abnormality of normal melanocytic development leading to an abnormal accumulation of melanocytic cells along migration pathways during normal development
- ☞ Congenital melanocytic nevus are usually obvious and deeply pigmented macules at birth and grow in proportion to the body with age
- ☞ Increase in terminal hair and rugosity are normal progression changes with age
- ☞ Congenital melanocytic nevus may be associated with abnormalities such as meningeal involvement, spina bifida, or meningocele when the nevus is located over the vertebral column
- ☞ A variety of proliferative neoplasms may develop in CMN, superficial spreading melanoma being the most significant
- ☞ Treatment indications are mainly cosmetic.

SUGGESTED READINGS

1. Anon. Consensus conference: precursors to malignant melanoma. JAMA. 1984;251:1864-6.
2. Bishop JAN. Lentigos, melanocytic naevi and melanoma. In: Burns T, Breathnach S, Griffiths C, Cox N (Eds). Rook's Textbook of Dermatology, 8th edition. India: Wiley-Blackwell; 2010. pp. 54.1-54.57.
3. Goodman RM, Caren J, Ziprkowski M, Padeh B, Ziprkowski L, Cohen BE, et al. Genetic considerations in giant pigmented hairy naevus. Br J Dermatol. 1971;85:150-7.
4. Grichnile JM, Rhodes AR, Sober AJ. Benign neoplasias and hyperplasias of melanocytes. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Pallar AS, Leffell DJ (Eds). Fitzpatrick's Dermatology in General Medicine, 7th edition. New Delhi: McGraw Hill; 2008. p. 1099.
5. Strauss RM, Bishop JAN. Spontaneous involution of congenital melanocytic nevi of the scalp. J Am Acad Dermatol. 2008;58:508-11.

CHAPTER 139

Seborrheic Dermatitis

Vibhu Mendiratta, Nikita, Sarita Sanke

INTRODUCTION

Seborrheic dermatitis (SD) is a chronic papulosquamous inflammatory disorder affecting the sebaceous gland rich areas of the skin. It is a benign self-limiting condition characterized by remissions and exacerbations. It occurs due to seborrhea, a pathologic overproduction of sebum, with subsequent infection and inflammation. It typically presents with scaly, flaky, greasy, and red skin. The severity ranges from mild dandruff to exfoliative erythroderma. It can occur in any age group; however, two age peaks are noted; in infants—during first 3 months of life and in adults—during 4th to 7th decade of life. These age peaks correlate with the high activity of sebaceous glands.

EPIDEMIOLOGY

Seborrheic dermatitis affects healthy individuals of any ethnicity, with no sex predilection. Estimates of SD prevalence and incidence are hindered by many cases being mild and poor case definition, so probably underestimate the true figure. Estimates are also limited due to absence of validated criteria for diagnosis. As per literature, SD affects 3–5% of the general population. Up to 70% of newborns are affected by SD in their first 3 months of life. Dandruff, the mildest form of SD effects 15–20% of the population. SD is especially prevalent in those with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome and chronic neurodegenerative disorders.

ETIOLOGY

The exact etiology remains uncertain. It involves a complex interaction between:

- Host factors
- Malassezia species
- Environmental factors.

Host factors: overactivity of sebaceous glands leads to excess production of sebum. Seborrhoeic dermatitis may be aggravated by illness, psychological stress, fatigue, sleep deprivation, and reduced general health.

In children, excessive vitamin A intake can cause seborrhoeic dermatitis. Lack of biotin, pyridoxine (vitamin B6) and riboflavin (vitamin B2) may also be a cause.

Those with immunodeficiency (especially infection with HIV) and with neurological disorders such as Parkinson's disease and stroke are particularly prone to it.

Malassezia species: the most implicated species are *Malassezia globosa*, others being *Malassezia furfur* and *Malassezia restricta*. Infantile SD is more commonly associated with *Malassezia furfur.* Patients with seborrhoeic dermatitis appear to have a reduced resistance to the yeast. *Malassezia* hydrolyze human sebum releasing a mixture of saturated and unsaturated fatty acids (FAs). They take up the required saturated FAs, leaving behind unsaturated FAs. The unsaturated FAs penetrate the stratum corneum and because of their non-uniform structure breach the skin's barrier function. This barrier breach induces an irritation response, leading to seborrhea and dermatitis.

Environmental factors: worsening of SD occurs in winters and early spring. Remission can be seen in summers.

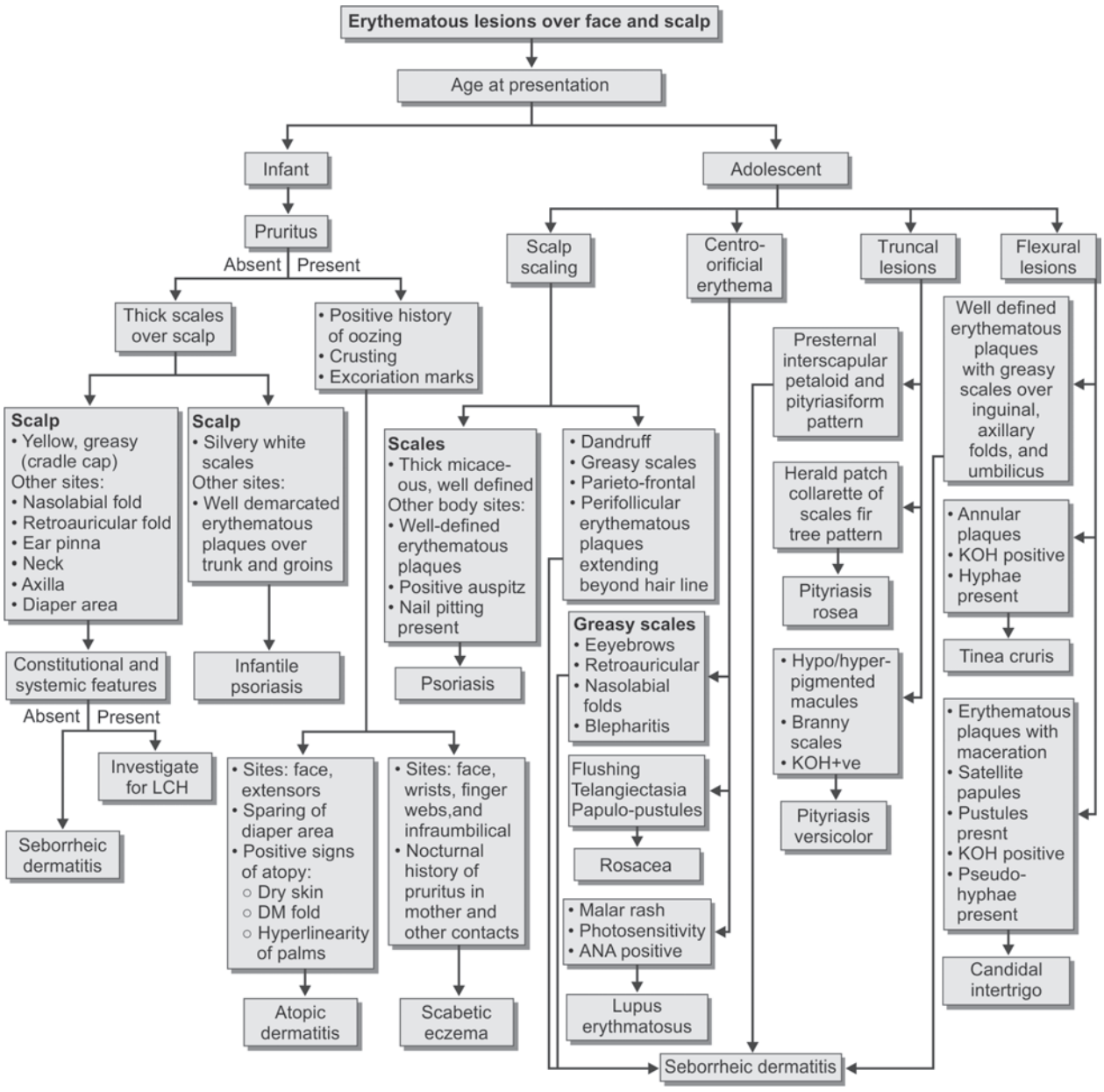
CLINICAL PRESENTATION AND APPROACH (ALGORITHM 1)

Infants

Cradle cap is the most common presentation in infants and usually appears in the first few weeks of life. There are greasy, yellow scales and crusts that may eventually coalesce to a thick, scaly plaque with underlying mild to moderate erythema. Overall, scalp is the most commonly affected site, followed by face. Areas of face commonly affected are forehead, eyebrows, nasolabial folds and retroauricular areas.Seborrheic dermatitis can also involve the thorax, upper back, external genitalia and flexures such as the axillae, inguinal folds. Involvement of perianal area in the form of diaper rash is also common.

ALGORITHM 1

Seborrheic dermatitis and its differentials: Diagnostic approach



Clinical Pearl

Seborrheic areas

- Scalp, retroauricular areas, medial eyebrows, nasolabial fold, anterior chest, interscapular area, axillae, groins, and diaper area.

The condition is not itchy unlike in adolescents. The condition usually resolves without treatment in weeks to months, although treatment may be used if needed.

On the other hand, patient with atopic dermatitis have scalp and facial involvement in the form of oozy plaques which are extremely pruritic. Extensors may also be involved. Diaper area is characteristically spared unlike infantile SD and psoriasis. If the infant exhibits systemic and constitutional features along with seborrhic dermatitis like lesions, he should be worked up for Langerhan's cell histiocytosis. Scabies with eczematisaton is also a close mimicker of the disease where presence of nocturnal exacerbation itching and lesions in contacts help differentiate the conditions.

Adolescents

Seborrhea of scalp in the form of dandruff is the most common presentation in adolescents and adults. Greasy white to yellow, fine scales with underlying erythema can be seen. This should be differentiated from well-defined plaques with micacious scales seen in scalp psoriasis. The sites of predilection are the same as in infants. However, in adolescents SD is usually worse in hair bearing areas of the face and involvement of flexures

and perianal area is less common. Centrofacial erythema is prominent with greasy scales over eyebrows, nasolabial folds and retroauricular region. Absence of flushing, telangiectasias help us differentiate it from rosacea where papulopustules are present on baseline facial erythema over convexities. Trunk may also be involved with perifollicular papules (petaloid pattern) and papulosquamous lesions (pityriasiform pattern) with greasy scales. Truncal lesions resemble pityriasis rosea and pityriasis versicolor. Candidal intertrigo and tinea cruris can mimic flexural SD which can be diagnosed with simple bedside testing with potassium hydroxide mount.

TREATMENT

The symptoms of SD can be effectively controlled with a combination of self-care measures and drug therapy.

Topical antifungal agents and topical corticosteroids are the principal forms of management for SD. Of these two treatment modalities, antifungals are the mainstay. However, during acute exacerbations, topical corticosteroids are often used as first line therapy.

Infant Seborrheic Dermatitis

Cradle cap usually resolves without treatment. However, it may require treatment in some cases. Regular emollients and mild non-medicated baby shampoos can be tried initially for infantile SD, especially if asymptomatic. For more widespread, symptomatic or persistent SD, topical ketoconazole 2% cream, mild corticosteroid ointments (hydrocortisone 1%, desowen lotion 0.05%, clobetasone butyrate 0.05%) or combination preparations containing hydrocortisone and miconazole can also be used—initially twice daily on affected areas, weaning down on improvement. The scales should be gently removed with a soft brush after shampooing. A small amount of emollient can be applied to the scalp overnight to loosen the scaly plaques. There is no role of oral antifungals in infantile SD.

Clinical Pearl

- Infantile seborrheic dermatitis is a physiological condition and usually does not require treatment.

Adolescent/Adult Seborrheic Dermatitis

Seborrheic dermatitis in adults is a chronic condition. Long-term maintenance treatment is often necessary.

Scalp Seborrheic Dermatitis

Dandruff (mild SD of the scalp) can be treated with anti-dandruff shampoos. Several types of anti-dandruff shampoos are available, with the main difference between them being the active ingredient. All of these treatments are equally effective after 4 weeks of use. The main active ingredients are:

- Selenium sulfide
- Tar
- Zinc pyrithione
- Ketoconazole.

Shampoos containing corticosteroids, propylene glycol and keratolytics like coal tar and salicylic acid can also be used for additional benefits. For best results, the shampoo should be left in place for 5–10 minutes before rinsing. The shampoo should be rinsed out of the hair completely.

The shampoo may be used every day initially, and then every other day as symptoms improve. These shampoos can be used for as long as needed.

Nonscalp Seborrheic Dermatitis

Seborrheic dermatitis of the face, trunk, and skin folds generally is treated with topical corticosteroids or antifungal agents.

Low potency topical corticosteroids (e.g., hydrocortisone 1% cream) may be tried initially. The cream is applied once or twice a day until symptoms improve with gradual tapering. Topical antifungal agents (ketoconazole 2%, miconazole) either alone or in combination with topical steroids can also be used. Long-term application of steroids should be avoided in view of side effects like atrophy, striae and telangiectasias.

The topical calcineurin inhibitors tacrolimus and pimecrolimus are effective in treating SD. Both can be used twice daily initially and weaned down as the SD improves. Proactive treatment of adult facial SD to maintain remission with 0.1% tacrolimus ointment once or twice per week is also effective.

For refractory or widespread SD where topical therapy is impractical, oral itraconazole 200 mg daily for 2–4 weeks is effective.

Clinical Pearls

Cradle cap: What to tell parents

- Regular scalp wash with mild baby shampoo
- Remove scales with a brush
- Emollients can be used to loosen the scales.

KEY POINTS

- ☞ Seborrheic dermatitis (SD) is physiological in infants below 3 months of age
- ☞ Cradle cap is the most common presentation
- ☞ It is a non-itchy condition characterized by greasy yellow scales in seborrheic areas
- ☞ Self-limiting course
- ☞ Psoriasis, intertrigo, pityriasisrosea, and rosacea are close mimickers for adolescent SD
- ☞ Antifungals and topical steroids form the main stay of treatment.

SUGGESTED READINGS

1. Bikowski J. Facial seborrheic dermatitis: a report on current status and therapeutic horizons. J Drugs Dermatol. 2009;8(2):125-33.
2. Gaitanis G, Velegraki A, Alexopoulos EC, Chasapi V, Tsigonia A, Katsambas A. Distribution of malassezia species in pityriasis versicolor and seborrhoeic dermatitis in Greece. Typing of the major pityriasis versicolor isolate M. globosa. Br J Dermatol. 2006;154:854-9.
3. Gupta AK, Bluhm R. Seborrheic dermatitis. J Eur Acad Dermatol Venereol. 2004;18(1):13-26.
4. Hay RJ, Graham-Brown RAC. Dandruff and seborrhoeic dermatitis: causes and management. Clinical and Experimental Dermatology. 1997;22(1):3-6.
5. Sheffield RC, Crawford P, Wright ST, King VJ. Clinical inquiries. What's the best treatment for cradle cap? J Fam Pract. 2007;56(3):232-3.
6. Smoker AL. On top of cradle cap. J Fam Health Care. 2007;17(4):134-6.

CHAPTER 140

Approach to Red Eye in Children

Suma Ganesh, Priyanka Arora

INTRODUCTION

Red eye is one of the most common reasons for acute eye-related visits to the pediatricians, while some causes are uncomplicated and resolve within a few days, many cases require prompt treatment to prevent the disease from worsening or spreading. The condition can be managed by pediatricians, but knowing when to refer the patient to ophthalmologist is crucial. In this chapter, we will be discussing the common causes of red eye in children and the approach to management of these causes.

CAUSES OF RED EYE

Conjunctivitis is the most common cause of red eye. It may be infectious (bacterial or viral) or noninfectious (allergic, chemical). At a leading cornea service (Will's Eye Hospital), blepharoconjunctivitis was the most common diagnosis in children, accounting for 15% of all pediatric referrals. Most cases of infectious conjunctivitis are self-limiting. Other common causes of red eye in children include blepharitis, corneal abrasion, foreign body, subconjunctival hemorrhage, keratitis, iritis, chemical burns, trauma, endophthalmitis, and severe dry eye. Some uncommon causes of red eye in children are iridocyclitis, episcleritis, contact lens related, due to chemical irritants like chlorine in swimming pools, head lice if they spread to ocular area, and congenital glaucoma (Table 1).

HISTORY AND EXAMINATION

A thorough patient history and eye examination may provide clues towards etiology of red eye (Table 2). Salient points in this history includes whether the condition is unilateral or bilateral, duration and type of symptoms, presence of discharge and its nature, visual changes, pain, photophobia, itching, and any previous treatments.

TABLE 1: Causes of red eye in children

Most common	Relatively common	Uncommon

• Conjunctivitis
  ○ Infectious
  – Bacterial
  – Viral
  – Chlamydial
  ○ Noninfectious:
  – Allergic conjunctivitis
  – Chemical irritants
• Foreign body
• Blepharitis
• Corneal abrasions
	• Trauma
	• Subconjunctival hemorrhage due to vigorous coughing
	• Stye/hordeolum
	• Keratitis/corneal ulcer
	• Ocular fatigue
		• Iridocyclitis or uveitis
		• Episcleritis
		• Scleritis
		• Contact lens related
		• Severe dry eye
		• Endophthalmitis
		• Glaucoma

Tips for an Effective Patient History and Examination

When a child presents with red eye, one must be able to identify potentially serious ocular conditions that require immediate referral. Includes these questions in a through histroy to aid in differential diagnosis:

- When did the symptoms start?
- Are they in one eye or both?
- Is there any discharge in the eye? If yes, what kind and how much?
- Is there any swelling or pain in eyes?
- Is there a history of similar complaints in any of the family member?
- Any recent history of:
  - Explosure to chemicals
  - Contact with another person with red eye
  - Injury to the eye
  - Upper respiratory tract infection (URI)

TABLE 2: Clinical pointers in history and examination to identify the causes of red eye

Signs	Symptoms	Likely diagnosis
• Purulent discharge	• Matting of eyelashes on waking up in morning (best predictor)	• Bacterial conjunctivitis
• Preauricular lymph-adenopathy	• Watery or serous discharge • Recent history of upper respiratory tract infection	• Viral conjunctivitis
• Larger cobblestone papillae under upper eyelid • Eye lid swelling	• Bilateral eye involvement • Intense itching • Ropy discharge	• Allergic conjunctivitis
• Lid vesicles • Decreased vision	• Painful red eye • Photophobia	• Herpes simplex virus keratitis
• Dandruff-like flakes on eyelashes • Missing eyelashes • Swollen lids	• Red, irritated eye • Worse in morning • Itchy crusted eyelids	• Blepharitis
• Corneal edema or haze • Blepharospasm • Profuse watering	• Unilateral foreign body sensation • Inability to open eyes • Profuse watering • Recent history of trauma (fingernail, paper)	• Corneal abrasions

- Is there a personal or family history of atopy, asthma, or eczema?
- Does the child were any contact lens?
- Is there any history of ocular surgery?

During examination, do not forget:

- To evert eyelids
- To examine periorbital skin for any lesions
- To palpate preauricular lymph nodes.

CONJUNCTIVITIS

It is a nonspecific term that means inflammation of the conjunctiva causing hyperemia, general discomfort, and other symptoms. A diverse range of etiologies present in a similar manner that can be challenging to differentiate. Salient points of each variety of conjunctivitis has been provided in table 3.

Bacterial Conjunctivitis

- Might be briefly unilateral, but usually becomes bilateral
- Red, sticky, gritty eyes with purulent discharge, but no pain/photophobia
- Family members are often affected (very contagious)

TABLE 3: Comparison of bacterial and viral conjunctivitis

Parameters	Bacterial	Viral
• Common organisms	• *Haemophilus influenzae* • *Streptococcus pneumoniae* • *Moraxella Catarrhalis* • *Neisseria gonorrhoeae* • *Chlamydia trachomatis*	• Adenovirus type 8 and 19 • Herpes simplex virus
Incubation period	24–72 h	1–14 days
Prevalent age group	Neonates to toddlers	School age to adults
Symptoms		
Photophobia	Mild	Moderate-to-severe
Blurred vision	Common due to discharge	Only if keratitis present
Foreign body sensation	Unusual	Yes
Signs		
Discharge	Purulent	Watery
Palpebral reaction	Papillary response	Follicular response
Preauricular	Unusual	Common
Chemosis	Moderate	Mild
Subconjunctival hemorrhage	Only with Haemophilus	Frequent
• Associated disorders	• Otitis media	• Pharyngitis • Upper respiratory tract infection
• End of contagious period	• 24 h after start of treatment	• 7 days after onset of symptoms

- Examination reveals diffuse conjunctival congestion, matted eyelashes, and normal visual acuity
- Treatment includes topical antibiotics 2 hourly for 2 days and four times a day for a week
- Refer if:
  - Decreased vision, photophobia, or pain at any stage
  - Does not improve in 2 weeks.

Clinical Pearl

- Otitis media associated with conjunctivitis is most frequently caused by nontypeable *Haemophilus influenzae* and occasionally by *Streptococcus pneumoniae* and by other bacteria.

Viral Conjunctivitis

- Involvement can be unilateral or bilateral
- Often history of recent URI

- Examination reveals diffuse conjunctival congestion with watering, follicular reactor on lid eversion, normal visual acuity, and preauricular lymphadenopathy
- Usually a self-limiting condition, but topical antibiotics an rarely necessary because secondary infection is uncommon
- Give conservative treatment, like cold compression and lubricating eye drops
- The disease is highly contagious and usually resolves spontaneously in 2 weeks.

Allergic Conjunctivitis

- Often associated with atopic diseases, like allergic rhinitis, eczema, and asthma
- Itching of the eyes is the most predominant symptom This can be seasonal, i.e., worse in spring season or chronic (associated with asthma, eczema, etc.)
- Watery or mucoid discharge which is usually not copious
- Examination of eyes reveals diffuse redness in the eyes with severe papillary reaction, especially under the upper eyelids
- Treatment includes avoiding exposure to possible allergens, topical mast-cell stabilizes like cromoglycate eye drops and lubricating eye drops
- Steroid eye drops should only be commenced under ophthalmic supervision if distressing symptoms persist.

BLEPHARITIS

- Chronic inflammatory condition of eyelid margins
- Usually associated with seborrhea of scalp (dandruff) or can be due to chronic staphylococcal infection of the lid margin by coagulase positive strains
- Children present with complaints of deposition of whitish material at lid margins associated with irritation, redness, and occasionally watering. There is a history of falling of eye eyelashes
- Treatment involves eyelid hygiene (cleansing with diluted baby shampoo), gentle lid massage, and water compresses. Associated seborrhea of the scalp should be adequately treated.

SUBCONJUNCTIVAL HEMORRHAGE

- Spontaneous appearance of bright red blood between the sclera and conjunctiva
- Often looks very dramatic and is worrisome to the patients, but is most of the times trivial
- It can occur spontaneously (without any evident cause) or may be associated with:
  - Severe coughing or straining
  - Enteroviral conjunctivitis
  - Trauma
  - Bleeding disorders like purpura, hemophilia, and scurvy
  - Bleeding dyscrasias like anemia and leukemia, etc.
  - Acute febrile systemic infections like malaria, typhoid, diphtheria, meningococcal septicemia, measles, and scarlet fever
- Condition is often noticed incidentally and is asymptomatic
- Reassure the parents about the benign return of the disease and that it could take 2 or more weeks for the redness to resolve
- Refer if recurrent, persistent or severe.

CORNEAL ABRASION

- Any break in the corneal surface is known as corneal abrasion
- The patient present with painful red eye with swollen eyelids, excessive watering, and blepharospasm
- It can be associated with a corneal foreign body
- The other eye is usually normal
- Treatment includes topical antibiotics and frequent instillation of artificial tears eye drops
- Referral to ophthalmologist is indicated if symptoms worsen or do not resolve within 48 hours
- Studies show that eye patches do not improve patient comfort or healing of corneal abrasions.

Clinical Pearl

- In patients with corneal abrasion, it is good practice to check for retained foreign body under the upper eyelid.

RED EYE IN A NEWBORN

- Red eye in a newborn can be an alarming sign to the pediatricians as well as parents
- The common causes could be:
  - Ophthalmia neonatorum (neonatal conjunctivitis)
  - Birth trauma: corneal injury during forceps delivery
  - Subconjunctival hemorrhage
  - Nasolacrimal duct obstruction/dacryocystitis

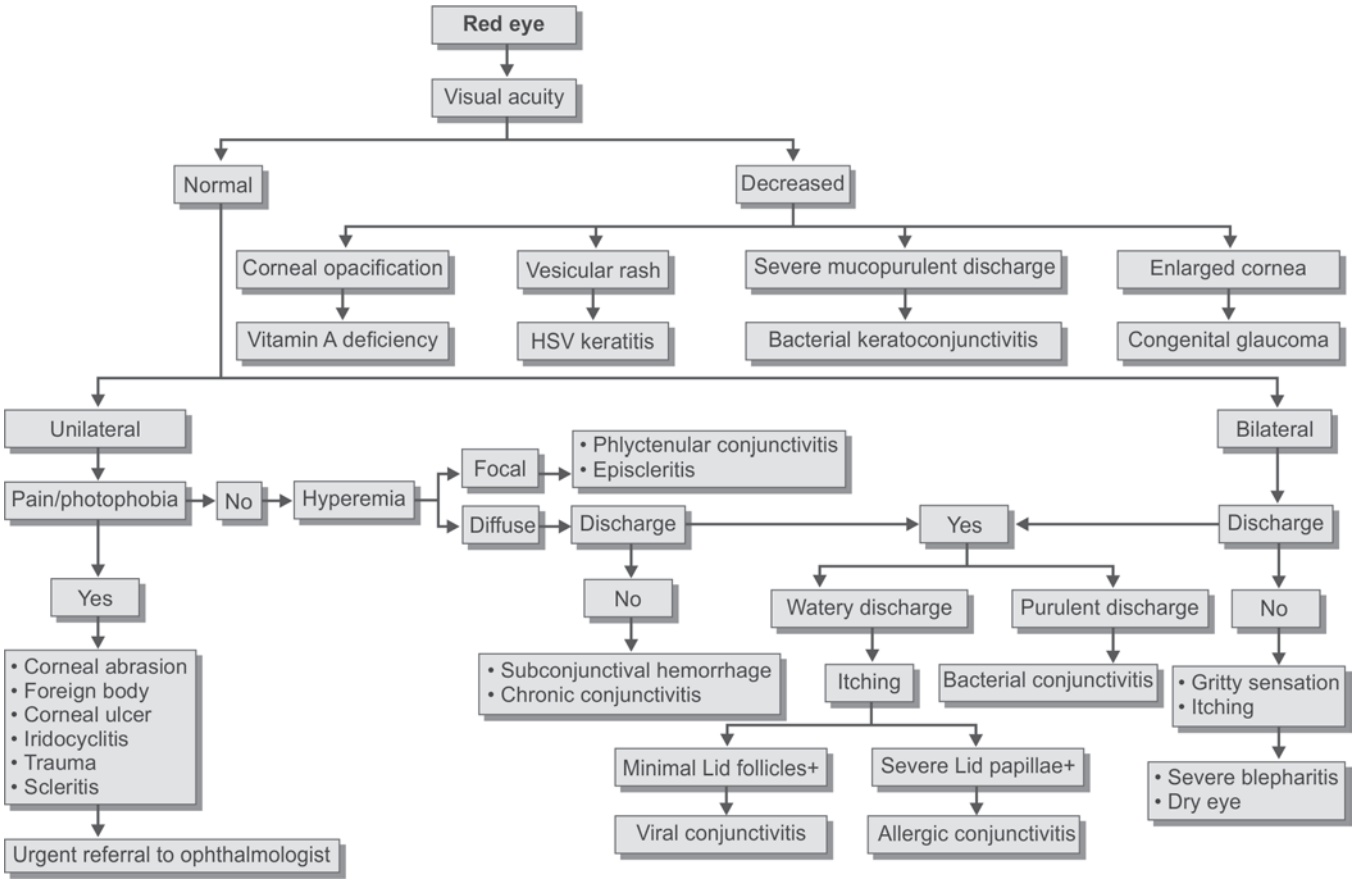
Ophthalmia Neonatorum (Neonatal Conjunctivitis)

It is an extremely common form of conjunctivitis in the first month of life and is the most common infection in the neonatal period. The cause of neonatal conjunctivitis is difficult to determine because the signs and symptoms do not vary by cause. The timing and presentation of neonatal conjunctivitis is very useful in identifying the cause. In order of occurrence, the common causes of neonatal conjunctivitis include: chemical, bacterial, and viral.

- Chemical conjunctivitis: It occurs within first 24 hours of life:
  - Watery discharge with mild redness of the eye
  - Minimal swelling of eyelids
  - Symptoms last for only 24–36 hours
- Gonococcal conjunctivitis:
  - Caused by *Neisseria gonorrhoeae*

ALGORITHM 1

Approach to red eye in children



HSV, herpes simplex virus.

- Newborn can be infected from the mother during passage through birth canal
- Presents typically 1–7 days after birth with sudden onset, severe, grossly purulent conjunctivitis
- This can be very serious and can cause:
  - Bilateral severe infectious corneal ulcers resulting in perforation of cornea and bilateral blindness
  - Bloodstream spread with fatal meningitis or encephalitis
- Needs intravenous antibiotics

- Chlamydial conjunctivitis
  - Less common than gonococcal, but can be serious
  - Presents at 2 weeks of age
  - Discharge can be variable: watery/purulent
  - Associated with chlamydial lung infection
  - Needs systemic antibiotics
- Herpes simplex viral conjunctivitis:
  - Accounts for less than 1% cases with neonatal conjunctivitis
  - Usually clear discharge with lid swelling
  - Mostly due to herpes simplex virus 2
  - Can be associated with photophobia, in case cornea is involved
  - Intravenous antivirals are indicated as it can be associated with severe systemic infection.

CONCLUSION

With careful questioning and thorough examination, pediatricians can accurately differentiate among the various causes of red eye in children and address the common benign conditions. All newborns with conjunctivitis in first week of life should be evaluated with Gram staining and culture and if Gram-negative diplococci are seen, should be treated with systemic antibiotics. Older infants and toddlers usually have bacterial conjunctivitis associated with otitis media. So, their ears need to be evaluated for otitis and if present, should be treated with oral antibiotics. Viral conjunctivitis mostly affects older children or adolescents and is associated with pharyngitis and preauricular lymphadenopathy. It is a self-limiting disease and requires only conservative treatment. Allergic conjunctivitis is marked by presence of

intense itching with associated rhinitis, asthma, or eczema. It is treated with antihistamines, decongestants, and mast-cell stabilizers. Referral to an ophthalmologist is necessary if child has visual loss, pain, copious purulent discharge, or corneal involvement.

KEY POINTS

- ☞ All cases of red eye with decreased vision, pain or photophobia require urgent referral
- ☞ Not every red eye is due to conjunctivitis. Look for other causes
- ☞ Never prescribe steroid eye drops unless asked by an ophthalmologist
- ☞ A newborn baby with red eyes and eye discharge has sight and life-threatening infections and require urgent referral.

SUGGESTED READINGS

1. Bielory L, Friedlaender MH. Allergic conjunctivitis. Immunol Allergy Clin North Am. 2008;28(1):43-58.
2. Hammersmith KM, Cohen EJ, Blake TD, Laibson PR, Rapuano CJ. Blepharoconjunctivitis in children. Arch Ophthalmol. 2005;123(12):1667-70.
3. Kleigman RM, Mar KJ, Jenson HB, Behrman RE. Nelson Essentials of Pediatrics, 5th ed. Philadelphia, PA, USA: Elsevier-Saunders; 2006.
4. Morrow GL, Abbott RL. Conjunctivitis. Am Fam Physician. 1998;57(4):735-46.
5. Teoh DL, Reynolds S. (2003). Diagnosis and management of pediatric conjunctivitis. [online] Available from www.fmed.ulaval.ca/pediatrie/fileadmin/docs/serveur_pediatrie/Acces_reserve/Medecins/Articles_scientifiques/recueil/Conjunctivitis.pdf. [Accessed November, 2015].
6. Turner A, Rabiu M. Patching for corneal abrasion. Cochrane Database Syst Rev. 2006;(2):CD004764.
7. Wirbelauer C. Management of red eye for the primary care physician. Am J Med. 2006;119(4):302-6.

CHAPTER 141

Compensatory Head Posture

Manav D Singh

INTRODUCTION

Compensatory or abnormal head posture (AHP) is not an uncommon condition in childhood with estimated incidence of 1.3%. Mostly congenital, it may be an acquired finding. Although it may be also of orthopedic or neurologic in origin, our focus will be the one of ocular origin (Box 1).

Box 1: Origin of abnormal head posture

- Orthopedic
- Ocular
- Neurologic

In the process of evolution, humans have acquired binocular vision with the aim to provide stereopsis or depth perception or simply accurate assessment of distance. There are three levels of binocular vision; viz.

1. Simultaneous perception (SP)
2. Fusion
3. Stereopsis.

In general, SP is essential for fusion and fusion is essential for stereopsis. The neuromuscular system of head and neck tries to compensate for certain abnormalities of the ocular motor system (which may be primary or secondary to sensory visual problems) in an effort to achieve single binocular vision, to avoid diplopia, or sometimes to achieve clear vision. This results in AHP.

Clinical Pearl

- Head posture is an adaptation of head and neck musculature to avoid diplopia and attain fusion and is mostly seen in congenital disorders.

COMPONENTS OF HEAD POSTURE

Observation of head posture is the first step in the examination of ophthalmic motor system. This should be done as soon as the patient enters the examination room before he becomes conscious of being examined. Compensatory head posture may be partially or totally lost by voluntary effort and lots of information may, thus, be lost. The abnormal head posture has three components (Box 2).

Box 2: Components of abnormal head posture

- Chin: elevation or depression (vertical component)
- Face turn: to right or left (horizontal component)
- Head tilt: to right or left shoulder (torsional component)

Each of them is compensation at different joints of head and neck to correct respective ocular motility disorders in an effort to achieve fusion by minimizing deviation. If the deviation is too large to develop any level of fusion, no effort may be made for the purpose and no AHP may develop. If unable to fuse, head posture may also develop to provide maximal deviation in an effort to suppress or ignore the peripheral image to avoid diplopia. It is also possible to develop AHP to permit fusion based on anomalous retinal correspondence (ARC). Occasionally, a patient with very poor vision in one eye may develop face turn in the direction of non-seeing eye in order to improve field of vision (Fig. 1) or to bring null point in straight gaze if he suffers from nystagmus (Fig. 2).

INTERPRETATION OF HEAD POSTURE

- Face turn:
  - *To right*: keeps eyes in levoversion to avoid manifestation of weakness of right superior rectus, right inferior rectus, left inferior oblique, and left superior oblique
  - *To left*: keeps eyes in dextroversion to avoid manifestation of weakness of right interior oblique, right superior oblique (RSO), left inferior rectus, and left superior rectus

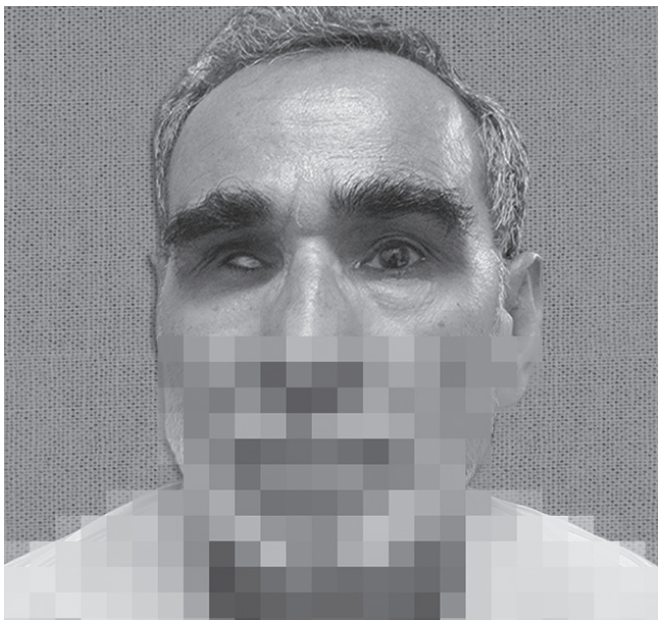


Fig. 1: Patient with phthisis bulbi of right eye showing face turn to right

- Head tilt:
  - *To right*: is a compensation for weakness of extorsion of right eye or/and intorsion of left eye
  - *To left*: is a compensation for weakness of intorsion of right eye or/and extorsion of left eye
- Chin: Elevation/depression:
  - *Up*: to compensate elevator weakness
  - *Down*: to compensate depressor weakness.

SENSORY AND MOTOR FUSION

It is instinctual to have clear view of any object lying in the field of vision. Therefore, once an object enters field of vision, eyes turn in a way so that its image lies on to fovea. Farther is the stimulated retinal element located from the fovea, higher is the incentive for the eye to move or higher is the retinomotor value of that retinal element. Not to mention, retinomotor value of fovea is zero. Two eyes of the same person have retinal elements that share common subjective visual directions. These are called corresponding retinal points. This sensory correspondence explains sensory fusion and is the essence of binocular vision. Alignment of eyes in a way that sensory fusion can be maintained is called motor fusion. The stimulus

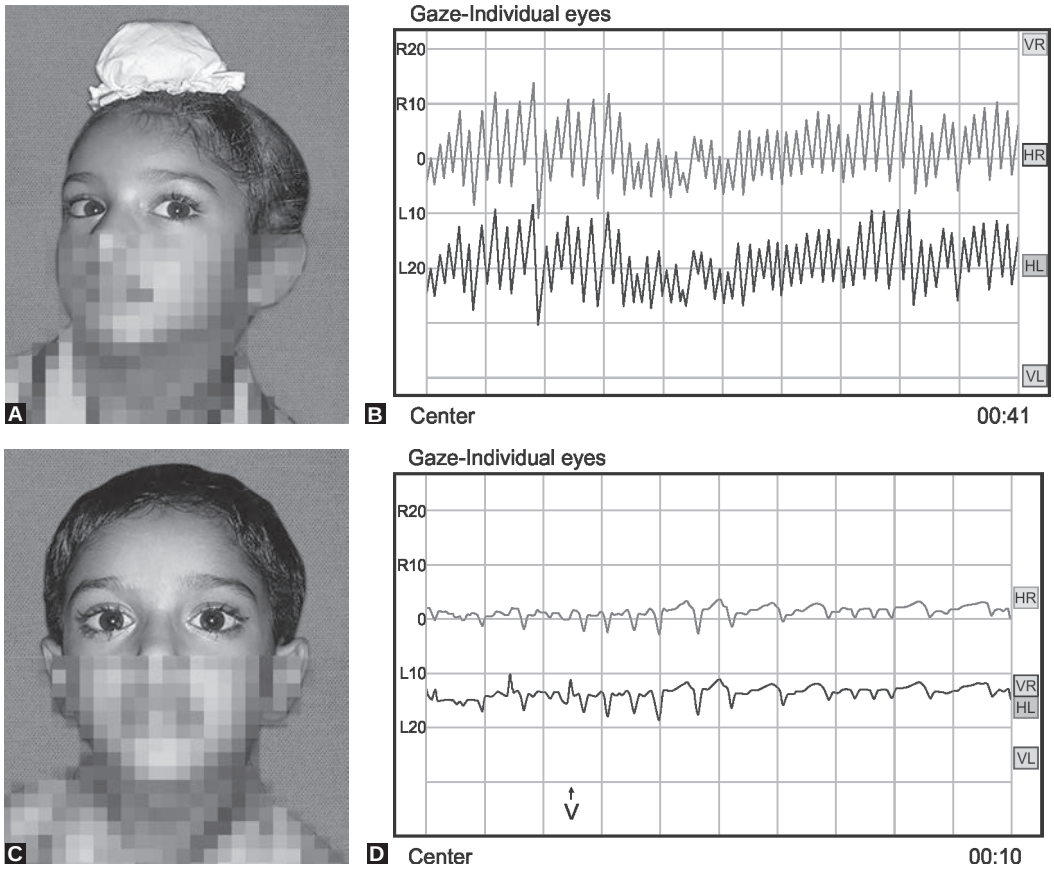


Fig. 2: Congenital pendular nystagmus with null point in levoversion showing: **A,** Face turn to right; **B,** Preoperative electronystagmogragh (ENG); **C,** Postoperative head posture and **D,** Postoperative ENG in primary gaze

Courtesy: Rohit Saxena.

for sensory fusion is the excitation of corresponding retinal elements and that of motor fusion is retinal disparity. However, the ultimate goal of all this is to achieve stereopsis. At retinal element level, it can be said that stereoscopic vision is the result of simultaneous stimulation of horizontally disparate retinal elements. The fusion of these (only horizontally not vertically) disparate images gives rise to a visual impression perceived in depth.

The Association of Sensory and Motor Visual System

The sensory visual system which consists of retinocerebral apparatus assisted by optico-refractory system of eye has the primary function of collection of information about the outside world. However, the visual motor system is entirely in the service of visual sensory system. Since motor system has no independent existence, it adapts itself to assist a malfunctioning sensory system in a way to get the best results in the form of binocular single and distinct vision at all points of time. The musculature of head and neck region may further assist the oculomotor system to achieve the same goal. Abnormal head posture is only one of such adaptations to regain this remarkable feature of binocular single vision inherent in human visual system which helps us to achieve the function of stereopsis.

Clinical Pearl

- Ocular motor system has no independent existence and adapts itself exclusively in the service of sensory visual system.

CONFUSION, DIPLOPIA, AND SUPPRESSION

In the presence of manifest deviation of eyes, images of all objects in binocular field of vision are shifted from corresponding retinal elements. Thus, images of different objects are formed on foveae of two eyes leading to a phenomenon called "confusion". At the same time, image of identical object is formed on noncorresponding retinal elements of two eyes leading to diplopia. To avoid them, the growing visual system in children has two mechanisms to develop, viz., "suppression" (more common) in which poor quality image is ignored by the retinocerebral system and ARC in which disparate retinal elements acquire the function of corresponding retinal elements. Diplopia is the most repugnant sensation and the oculomotor system makes every effort to avoid this. In congenital and early childhood extraocular muscle paralysis, suppression will generally ensue if head posture fails to develop fusion.

Clinical Pearls

- Diplopia is the most repugnant sensation
- In childhood abnormalities, if head posture fails to develop fusion, diplopia will invariably be eradicated by suppression or anomalous retinal correspondence (ARC)
- Suppression, amblyopia, and ARC are general features of concomitant squint. However, they can develop in congenital or early childhood paralytic squint as well.

CAUSES OF ABNORMAL HEAD POSTURE

The cause of the AHP can be ocular, orthopedic, and neurologic. The orthopedic causes of AHP include congenital tightness of the sternocleidomastoid (SCM) muscle, Klippel-Feil anomaly, and brachial-plexus injury. Neurologic causes of AHP are mainly related to brain tumors, postinflammatory central nervous system conditions, psychomotor delay, and focal dystonia. However, only ocular causes will be discussed in detail.

Incomitant Squint

Paralytic or restrictive musculofascial anomalies can lead to abnormal head posture. Most patients with paralytic strabismus habitually hold their head in a position so as to avoid the field of action of paretic muscle. Diplopia is, thus, eliminated and binocular single vision attained. A classical example is congenital superior oblique (SO) palsy (ocular torticollis) in which patient maintains binocular vision with the help of compensatory head posture. In case of RSO palsy (Fig. 3), the child will have chin depression, face turn to left, and head tilt to left shoulder. The head posture ensures that the paretic muscle is always in the state of relaxation. Position of head is then so adjusted that the visual axes are directed straightforwards. Thus, in case of RSO palsy, with its main action as depression, chin depression develops and its secondary action as intorsion, head tilt towards opposite shoulder develops. Face turn towards left brings the eye in abduction, so that vertical movements can be executed exclusively by vertical rectii. Causes of ocular head posture are given in table 1.

It is important to distinguish, especially from pediatrician's point of view, between congenital and ocular torticollis

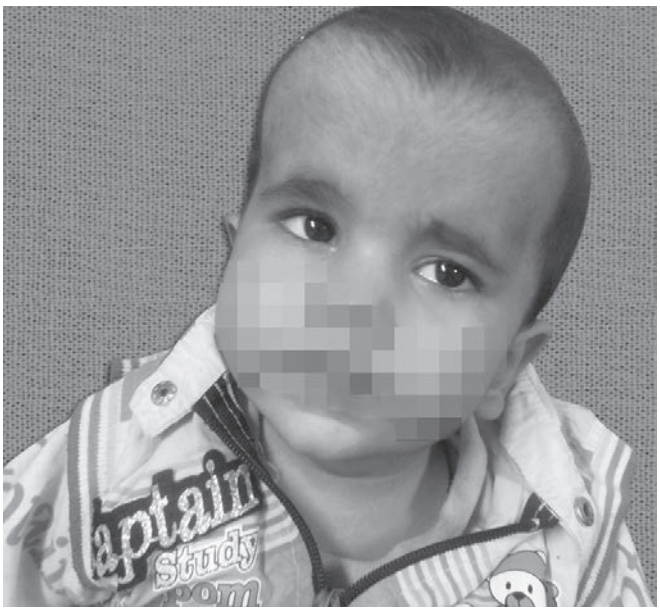


Fig. 3: A child with right superior oblique palsy showing marked head tilt to left, mild face turn to left, and minimal chin depression.
Courtesy: Dr Zia Chaudhury

TABLE 1: Differential diagnosis of ocular head posture

Face turn	• Sixth nerve palsy [the face is turned to the side of the paralyzed eye to maintain binocular single vision (Fig. 4)] • Duane syndrome • Congenital nystagmus (face turn may put the eyes in a particular position which reduces the nystagmus and increases the visual acuity)
Head tilt	• Fourth nerve palsy or superior oblique muscle weakness of whatever cause • Inferior oblique palsy (the face is turned to the uninvolved side with the head tilting to the affected side and the chin is elevated. Uncommon clinical case) • Superior rectus palsy (uncommon case; the tilt can be to either side) • Inferior rectus palsy (uncommon case; the tilt can be to either side) • Brown's syndrome (head tilt to the involved side, face turn to the normal side and chin elevation) • Dissociated vertical deviation (can be to either side)
Chin elevation	• A-pattern esotropia • V-pattern exotropia • Ptosis • Blow-out fracture with entrapment of inferior rectus • Brown's syndrome (bilateral case)
Chin depression	• V-pattern esotropia • A-pattern exotropia • Bilateral fourth nerve palsy

TABLE 2: Differences between congenital and ocular torticollis

Feature	Congenital torticollis	Ocular torticollis
Age at onset	<6 months	>18 months
Restriction of passive movements	Present	Absent
Hardening of sternocleidomastoid muscle	Present	Absent
Visual disturbances	None	Diplopia on straightening or tilting of head to opposite side
Influence of occlusion	No effect of occlusion	None if normal eye occluded. Head straightens if eye with paretic muscle occluded unless secondary skeletal changes developed

(Table 2). Former is caused by malformation of cervical vertebrae or fibrosis of SCM muscle, usually secondary to birth trauma and later by congenital SO palsy. In case of congenital torticollis, torticollis sets in within 6 months of age, passive straightening of head is difficult, palpation may suggest hardening of SCM muscle, no visual disturbances are present and torticollis is not influenced by occlusion of either eye.

Fig. 4: Adult showing acquired left lateral palsy with face turn to left
Courtesy: Dr Zia Chaudhury.

Ocular torticollis, caused by SO palsy, on the other hand develops later; the head can be moved easily passively or by voluntary effort of the patient and SCM muscle if soft like in any normal human being. However, if an effort is made to correct the head posture, diplopia generally ensues. If eye with paretic muscle is occluded, head will straighten by itself unless some secondary skeletal changes have developed over a period of time.

Incomitance in Concomitant Squint (A or V Phenomenon)

Vertical incomitance is not uncommon in horizontal concomitant deviations (eso- or exotropias). Here, strabismus is comitant in primary gaze, but becomes incomitant in up or down gaze or both. They are called A or V patterns. The characters of common errors are given in table 3.

In these cases, dysfunction of oblique muscles is the most common clinical finding and treatment is based on clinical findings.

Nystagmus

Nystagmus is a regular, rhythmic, to and fro movement of eyes. Two common types of nystagmus are pendular and jerk nystagmus. Pendular is smooth sinusoidal oscillations

TABLE 3: Characters of common errors

Pattern	Deviation
A - Exotropia	Exodeviation more in downgaze, less in upgaze
V - Exotropia	Exodeviation more in upgaze, less in downgaze
A - Esotropia	Esodeviation less in downgaze, more in upgaze
V - Esotropia	Esodeviation less in upgaze, more in downgaze

(commonly due to sensory deprivation) whereas jerk nystagmus has a slow and a fast component. Although fast component is conventionally labeled as the direction of nystagmus, the fact is that the primary abnormality causes slow drift and fast component is the corrective movement. In case of jerk nystagmus, there may be a gaze, where it cannot be elicited. This is called the null zone. Cases of nystagmus that have a null point may have a head posture which can have any of the three component(s) of head posture (Fig. 2).

Clinical Pearls

- Head posture is present only in jerk nystagmus with null point
- The purpose of head posture is to bring null point in straight gaze for clear vision
- It is the congenital motor nystagmus that responds best to surgery.

The surgical correction mainly involves shifting of null point to primary gaze with the hope that it will lead to correction of head posture. Workup of a case of abnormal head posture is given in algorithm 1.

Other Causes

Some uncommon/atypical causes of AHP may also be seen in clinical situations:

- Ptosis, especially if bilateral, may lead to chin elevation to minimize restriction of superior field of vision
- One eyed persons (Fig. 1) or those with homonymous hemianopia (Fig. 5) may assume a head posture to center their gaze to the available field
- Strabismus fixus is an extremely large esotropic deviation of both eyes seen in patients with maximum contracture of medial rectus (MR) muscles secondary to replacement by fibrous tissue. A rarer variety may have fibrous band replacing lateral rectii leading to anchorage of both eyes in abduction (Fig. 6A). Patient may adopt a head posture to center his/her gaze through the better seeing eye (Fig. 6B)
- Undercorrected glasses may result in head posture in an effort to take advantage of higher effective power in peripheral part of the lens
- Ocular/systemic syndromes like Brown's (SO tendon sheath) syndrome or Duane syndrome, Mobius syndrome, progressive external ophthalmoplegia (alone or as part of Kearns-Sayre syndrome) may also lead to AHP
- Orthopedic and neurologic causes more than what has already been mentioned are beyond the scope of this chapter.

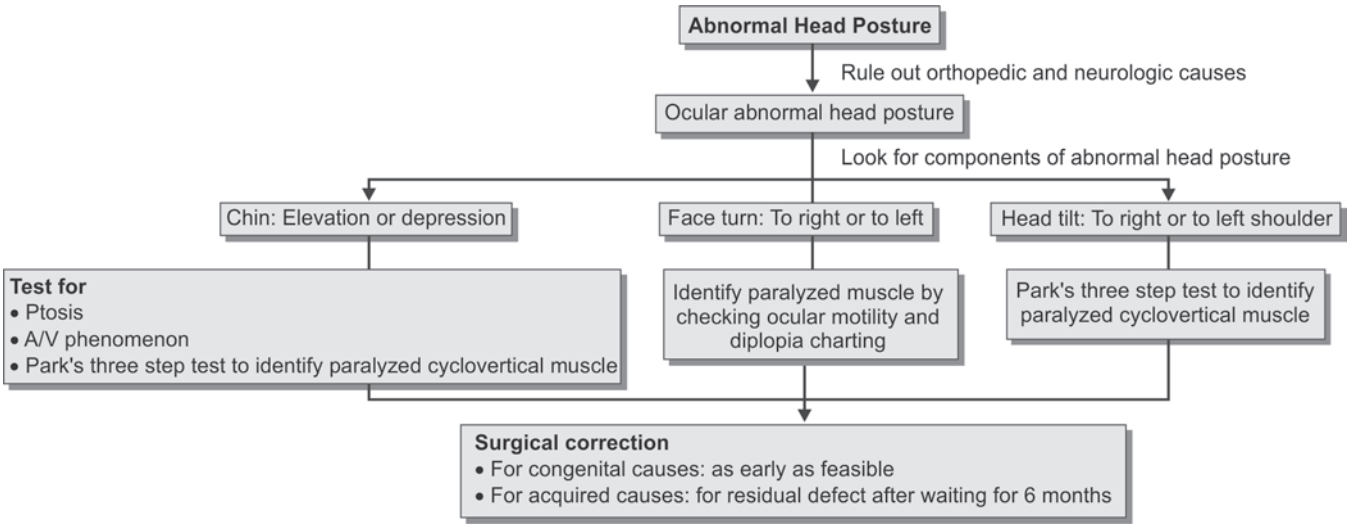
HISTORY AND EXAMINATION

History starts with age of patient at time onset of head posture, whether congenital or acquired. Sometimes, parents may have noticed it much later than its actual appearance. This can be confirmed by a careful scrutiny of family photographs. Associated visual disturbances, refractive errors, ocular motility disturbances, presence of diplopia at present or in past, abnormal movements of eyeballs, problems of movement of head and neck region are all very important to find out the cause and plan management. History of neurological symptoms like headache, vomiting, convulsions, or of infections like meningitis and encephalitis are also important in relevant cases.

Assessment of head posture is the first step in any ophthalmic examination and especially so in a squint clinic. It is prudent to start this examination as soon as patient enters examiners room and certainly before the child becomes conscious of the fact that he is being examined. Examiner should not only look for components of head posture, but also do a comprehensive eye examination. Visual acuity, refractive status, presence of any amblyopia, squint, restriction of ocular motility in any of the nine directions of gaze, difference in

ALGORITHM 1

Workup of a case with abnormal head posture



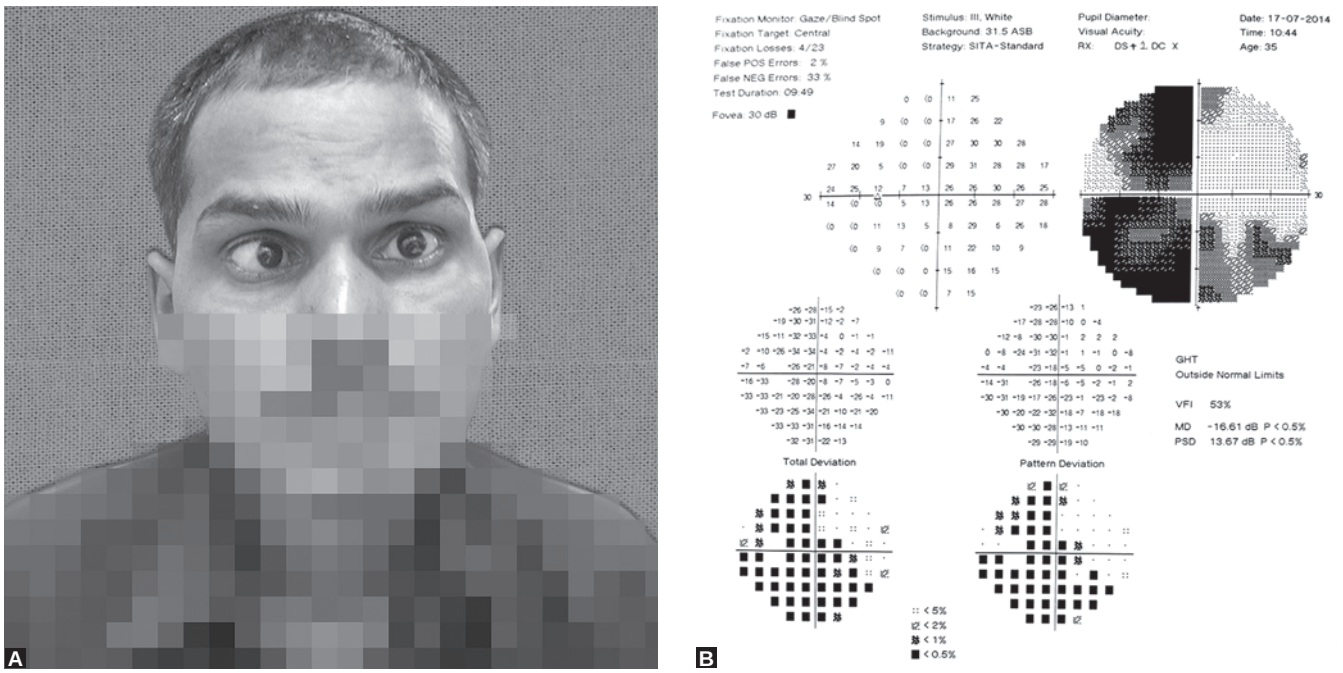


Fig. 5: **A,** 34-year-old male with sellar tumor and right lateral rectus (RLR) palsy and face turn to left. Cause of face turn is not RLR palsy as this eye is blind but is hemianopic visual field defect of left eye; **B,** visual field of left eye showing temporal hemianopia.

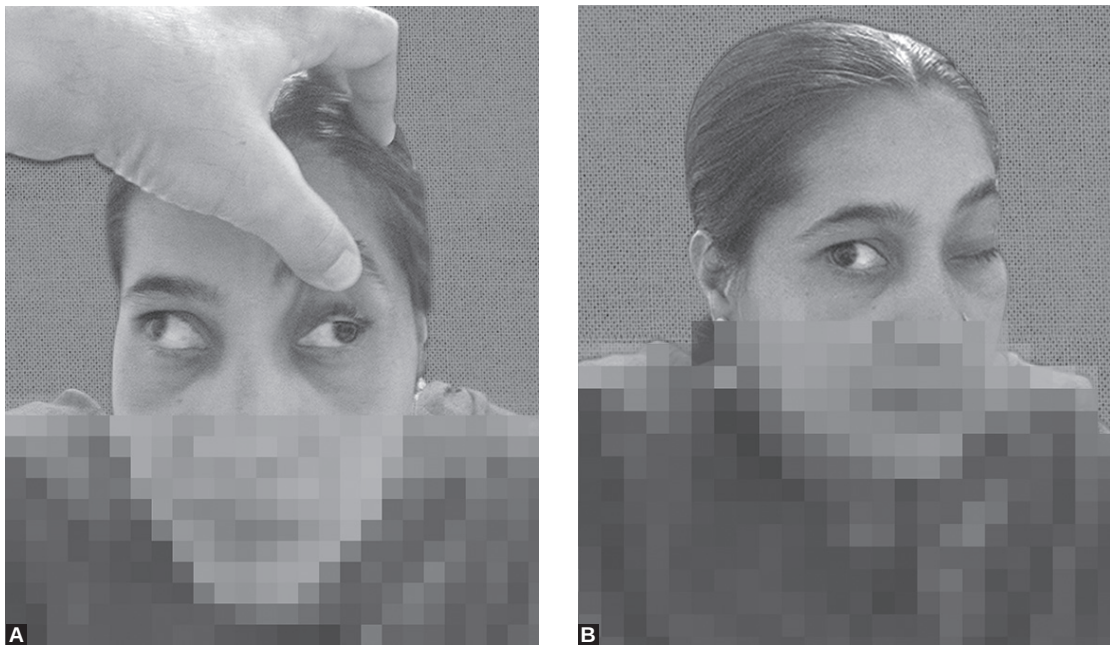


Fig. 6: **A,** A rare variety of strabismus fixus with both eyes anchored in abduction in a young lady; **B,** showing face turn towards left to get best possible vision in the central field.

ocular deviation in different directions of gaze and while separately fixing each eye, presence of nystagmus, effect of occlusion of individual eye on the head posture need to be assessed. Diagnosing horizontal muscle palsy is, generally, not difficult. However, diagnosis of isolated cyclovertical muscle paresis, e.g., trochlear nerve paresis requires three-step evaluation, viz., side of hyperopia, side of gaze in which vertical deviation increases, and then tilting the head towards shoulders and observing on which side the vertical deviation increases. Patient maintains a head posture of head tilt with least disparity, the disparity increases if head is forced towards the shoulder on the side of the paretic SO (Bielschowsky sign). Assessment for restriction of passive movements of neck and hardness in SCM muscle is very essential to exclude nonocular causes of head posture (Algorithm 1). Forced duction test is invaluable in cases of suspected restrictive problem. One may

refer to any standard book on squint for details of methods of examination. Examination of nervous system, especially of cranial nerves, may be very informative in relevant cases.

INVESTIGATIONS

Apart from specific ophthalmic investigations like Hess's (or Lee's) charting, imaging of brain using computed tomography (CT) or magnetic resonance imaging (MRI) scan may be required, especially in acquired cases to find out the cause or to plan the treatment. Certain electrophysiological investigations like electromyography and electronystagmography (Fig. 2) may be invaluable in the management of certain case, and also from academic point of view.

MANAGEMENT

Management depends on age at presentation and cause. Among congenital conditions, although no treatment is warranted in certain cases, early treatment may be indicated in others before permanent secondary skeletal changes get established. However, in acquired cases, generally, a 6-month waiting period is given for the system to heal by itself (Algorithm 1). However, nonsurgical treatment like prisms or occlusion may be temporarily prescribed to give relief to the patient from intractable diplopia. Indications of therapy are diplopia in the practical field of fixation and inability to maintain fusion without cosmetically acceptable head posture.

Nonsurgical Treatment

Correction of refractive error and amblyopia should be done in all cases. Prisms (in small ocular deviations) and occlusion may be indicated to avoid diplopia during acute phase or while waiting for surgery. Prisms are usually effective in correcting diplopia up to a deviation of 10 prism diopter. Chemodenervation with botulinum toxin may be helpful in cases of acute horizontal muscle paralysis, in dissociated vertical deviations, and as postsurgical adjunct.

Surgical Treatment

The aim of treatment is to develop single binocular vision or provide clear vision without the presence of AHP. Type of preferred surgical technique depends on the cause and duration of problem.

Paralytic Squint

In paralytic squint, general principle is to wait for 6 months for natural recovery and then to weaken the antagonist and to minimize innervations to the paretic muscle. Strengthening operations for paretic muscle are less effective. In case of paralysis of sixth nerve, surgery will generally consist of MR recession and lateral rectus (LR) resection or transposition of vertical rectii lateral along with weakening of MR. Congenital superior rectus palsy with significant head posture should undergo surgery, as soon as diagnosis is confirmed, to prevent permanent torticollis, facial asymmetry, and scoliosis. For acquired fourth nerve paresis, after ruling out underlying disease and waiting for spontaneous recovery, recession of antagonist muscle or weakening of yoke muscle of paralyzed muscle may be done depending on presence or absence of contraction of antagonist. In congenital third nerve palsy, surgery is required for exotropia, hypotropia, and ptosis. Bell's phenomenon should be evaluated as there is significant risk of exposure keratitis following surgery. Acquired third nerve palsy is in children, is generally because of trauma, infections, tumors, aneurysm, or migraine. Treatment is of underlying cause. Residual diplopia and/or ptosis may require surgical correction depending on individual situation as the palsy is generally incomplete.

A and V Phenomenon

In cases with oblique over action, oblique muscles should be weakened (inferior oblique for V patterns and SO for A patterns) in addition to recession resection of horizontal rectii. However, in the absence of this feature, 5–8 mm of vertical transposition of horizontal rectii combined with their recession-resection may suffice. For the correction of A patterns, MR is shifted up and LR is shifted down. The opposite is done for patients with V patterns.

Nystagmus

Surgery for nystagmus is based on three principles, viz.,:

1. To shift null point to primary position (Fig. 2)
2. To induce extra convergence innervations by weakening medial recti
3. To reduce muscle force by weakening all rectii to dampen amplitude of nystagmus.

Other Causes

Ptosis is generally corrected by resection of levator palpebrae superioris (LPS) muscle or by sling surgery. The choice of operation is generally dependent on amount of ptosis, LPS action present, Bell's phenomenon, and associated features. Causes of head posture other than these are treated by surgical/nonsurgical methods from case-to-case basis.

ACKNOWLEDGEMENT

The author would like to thank Dr Rohit Saxena, additional professor at AIIMS and Dr Zia Chaudhury, professor at Lady Hardinge Medical College, for providing me some photographs and Dr Shashi Vashisht for her constant encouragement.

SUGGESTED READINGS

1. Bagolini B, Campos EC, Chiesi C. Plagiocephaly causing superior oblique deficiency and ocular torticollis. A new clinical entity. Arch Ophthalmol.1982;100(7):1093-6.
2. Pavan-Lagston D. Manual of ocular diagnosis and therapy. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
3. Nucci P, Curiel B. Abnormal head posture due to ocular problems: a review. Curr Pediatr Rev. 2009;5(2):105.
4. Nucci P, Kushner BJ, Serafino M, Orzalezi N. A multi-disciplinary study of the ocular, orthopedic, and neurologic causes of abnormal head postures in children. Am J Ophthalmol. 2005;140(1):65-8.
5. Von Noorden GK. Binocular vision and ocular motility. 5th ed. St Louis: Mosby; 1996.

CHAPTER 142

Pediatric Epiphora

Shashi Vashisht

INTRODUCTION

Ocular surface is covered by a thin tear film which provides a smooth optical surface, keeps the ocular surface moist and plays an important role in the nutrition and protection of cornea. Overflow of tears leads to watering from the eyes.

Tear film consists of three layers:

1. Superficial lipid layer: derived from secretions of Meibomian, Zeiss, and Moll glands
2. Middle aqueous layer: secreted by lacrimal and accessory lacrimal glands
3. Deep mucus layer: secretions principally from conjunctival goblet cells.

THE OUTFLOW PATHWAY FOR TEARS

- Lacrimal puncta: a small oval opening near the inner canthus on upper and lower lids
- Lacrimal canaliculi: two superior and inferior lacrimal canaliculi extending from superior and inferior lacrimal puncta, respectively, to lacrimal sac. They are directed 2 mm vertically and 8 mm horizontally. Before entering into the lacrimal sac, they join and form a common canaliculus in majority of cases
- Lacrimal sac: it is located in lacrimal fossa in anterior part of medial orbital wall
- Nasolacrimal duct (NLD): it is a continuation of the lacrimal sac. It is about 18 mm long, directed downwards, backwards, and laterally and opens in the inferior meatus of nose.

DEVELOPMENT OF LACRIMAL DRAINAGE SYSTEM

The lacrimal drainage system is ectodermal in origin. The lacrimal sac develops as a solid cord of ectoderm which sends two columns to the lids which form the canaliculi. The solid cord descends down to form the NLD. This is met by a similar structure from the primitive nasal cord. This solid cord starts canalizing around 3 months of intrauterine life to form the NLD. It is generally canalized by birth or few weeks before. However, in some cases, ectodermal debris or a membrane may remain at the nasal end of the NLD resulting in congenital NLD block. Tear formation generally starts after second week of birth (Fig. 1).

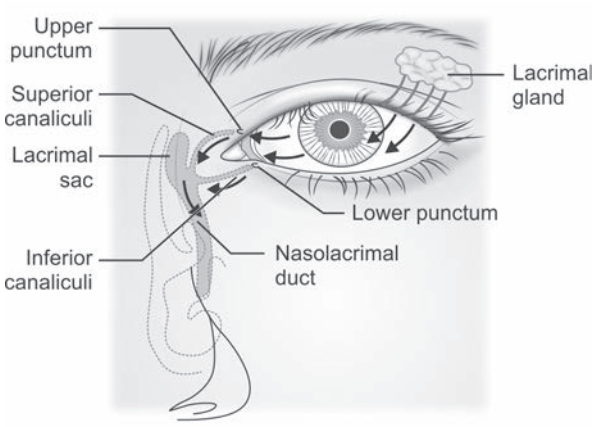


Fig. 1: Tear production and outflow pathway (lacrimal pathway)

CAUSES OF WATERING OF EYES IN RELATION TO LACRIMAL SYSTEM

Hyperlacrimation

There is increased secretion of tears due to any of the following causes:

- Primary: overproduction from lacrimal gland, which is rare
- Reflex: secondary to ocular inflammation or ocular surface disease (cornea and conjunctiva) due to stimulation of sensory branches of fifth nerve.

Epiphora

This is a condition that constitutes inadequate drainage of tears due to any of the following reasons:

- Physiological: lacrimal pump failure secondarily to lower lid laxity or weakness of orbicularis muscle
- Mechanical: obstruction in outflow pathway involving any of its components, i.e., punctum, canaliculus, lacrimal sac, or NLD. Treatment is discussed later. Causes and management of epiphora in infants and children are enlisted in table 1.

Infective Causes

Depending on the causative organism suspected antimicrobial/antiviral eye drops/ointment started under ophthalmic supervision.

TABLE 1: Causes and management of epiphora in infants and children

Causes	Management
Lacrimal drainage related • Agenesis or stenosis of punctum • Canalicular obstruction • Mucocele • Encysted mucocele • Nasolacrimal duct obstruction	• Surgical intervention • Conjunctivodacryocystorhinostomy • Dacryocystorhinostomy (DCR) • Dacryocystectomy • Discussed later
Lid related • Entropion, ectropion, coloboma	• Surgical intervention
Infections • Conjunctivitis (bacterial, viral, chlamydial), ophthalmia neonatorum	• Treat with appropriate antibiotics or antivirals
Allergic • Vernal keratoconjunctivitis	• Medical management
Refractive errors	• Good cycloplegic refraction
Corneal problems • Abrasions, keratitis	• Medical/surgical management
Foreign body	• Removal and medical management
Congenital or juvenile glaucoma • Child presents with watering, photophobia, and blepharospasm	• Ophthalmic referral
Other causes • Uveitis, episcleritis, scleritis, injuries. Some eye drops, like pilocarpine, echothiophate, and epinephrine, can cause watering	• Ophthalmic referral; treat the cause

Ophthalmia Neonatorum

Ophthalmia neonatorum (ON) is generally seen in the first week of birth. Any infection in the first month of a baby's life can be classified as ON. There is copious discharge, swollen lids, and watering without regurgitation. Conjunctival swab should be sent for Gram's stain and culture (Table 2).

Clinical Pearl

- Watering and discharge from eyes in first week after birth, diagnosis should be ophthalmia neonatorum.

Allergic Conjunctivitis

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) or spring catarrh is seen in children of 4–20 years of age. This condition is more common in boys than girls. It is an immunoglobulin E-mediated hypersensitivity reaction to exogenous allergens. Recurrent bilateral redness, itching, photophobia, and watering occur with onset of summer season. The term "spring catarrh" is a

TABLE 2: Ophthalmia neonatorum

Etiology	Causative factor	Incubation period	Treatment
Gonococcal	*Neisseria gonorrhoeae*	2–4 days	• Erythromycin eye ointment QID • Bacitracin eye ointment QID • Penicillin 10,000 IU/mL eye drops • Systemic therapy
Bacterial (other than gonococci)	• *Staphylococcus aureus* • *Streptococcus haemolyticus* • *Streptococcus pneumoniae* • *Pseudomonas aeruginosa*	2–5 days	• Antibiotic eye drops (depending on susceptibility)
Neonatal inclusion conjunctivitis	• *Chlamydia trachomatis* serotype D to K	5–14 days	• Tetracycline 1% eye ointment QID • Erythromycin eye ointment 0.5% QID • Systemic treatment
Herpes simplex	Herpes simplex II virus	5–7 days	Topical antiviral

misnomer. Condition subsides in cooler months. About 95% of cases undergo remission in late teens. Pharmacological treatment constitutes following:

- Mast cell stabilizers, e.g., sodium cromoglycate 2% eye drops
- Topical antihistaminics, e.g., olopatadine 0.1% eye drops
- Topical steroids eye drops give a quick relief, but their use should be minimized and monitored as indiscriminate use of steroids can lead to steroid-induced glaucoma
- Topical cyclosporine 1% eye drop.

Clinical Pearl

- In a child complaining of recurrent redness, itching, and watering in both the eyes with onset of summer season, most common cause is vernal keratoconjunctivitis.

WORKUP

History

Complete history should be taken including time of onset and duration of watering, unilateral/bilateral, any contributory cause, associated symptoms, seasonal variation, and previous treatment taken.

Clinical Examination with Torch light

- Examine the lacrimal sac area for fullness, redness, or fistula
- Regurgitation test: reflux of mucoid or mucopurulent material from the punctum on pressure over the lacrimal sac area suggests blocked NLD or mucocele
- Inspect lacrimal puncta for eversion or stenosis
- Examine eyelids for any skin lesions, entropion, ectropion, trichiasis, stye, blepharitis
- Examination of the conjunctiva for congestion, discharge, foreign body, tear, cyst, discoloration, chemosis, follicles, papillae (VKC), concretions, pterygium, pinguecula, tumors, or any other abnormality
- Further examination should be done by an ophthalmologist.

Features of Congenital Obstruction of Nasolacrimal Duct

- The lacrimal gland starts secreting around 2–3 weeks after birth. Therefore, effect of NLD block is not seen at birth. This is seen in around 4–8% of newborns. It is more common in premature children. It may be uni- or bilateral and has no sex predilection. A membranous block at the lower end of NLD (valve of Hasner) is common, as this portion of NLD is last to canalize. Spontaneous resolution usually occurs in 90% of cases in first year. Other causes could be stenosis of opening of NLD or a hypertrophied inferior nasal turbinate
- Watering with or without mucoid/mucopurulent discharge and/or matting of lashes is seen
- It may be constant or intermittent. Severity of signs and symptoms can vary with upper respiratory tract infection (URI), exposure to cold and wind. Pressure over the sac may result in positive regurgitation from the puncta. Gradually, secretions start stagnating in the sac and can give rise to recurrent infection. Chronic infection can lead to dacryocystitis and fistula formation
- Congenital block can involve any other part of the drainage system.

Clinical Pearl

- Blocked nasolacrimal duct is the most common cause of watering in infants.

Tests to Check for Nasolacrimal Duct Block

Sac Syringing

It is done to know patency of lacrimal drainage system. Under local/limited general anesthesia lower punctum is dilated with a punctum dilator. A blunt tipped lacrimal cannula on a 2 mL syringe filled with saline is inserted into lower punctum and canaliculus and the plunger is pushed slowly. Management is done as per observations after syringing.

Jones Dye Test

- Primary test: it is a test for lacrimal outflow function
- Secondary test: it is done in cases of negative primary test.

Fluorescein Dye Disappearance Test

Fluorescein 2% drops are instilled in both conjunctival fornices. Normally, no dye remains after 3 minutes. Prolonged retention is inferred as inadequate lacrimal drainage.

There are multiple other tests, like contrast dacryocystography, nuclear lacrimal scintigraphy, Schirmer's test, tests to check tear film and ocular surface but they are done at an ophthalmic set-up.

Clinical Pearl

- When cause of watering is in doubt, ophthalmology reference is mandatory.

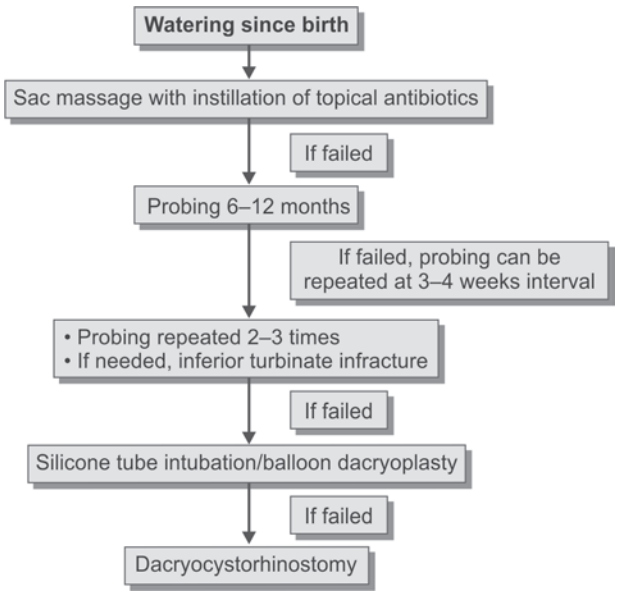
MANAGEMENT OF CONGENITAL BLOCKAGE OF NASOLACRIMAL DUCT

Sac massage is the mainstay, as spontaneous resolution occurs in 90% of cases within first year. Management of congenital blockage of nasolacrimal duct has been outlined in algorithm 1.

- Sac massage: the child's head should be held firmly. Mother is instructed to compress the sac area by applying firm, gentle pressure with the pulp of index finger such that finger blocks the common canalicular opening. This finger is then

ALGORITHM 1

Management of congenital nasolacrimal duct block



firmly moved down the side of nose. Procedure is repeated 3–4 times a day (4–5 times every sitting) and it is followed by instillation of antibiotic (tobramycin or ciprofloxacin eye drops). By doing this massage, hydrostatic pressure in the lacrimal sac increases and it may rupture membranous obstructions and/or displace the debris

- Probing: if sac massage fails, probing and syringing is done under general anesthesia. Age at which massage should be discontinued and probing done is controversial. Early intervention at 6–8 months of age has advantage of high success rate and prevents long-standing infections. Late intervention at about 12 months has an advantage as many cases show spontaneous resolution by a year. This obviates the need of surgical intervention. Probing should be avoided if the child has URI. Sac massage should be continued after probing.

In case of failure, probing can be repeated after 3–4 weeks. If need be, inferior turbinate infracture can be done at the same time.

- In case of failed probing:
  - Intubation with silicone tube can be done
  - Balloon dacryoplasty can be done
  - Dacryocystorhinostomy (DCR): if child presents late, after 3 years of age or if repeated probing fails, then DCR is done. In this procedure, NLD is bypassed by surgically creating anastomosis between the sac and nasal mucosa. This procedure can be performed by external approach or nasal approach.

CONCLUSION

Watering from eyes in childhood is a fairly common complaint. The cause needs to be diagnosed before starting treatment.

KEY POINTS

☞ Proper history taking and examination is important to come to a diagnosis. It nasolacrimal duct obstruction is the most common cause of epiphora in infants. In most of the cases, it can be treated conservatively. It is imperative that the proper procedure of sac massage be explained to the attendant and reassurance given. When in doubt, ophthalmic referral must be done.

SUGGESTED READINGS

1. Abdu L, Salisu AD. Pattern and outcome of surgical management of nasolacrimal duct obstruction in children: A five-year review. Ann Afr Med. 2014;13(3):130-3.
2. Balasubramaniam SM, Kumar DS, Kumaran SE, Ramani KK. Factors affecting eye care-seeking behavior of parents for their children. Optom Vis Sci. 2013;90(10):1138-42.
3. Bremond-Gignac D, Chiambaretta F, Milazzo S. A European perspective on topical ophthalmic antibiotics: current and evolving options. Ophthalmol Eye Dis. 2011;3:29-43.
4. Bremond-Gignac D, Nezzar H, Bianchi PE, Messaoud R, Lazreg S, Voinea L, et al. Efficacy and safety of azithromycin 1.5% eye drops in paediatric population with purulent bacterial conjunctivitis. Br J Ophthalmol. 2014;98(6):739-45.
5. Chirinos-Saldaña P, Bautista de Lucio VM, Hernandez-Camarena JC, Navas A, Ramirez-Miranda A, Vizuet-Garcia L, et al. Clinical and microbiological profile of infectious keratitis in children. BMC Ophthalmol. 2013;13:54.
6. Davey J, Billson FA. Watering eyes: an important sign of congenital glaucoma. Med J Aust. 1974;2(14):531-2.
7. Kumar R, Mehra M, Dabas P, Kamlesh, Raha R. A study of ocular infections amongst primary school children in Delhi. J Commun Dis. 2004;36(2):121-6.
8. Nemet AY, Fung A, Martin PA, Benger R, Kourt G, Danks JJ, et al. Lacrimal drainage obstruction and dacryocystorhinostomy in children. Eye (Lond). 2008;22(7):918-24.
9. Saboo US, Jain M, Reddy JC, Sangwan VS. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care center in India. Indian J Ophthalmol. 2013;61(9):486-9.
10. Sielicka D, Mrugacz M, Bakunowicz-Lazarczyka A. [Nasolacrimal duct disorders in children. Part I. Anatomy, physiology and clinical signs]. Klin Oczna. 2010;112(10-12):342-5.
11. Stepankova J, Odehnal M, Malec J, Dotrelova D. [Corneal foreign bodies in children]. Cesk Slov Oftalmol. 2012;68(4):142-5.
12. Vichyanond P, Pacharn P, Pleyer U, Leonardi A. Vernal keratoconjunctivitis: a severe allergic eye disease with remodeling changes. Pediatr Allergy Immunol. 2014;25(4):314-22.

CHAPTER 143

Deviation of Eyes

Taru Dewan, Harshika Chawla

INTRODUCTION

Early and accurate detection of ocular motility disorders in children can present a challenge for family physicians. Children may not be willing to participate in the screening process, and interesting fixation devices are often not available in the office. In addition, some of the diagnoses are complex. The involvement of pediatric ophthalmologists with specialized training, expertise, and examination equipment is, therefore, often required. Despite these difficulties, most significant eye problems in children can be identified with effective screening techniques.

STRABISMUS

Strabismus may result from a variety of ocular or systemic conditions. On the other hand, it can lead to severe visually disabling consequences (amblyopia, abnormal head posture, loss of binocularity, etc.).

The term "strabismus" is derived from the Greek word *strabismos*, to squint/to look obliquely/askance. Strabismus means ocular misalignment. The image is therefore not in corresponding areas of both eyes, which may result in eventual amblyopia in childhood or diplopia in adulthood.

CLASSIFICATION

There are several classifications that are used for strabismus.

Based on Direction

- Horizontal deviations are classified into two varieties:
  - Eso—describes inward (Fig. 1A)
  - Exo—describes outward misalignment (Fig. 1B)
- Vertical deviations can be:
  - Hyper—the term for an eye whose gaze is directed higher than the fellow eye
  - Hypo—the term for an eye whose gaze is directed lower
- Torsional strabismus: occurs when the eyes rotate around the anterior-posterior axis to become misaligned, viz., incyclotorsion and excyclotorsion.
- Combined: can be horizontal, vertical, torsional, or any combination thereof.

Based on Latency

- Latent squint (heterophoria): it is present only when binocularity is disrupted, e.g., when covering an eye. Such a patient has normal fusion mechanisms. Latent strabismus is precipitated in conditions of ocular fatigue, general debility, etc.

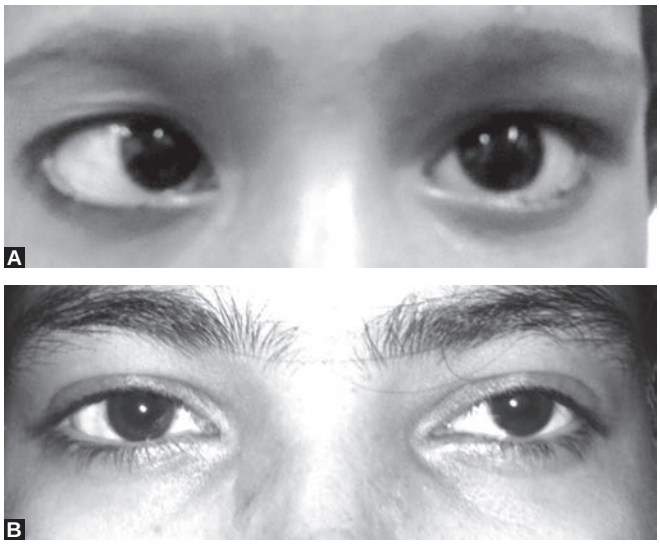


Fig. 1: Horizontal deviations in strabismus. **A,** Esodeviation. **B,** exodeviation

- Manifest squint (heterotropia): it is present even when patient views binocularly, i.e., even without occluding an eye. Such patients cannot align gaze to achieve fusion and children with manifest squint usually develop amblyopia and adults present with diplopia.

Based on Onset

- Infantile: deviation documented at birth or before 6 months of age, presumably related to a defect present at birth
- Acquired: a deviation with later onset, after a period of apparently normal visual development.

Based on Constancy

- Constant: when one eye consistently deviates
- Intermittent: when the deviation is not present all the time and may be noticeable for limited time during the day.

Based on Comitance

- Comitant strabismus: the size of deviation does not vary significantly with the gaze or eye used for fixating
- Noncomitant (incomitant) strabismus: the deviation varies in size significantly with the gaze or eye used for fixating.

Based on Etiology

- Paretic strabismus: due to paralysis of one or several extraocular muscles
- Non-paretic strabismus: due to causes other than paralysis of extraocular muscles.

Clinical Pearl

- Pseudostrabismus is the false appearance of strabismus. It generally occurs in infants and toddlers whose bridge of the nose is wide and flat, causing the appearance of esotropia. With age, the bridge of the child's nose narrows and the folds in the corner of the eyes become less prominent. Pseudoexotropia occurs with a wide interpupillary distance or a positive angle kappa.

ETIOLOGY

Etiology of strabismus is generally presumptive, especially in congenital and nonparalytic cases. Development of nonparalytic squint is a result of factors which affect development of normal binocularity. Binocular vision and coordination of ocular movements is an acquired process which completely develops by the age of 5–6 years.

Factors, which hinder normal binocular development, can be:

- Sensory: uncorrected refractive error, corneal opacity or cataract, optic atrophy, macular disorder, etc.
- Motor: abnormal extraocular muscles or fascia, abnormal accommodation or convergence
- Central: abnormal cortical control of ocular movements.

Heredity does play a major role but a distinct genetic pattern for strabismus has not been identified.

Clinical Pearl

- The type of squint and the response to treatment in other family members may be similar.

CLINICAL FEATURES

- Patient may present with any of the following features:
  - Parental concern due to the presence of a manifest squint
  - Asthenopia
  - Detection at a preschool screening clinic
  - Compensatory abnormal head posture
- Special points in history:
  - Age of onset of deviation
  - Whether it was preceded by trauma or illness?
  - Constant or intermittent?
  - Unilateral or alternating?
  - Does the child close one eye?
  - History of double vision or abnormal tilting of head?
  - Family history of strabismus or amblyopia, the type of squint and the response to treatment
  - Prematurity, birth weight; neonatal history
  - Development milestones
  - Treatment history such as amblyopia treatment, squint surgery, spectacle corrections.

Clinical Pearl

- Increased prevalence of strabismus has been reported in association with assisted delivery (forceps or cesarean section), low-birth-weight (including premature infants) and maternal drug abuse.

EXAMINATION

- Visual acuity: special tests can be used depending on the age of the child to determine visual acuity for near and distance (Table 1)
- Inspection: make a note of:
  - Large angle squint
  - Facial asymmetry/presence of epicanthal folds/ptosis or proptosis to rule out pseudostrabismus
  - Abnormal head posture

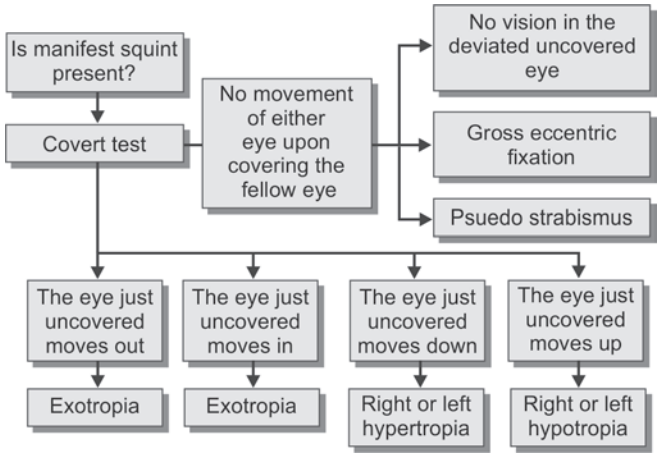
TABLE 1: Visual acuity

Infants	Preschool children	School-aged children
Fixation behavior tests	Marble game test	Snellen's test chart
Preferential looking test	Hand figure test	Landolt's broken C chart
Optokinetic nystagmus	Sheridan-Gardiner HOTV test	E chart
Visually evoked potential	Pictorial vision tests	–

- Pupillary reactions: light reflex may be abnormal in diseases of optic nerve or retina
- Hirschberg's reflex test: it gives a rough estimate on the degree of manifest squint. Shine a pen torch into the patient's eyes at an arm's length away and ask them to look at the light (babies will tend to look towards it). Observe where the reflection of the pen torch lies with respect to the cornea. Normally, it should be central bilaterally. One millimeter of decentration of reflex corresponds to about 7° of deviation. When the reflection is at the margin of the pupil, there is approximately 15° deviation, and, if it lies at the edge of the cornea, there is approximately 45° deviation
- Perform the cover/uncover test; if this appears to be normal, try the alternate cover test:
    - Cover/uncover test: it confirms the presence of heterophoria. Patient is asked to focus on a target held in front of him (at 33 cm). One eye is completely occluded for several seconds and the uncovered eye is observed for movement as it focuses on the object. This eye is then covered and the other eye is observed for movement. Movement of the eye outwards confirms that there is an esodeviation (i.e., the eye was turned inwards initially) and vice versa for exodeviation. The test is repeated for objects at 6 m
    - Alternate cover test: it differentiates comitant from noncomitant variety and it also tells us about the fixation behavior. The occluder is rapidly switched from one eye to the other. Observing the eye movement as the occluder is removed, depending on whether it moves inwards (i.e., there is an exophoria and the eye has to move in to see again) or outwards (revealing an esophoria) confirms the type of strabismus
    - Prism bar cover test (Algorithm 1): it is the most popular and informative method to estimate the amount of squint objectively. Prisms of increasing strength with apex towards the direction of deviation are placed over one eye and patient is asked to fixate a target with the other eye. Alternate cover test is done till there is no recovery movement of the deviating eye under the prism bar
    - Krimsky prism bar reflex test (PBRT): in cases with poor vision in one eye, when patient cannot focus on fixation target, use of PBRT comes into play.

ALGORITHM 1

Prism bar cover test



MANAGEMENT

- Referral: a neonate with a constant squint or with a squint that is worsening should be referred to an ophthalmologist. The earlier the referral, the better chance the child has of avoiding the possibility of amblyopia
- Assessment: there will be both an orthoptic assessment (to assess the visual acuity and ascertain the presence and nature of the squint) as well as a medical review to ensure that the eye is otherwise healthy
- Detailed neurological assessment may be required only in cases of paretic squints
- General approaches (Algorithms 2 and 3):
    - Treatment is guided by the exact nature of the squint and by the patient's age
    - Correction of refractive errors will be the first step. In the subset of accommodative esotropia, appropriate refractive correction might be the only thing required. The true amount of surgically correctable deviation is assessed only after refractive correction
    - Any concurrent amblyopia will need treating too
    - Practical considerations include using plastic instead of glass lenses for spectacles made for children and ensuring that the lenses are large enough to prevent the child from looking over them
    - Frequent refractions under full cycloplegia may be required at short time intervals
    - Some patients are treated with prisms (placed on spectacle lenses), miotics or other methods of nonsurgical management
    - Most patients may require surgical alignment which may be done using muscle recession (it is moved backwards on the globe and so its action is weakened) and/or antagonistic muscle resection (a segment of muscle is removed, so strengthening its action). Sometimes, it takes more than one procedure to get the satisfactory result.

Clinical Pearl

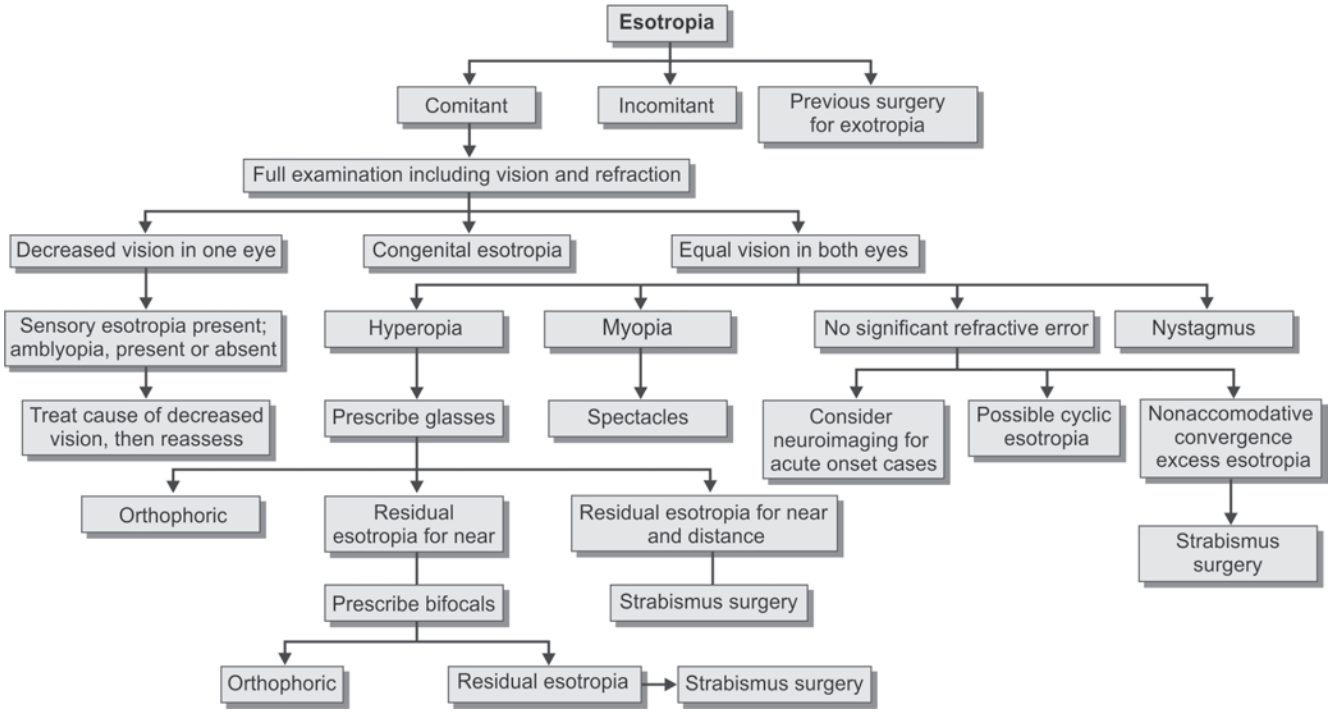
- Infantile esotropia is best managed with early surgical intervention to optimize outcome. There is evidence that early surgery is associated with better binocular outcome.

PROGNOSIS

This depends on the nature and degree of the squint and level of sensory development. Generally, early intervention should produce good alignment and limit any amblyopia but perfect stereopsis is rarely achieved.

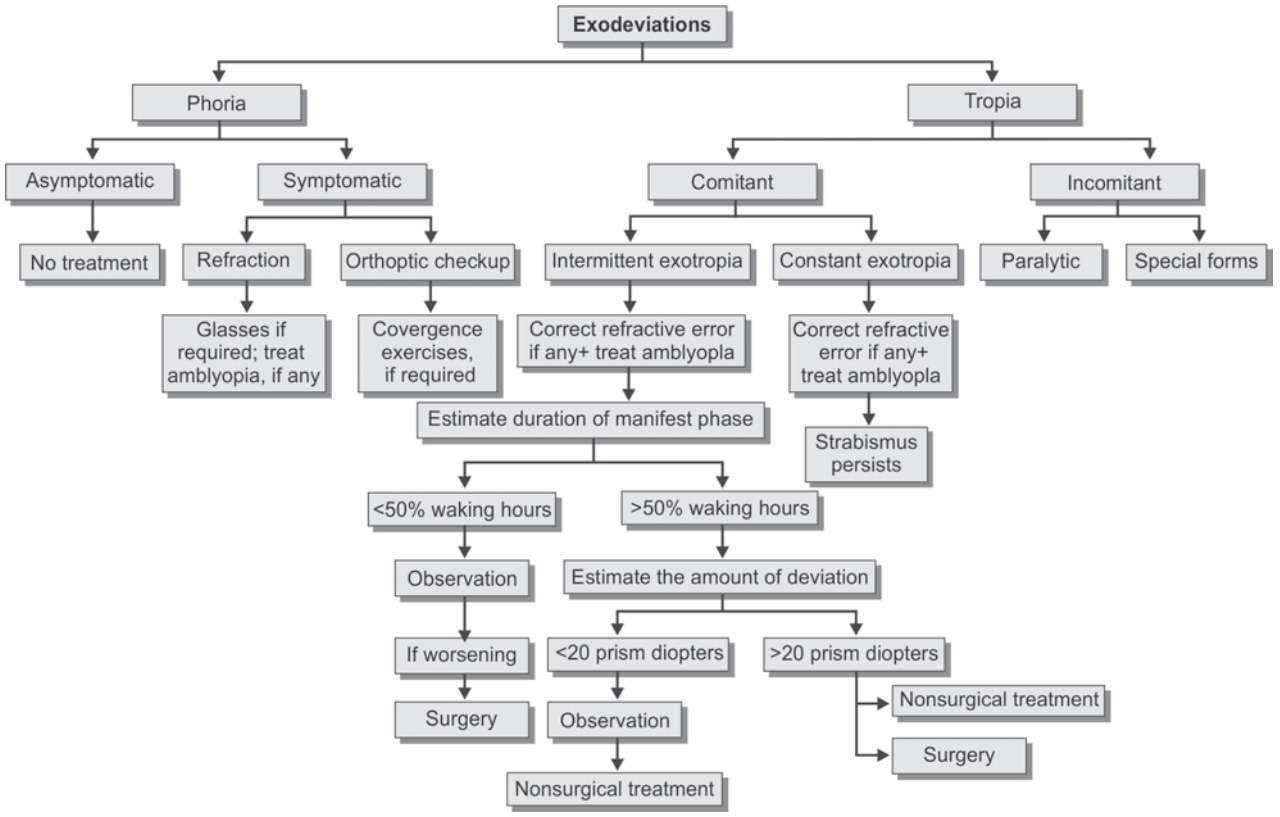
ALGORITHM 2

Algorithmic approach to esodeviation



ALGORITHM 3

Algorithmic approach to exodeviations



KEY POINTS

- A small degree of heterophoria occurs in most normal subjects and must be considered physiologic
- Approximately 50% of all childhood esotropias are either fully or partially accommodative. Cycloplegic refraction is indispensable for the same
- Unlike exodeviations, which are frequently intermittent or latent, most esodeviations are manifest
- A constant exotropia is clinically significant regardless of the angle of deviation or the cause
- An anomalous head posture should raise concern because it may cause neck strain; if left untreated, secondary scoliosis, contracture of the neck muscles and facial asymmetry may occur.

SUGGESTED READINGS

1. American Academy of Ophthalmology. 2013-2014 Basic and Clinical Science Course, Section 6: Pediatric Ophthalmology and Strabismus. 2013.
2. Khurana AK. Theory and Practice of Squint and Orthoptics, 2nd ed. New Delhi, India: CBS Publishers and Distributors; 2013.
3. Maguire JI, Murchison AP, Jaeger EA (Eds). Wills Eye Institute 5-Minute Ophthalmology Consult. Philadelphia, PA, USA: Wolters Kluwer (India); 2012.
4. von Noorden GK, Helveston EM. Strabismus: A Decision Making Approach. St. Luis, MO, USA: Mosby-Year Book; 1994.
5. von Noorden GK. Binocular Vision and Ocular Motility: Theory and Management of Strabismus, 6th ed. St. Luis, MO, USA: Mosby-Year Book; 2002.

CHAPTER 144

Decreased Vision in Children

Shikha Jain

INTRODUCTION

Decreased vision in children should be a cause of concern for all ophthalmologists, as well as nonophthalmologists; because if not corrected appropriately in time, it can cause amblyopia leading to permanent vision loss.

NORMAL VISUAL DEVELOPMENT

Visual development is a highly complex maturation process. Visual system is immature at birth. Myelination of optic nerve, development of visual cortex, and growth of lateral geniculate body occur over the first 2 years of life.

Visual Milestones

Pupillary light reflex is usually present after 31 weeks of gestation but it can be difficult to evaluate due to miosis in newborn. A blink reflex to light is usually present several days after birth. At 6 weeks of age, baby should be able to make and maintain eye contact and react with facial expressions. At 2–3 months of age, a child is usually interested in bright lights although premature infants may reach these landmarks later. Disconjugate eye movements may be noted initially but should not persist beyond 4 months.

Signs of Poor Visual Development

Some of the findings which should point to the examining pediatrician for a need for detailed examination and referral to an ophthalmologist are:

- Wandering eye movements
- No response to familiar faces and objects
- Nystagmus
- Staring at bright light and forceful rubbing of eyes in a visually disinterested infant (oculodigital reflex).

The common causes of decreased or blurred vision in children are given in table 1.

TABLE 1: Common causes of decreased or blurred vision in children

<2 years	>2 years
• Cataract • Congenital glaucoma • Strabismus • Corneal opacity/corneal ulcer • Orbital cellulitis	• Refractive errors • Trauma • Trachoma • Hyphema/hypopyon • Iridocyclitis • Retinoblastoma • Xerophthalmia

Approach to an Infant with Decreased Vision

History

A careful history is essential. Antenatal history should include maternal infection, radiation, drugs, or any history of trauma. Perinatal history should include prematurity, birth weight, intrauterine growth retardation, fetal distress, meconium staining, forceps delivery, and any history of supplemental oxygen therapy in immediate postpartum period

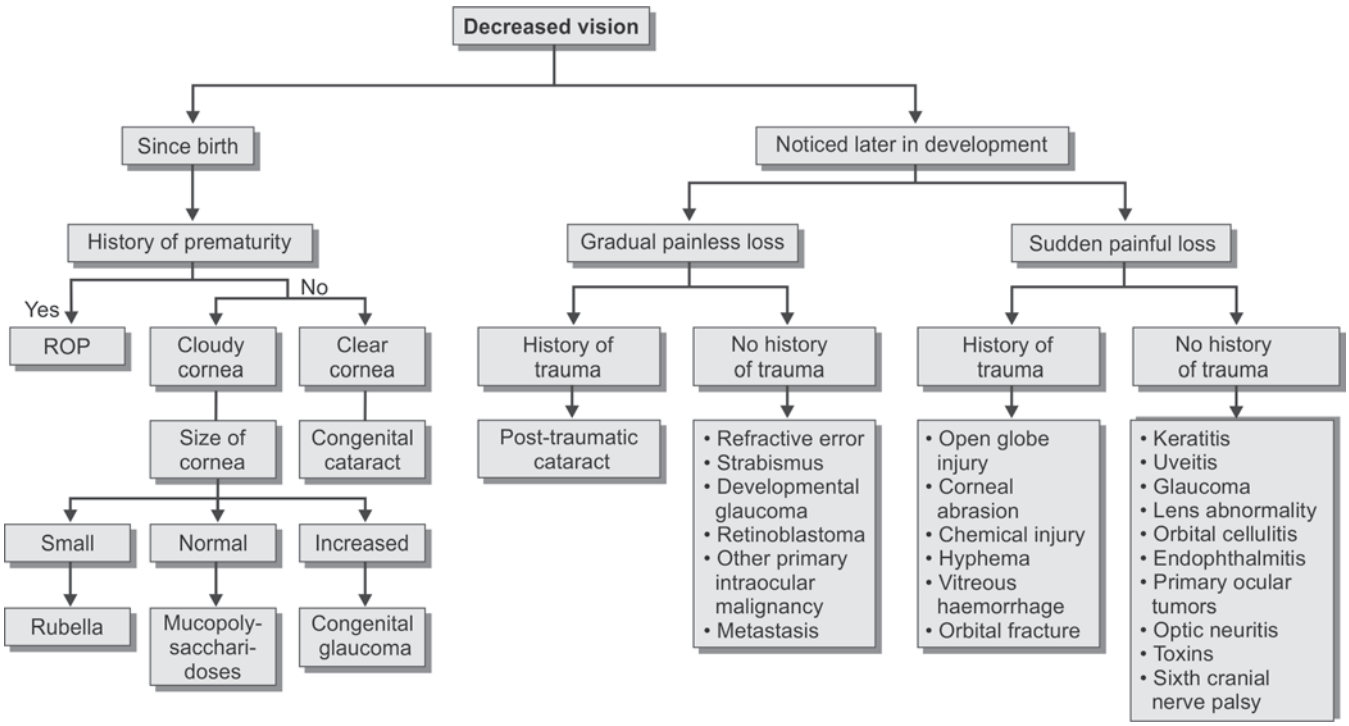
Examination

For a pediatrician, a thorough torch light examination can yield rewarding results. Following points should be carefully documented:

- Ptosis: normally the upper lid covers one-sixth of the cornea and the lower lid rests at the inferior margin of cornea. Any dropping of lids more than this can be classified as ptosis. In severe ptosis, the lower margin of the lid may cover the pupil resulting in decreased vision
- Visual fixation of the child should be noted. This is done by shining a torch light and noting the corneal reflex. The reflex should be in the center of the pupil and the child should follow the light as it is moved to and fro

ALGORITHM 1

Decreased vision in children



- Ocular alignment, motility, and the presence of nystagmus or roving eye movements are important to be documented. Monocular cover-uncover test is the most important test for detecting the presence of manifest strabismus. As one eye is covered, the examiner watches for any movement in opposite noncovered eye, such movement indicates the presence of a tropia. Movement of covered eye in opposite direction as the cover is removed indicates a phoria that becomes manifest when binocularity is interrupted
- Cornea: any obvious corneal haze or opacity should be documented. It can be an indicator of glaucoma, Peters anomaly, sclerocornea, and mucopolysaccharide storage disorders among other causes
- Pupil: it is normally grayish black in color. White reflex of the pupil is known as leukocoria.

Causes of leukocoria are:

- Cataract
- Retinoblastoma
- Retinopathy of prematurity
- Chorioretinal colobomas
- Uveitis
- Toxocariasis
- Tumors, e.g., hamartomas, choroidal hemangiomas. Size of the normal pupil is 3–4 cm. A dilated or a miosed pupil may indicate some pathology, e.g., optic nerve lesion may have a dilated pupil while Horner's syndrome and some poisoning present with miosed pupil
- Pupillary reflex: a note should be made of the equality and briskness of pupillary responses.

ASSESSMENT OF VISUAL ACUITY

Infants

In infants it can be assessed by various methods:

- Fixation behavior: It has three components—central, steady, and maintained (CSM) fixation.
  - C: after covering one eye of the patient corneal light reflex is noted as the patient fixates the examiner's light. The light reflex should be near the center of cornea
  - S: steadiness of fixation as the light is held motionless and then moved slowly
  - M: ability to maintain alignment with both eyes as the other eye is uncovered
- Optokinetic nystagmus: the patient follows a moving object, which then moves out of the field of vision at which point the eyes move back to the original position.The reflex develops at about 6 months of age
- Preferential looking: the child is presented with two stimulus fields, one with alternating stripes and the other with a homogeneous gray area of the same average luminance as the striped field. It is based on the concept that the child will prefer to look at the more interesting stripes if he/she can detect them
- Visual evoked potential: it measures acuity by assessing the response of the brain to alternating black and whites stripes or checks. Three small electrodes are placed on the child's head which are connected to a computer. When the child looks at the stripes, the signal is picked up by the electrodes.

Toddlers

Allen's picture cards are used which consist of familiar objects, e.g., cake, car, horse, duck, etc. (Fig. 1).

Preschoolers

Matching cards are used, e.g., HOTV cards, where the child has to pick a matching card to that shown from a group of cards (Fig. 2). Other useful tests include Landolt Rings (C) test or Tumbling "E" test (Fig. 3).

School-aged Children

In school-aged children, Snellen's visual acuity is usually done (Fig. 4).

Fig. 1: Allen picture cards

Fig. 2: HOTV cards

Fig. 3: Tumbling E's and Landolt C's

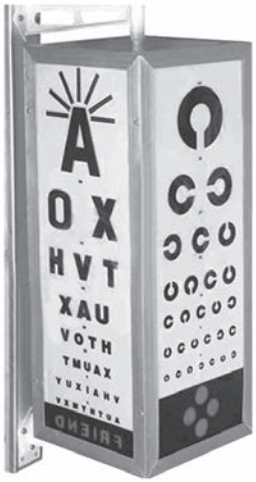


Fig. 4: Snellen's chart

Clinical Pearl

- Use of pinhole helps to give us an estimate of best corrected visual acuity though it can be cumbersome in children.

CONCLUSION

In conclusion, it can be said that various features picked up on a simple torch light examination when taken in conjunction with the presenting symptoms give a fair idea of the need for an appropriate and timely ophthalmological reference.

KEY POINTS

- ☞ Nystagmus is an indicator of decreased vision and is not present at birth but usually appears around 2–3 months of age. It implies presence of at least some visual function. On the contrary, roving eye movements suggest total or near total blindness
- ☞ In infants exotropia is more common as a form of abnormal binocular alignment whereas after 1 year of age esotropia becomes more common
- ☞ Both direct and consensual pupillary responses are important. If direct response is defective, it indicates lesion in optic nerve while consensual indicates the motor pathway (oculomotor nerve) is defective
- ☞ Pupillary response is normal in cortical visual impairment.

SUGGESTED READINGS

1. American Academy of Ophthalmology. Pediatric Ophthalmology and Strabismus: Basic and Clinical Science Course. Section 6. 2007-2008.
2. Nelson LB, Olitsky SE, Harley RD (Eds). Harley's Pediatric Ophthalmology, 5th ed. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 2005.
3. Taylor D. Pediatric Ophthalmology, 2nd ed. Cambridge, MA, USA: Blackwell Science; 1997.
4. Atkinson J. Human visual development over the first 6 months of life. A review and a hypothesis. Hum Neurobiol. 1984;3(2):61-74.

CHAPTER 145

Hearing Screening and Management in Newborn

Atul Ahuja

INTRODUCTION

The importance of hearing screening in the newborn cannot be overemphasized. Though it is one of the most common congenital anomalies it is not obvious to the uninitiated till very late (Table 1).

It is therefore surprising that the newborn screening programs of most hospitals screen for many of the less frequent conditions while omitting the newborn hearing screening.

One of the reasons cited is that for a newborn to be screened the presence of risk factors is a must. For this an High Risk Register (HRR) was used (Box 1).

Clinical Pearl

- Almost 50% children born with hearing impairment have no known risk factors
- Therefore high risk register is not good enough.

IMPORTANCE OF SCREENING THE NEWBORN

Unlike many other congenital deformities the consequences of a hearing impairment keep worsening as the child grows older. Unfortunately hearing loss is not detected early as it is invisible and no antenatal predictive tests.

TABLE 1: comparison of the incidence of common congenital anomalies

Disorder	Rate per 100,000
Adrenal hyperplasia	2
Galactosemia	2
Phenylketonuria	3
Sickle cell disease	47
Hypothyroidism	28
Down's syndrome	100–125
Hearing impairment	200–400

Box 1: The high risk register

List of situations where a hearing impairment can be expected:

- Family history of permanent childhood sensorineural hearing loss
- In utero infection such as cytomegalovirus, rubella toxoplasmosis or herpes
- Craniofacial anomalies, including those with morphological abnormalities of the pinna and ear canal
- Neonatal indicators, specifically hyperbilirubinemia at a serum level requiring exchange transfusion, persistent pulmonary hypertension of the newborn (PPHN) associated with mechanical ventilation, and conditions requiring the use of extracorporeal membrane oxygenation (ECMO)
- Postnatal infections associated with sensorineural hearing loss, including bacterial meningitis
- Stigmata or other findings associated with a syndrome known to include a sensorineural or conductive hearing loss or eustachian tube dysfunction
- Syndromes associated with progressive hearing loss such as neurofibromatosis, osteopetrosis, and Usher syndrome
- Neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Charcot-Marie-Tooth syndrome
- Parental or caregiver concern regarding hearing, speech, language, and/or developmental delay
- Head trauma
- Recurrent or persistent otitis media with effusion lasting for at least 3 months

The development of speech, social development and emotional bonding of a child are dependent on normal.

During the first few months the child's brain grows tremendously. During this period the areas of brain responsible for hearing if not stimulated consistently by sound are reallocated other functions (encroachment), pathways fail to develop and the ganglion cell population decreases.

Once this critical time period elapses even proper amplification will not help this child.

It is therefore important to detect hearing loss early. Studies have revealed that early intervention (before 6 months of age) allows infants to develop normal speech and language at par with his normal hearing peers. Even children receiving help after 7 months of age lag behind those receiving amplification before 6 months of age.

Traditional techniques detect hearing impairment at an average age of 2.5 years. Although children who had severe-to-profound hearing loss or multiple disabilities were identified at or before age 2.5 years, children with mild-to-moderate hearing loss were often not identified until school age (i.e., 4 years). Studies have indicated that, as a result of the universal newborn hearing screening program in various countries, the mean age of diagnosis was 3.9 months, with a mean age of intervention of 6.1 months.

Another common myth amongst clinicians is that simply clapping next to the infant is enough to assess the hearing. There are major pitfalls to this technique:

- Children can compensate for hearing loss and clapping may create a slight breeze to which the baby may react. The child may even react to parental expressions reactions or even shadows
- Even if this were to elicit a startle response, it does not properly assess the babies hearing. As mentioned before mild to moderate hearing loss can also be damaging to the speech and language development of the child.

SCREENING TECHNIQUES

Clinical Pearl

- Traditional techniques of bedside testing are inadequate and cannot detect moderate hearing impairment, which is responsible for most speech delays.

Automated Otoacoustic Emission (Kemp, 1978)

Tests the integrity of the cochlea:

A small soft tipped earpiece (with and integrated mike and speaker) is placed in the outer part of the baby's ear; this sends very soft clicking sounds down the ear.

This sound is transmitted to the tympanic membrane, the ossicles and eventually the cochlea. Within the cochlea the sound is picked up by the outer hair cells which start vibrating, moving tectorial membrane. This in turn stimulates inner hair cells.

The vibration of outer hair cells transfers energy back to endolymph and perilymph. These vibrations are transmitted back along the same path through which they were conducted.

These are then picked up as clicks by a microphone which is integrated into the same earpiece.

Automated oto-acoustic emissions are fast, efficient and objective screening test of peripheral auditory sensitivity (preneural cochlear function). Overcoming major hurdles in neonatal testing.

However, the effectiveness of the test is reduced by contamination with low-frequency ambient noise in a busy nursery, vernix in the ear canal, or any middle ear pathology.

Automated oto-acoustic emissions alone however may not be a sufficient screening tool in infants who are at risk for neural hearing loss (e.g., auditory neuropathy/dyssynchrony) as they test only the cochlea, not the nerve (Fig. 1).

Automated Auditory Brainstem Responses

Automated auditory brainstem response (AABR) is a rapid electrophysiologic test that is used to assess auditory function from the eighth nerve through the auditory brainstem. This test was developed to supplement the results of AABR. Though quite specific it is not as sensitive as an ABR (Auditory Brainstem Responses/Brainstem Evoked Response Audiometry). Together with AOAE, AABR forms a very powerful screening tool in newborn and infants.

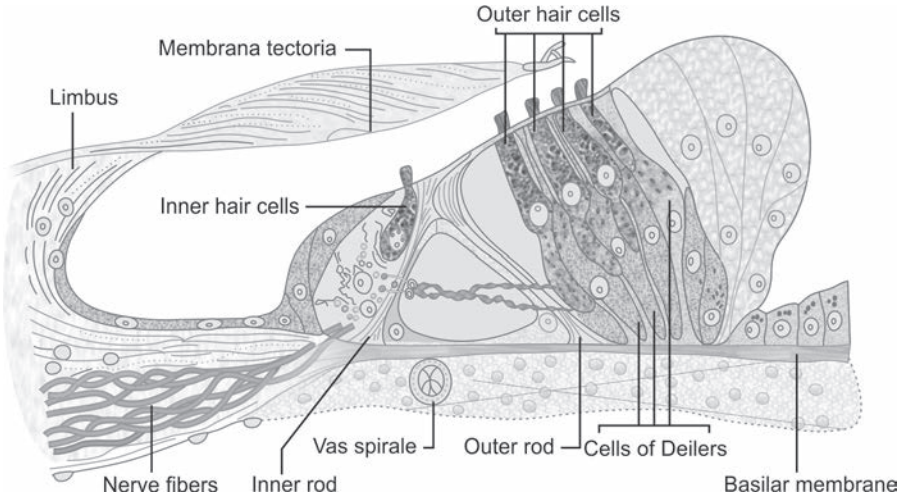


Fig. 1: Organ of corti

For the purpose of AABR measurements disposable surface electrodes are placed high on the forehead and on the mastoid and electrical activity traced. The stimulus is in the form of clicks [generally set at 35 dB hearing level (HL)] is delivered using small disposable earphones designed to attenuate background noise.

Automated auditory brainstem response system as the name suggests automatically first checks the reproducibility of the wave forms, then compares the infant's waveform with that of a template. This has been developed from normative ABR infant data. The results of this test are just in the form of either pass or fail, and the test can be conducted in the presence of background noise.

It lacks frequency-specific information.

The AABR test is solely a screening technique designed to identify infants who require follow-up testing. It cannot be used to determine the degree or nature of the hearing loss.

Automated auditory brainstem responses cannot however detect mild hearing loss and thus should be combined with AOAE.

Auditory Brainstem Responses

The most common application of auditory evoked responses is ABR audiometry. These were first described by Jewett and Williston in 1971.

In ABR an insert phone is introduced into the external auditory canal and sound inputs in the form of clicks or tone beeps given. This generates an electrical response in the auditory (neural) pathways. These responses are picked up by electrodes placed on the forehead or the vertex and mastoid processes. The sum total of the electrical responses is calculated and mapped out as waveforms. These are charted out as a function of time much like an ECG. These are usually detected within 10 milliseconds of a click stimulus. These are consistently picked up with click stimuli in the amplitude range of 70–90 dB. These waveforms are labeled as waves I–VII, each denoting an important structure in the auditory pathway. Though the origin of the waveforms is still being debated, the following are the most commonly accepted.

- Cochlear Nerve—I
- Cochlear Nucleus—II
- Sup Olivary Nuc—III
- Lat. Laminiscus—IV
- Inf. Colliculus—V
- Med. Geniculate—VI
- Auditory Radiatn—VII

Auditory brainstem response gives us a good idea about the integrity of the auditory pathways and to some extent the threshold of hearing; however, it should be used in conjunction with clinical assessment and behavioral audiometry as it is not a substitute for these.

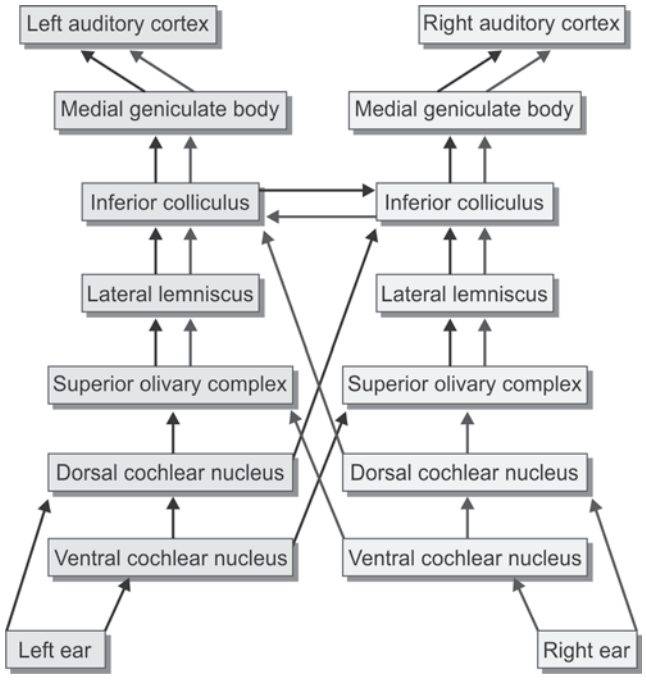


Fig. 2: The auditory pathway.

Auditory Steady State Response

This is an advance over the ABR/BERA as it tests both the bone and air conduction for four frequencies, i.e., 500, 1000, 2000, and 4000 Hz. This gives us a good idea about the sound conduction through the middle ear system and the auditory pathways. It allows us to assess children not assessable through behavioral methods and since it gives us a fair idea of frequency specific thresholds, it helps in fitting hearing aids as well.

SCREENING PROTOCOLS FOR NEWBORN

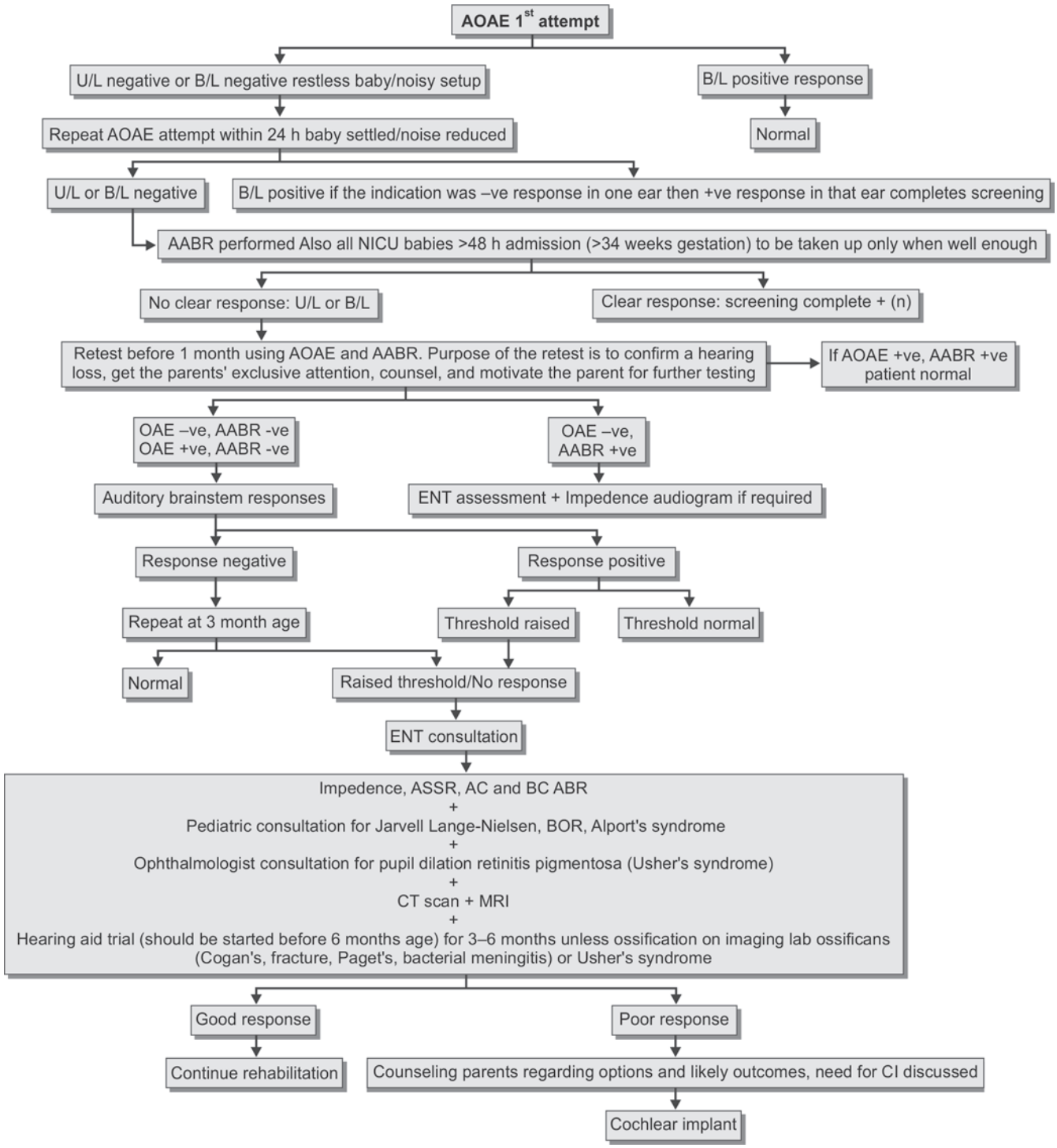
All patients with unilateral atresia, suspected/confirmed bacterial meningitis undergo era directly.

Clinical Pearls

- If there is a delay in sound stimulation, cortical areas in the brain get encroached and subsequent amplification does not have the desired effect
- Unless amplification is initiated before 6 months of age an infant does not keep up with its peers
- Hearing impairment could also be a sign of associated syndromic disorders. Patients should have a thyroid profile, eye exam, renal and cardiac assessment
- It is valuable to take a detailed consultation with an experienced pediatric neurologist to assess milestone delays and development.

ALGORITHM 1

Suggested algorithm for workup of hearing impaired infants



AOAE, automated otoacoustic emission; AABR, automated auditory brainstem response; NICU, neonatal intensive care unit; CI, cochlear implant; OAE, otoacoustic emission testing, ABR, auditory brainstem responses; BOR, branchiootorenal; CT, computed tomography; MRI, magnetic resonance imaging; AC, air conduction; BC, bone conduction; ENT, ear, nose, and throat; U/L, unilateral; B/L, bilateral.

KEY POINTS

- ☞ The importance of hearing assessment in neonates cannot be overemphasized
- ☞ The traditional techniques of assessment are not very accurate and cannot detect mild to moderate hearing impairment. By the time it becomes apparent to the parents its quite late and such children seldom catch up with their peers since amplification is started too late
- ☞ The policy of screening neonates falling in the high risk register again is full of errors as at least 50% of congenitally hearing impaired have no known risk factors
- ☞ The detection of hearing loss should also alert the clinician to the possibility of associated syndromic conditions.

CHAPTER 146

Hoarseness in Pediatric Age Group

Kumud K Handa, Aru C Handa, Dilip Samal

INTRODUCTION

Hoarseness or dysphonia is defined as an abnormality in voice quality that arises because of dysfunction in vocal cord vibratory function, causing impairment in proper communication. Normal voice is produced by the fine vibratory function of the vocal cords that may get deranged because of structural abnormality of vocal cords or due to any functional deficit.

Childhood hoarseness is not an uncommon entity. Although, it is an underdiagnosed entity, its prevalence may be as high as 23.4% in school-going children with boys affected more than girls. The causes may be benign vocal cord lesions, infections, inflammations, congenital, neurological, or traumatic.

It may impair quality of life in regards to speech. Children with vocal nodules, vocal fold paralysis and paradoxical vocal cord movements had statistically significant pediatric voice-related quality-of-life-impairments as compared to their age matched normal counterparts as per study conducted in 2008 by Merati et al. This requires a more aggressive evaluation and required intervention of dysphonia in pediatric ages.

ETIOLOGY

Vocal abuse plays a major role causing hoarseness in pediatric age group. It is more commonly observed in boys, in view of more aggressive nature as compared to girls.

The etiology of hoarseness may be:

- Benign vocal cord lesions like vocal nodule, polyp
- Vocal cord cysts, sulcus vocalis
- Juvenile laryngeal papillomatosis
- Vocal fold paresis
- Laryngopharyngeal reflux
- Acute or chronic laryngitis
- Foreign body inhalation
- Malignant lesions of larynx
- Systemic illness like hypothyroidism
- Post-surgery (Iatrogenic)

Vocal Nodules

Vocal nodules are by far the most common pathology causing hoarseness in childhood with an incidence of 38–78%, which causes abnormality in vibratory function of cords with decreased mucosal waves on stroboscopic examinations. The prevalence of vocal fold nodules varies affecting 21.6% in males and 11.7% in females. Vocal nodules are usually bilateral and formed at the junction of anterior and mid third of vocal cords. Vocal nodule arises due to the mechanical trauma, injury and with secondary hyalinization at the free edge of vocal cords (Fig. 1).

Clinical Pearls

- Hoarseness in children, with vocal abuse, is commonly due to vocal nodules
- It is very important to examine the larynx, even in children, to know the exact pathology.

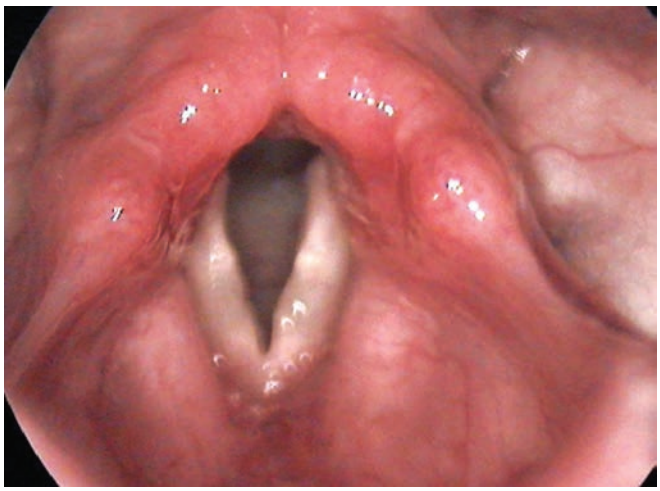


Fig. 1: Five-year-old child with hoarseness and cystic swelling free edge of left true cord

Vocal Polyps

Vocal polyps are less infrequent entity, usually unilateral, may be pedunculated or sessile. Polyps are formed due to phonotrauma and occur at the site of exertion of maximum muscular and aerodynamic force. These are formed as a result of circulation impediment, thrombosis, exudation, edema due to inflammation of the vocal cords.

Vocal Cord Cysts

Vocal cord cysts usually present as unilateral submucosal swelling with reduced mucosal waves on stroboscopy (Fig. 2).

Sulcus Vocalis

It has epithelium invaginates and adheres to vocal ligament forming a longitudinal furrow with incomplete vocal cord closure on stroboscopy. Both are believed to be either congenital or may be acquired lesions having variable presentations of hoarseness, vocal fatigue or voice breakage. They have a poor response to speech therapy and may require surgical intervention (Fig. 3).

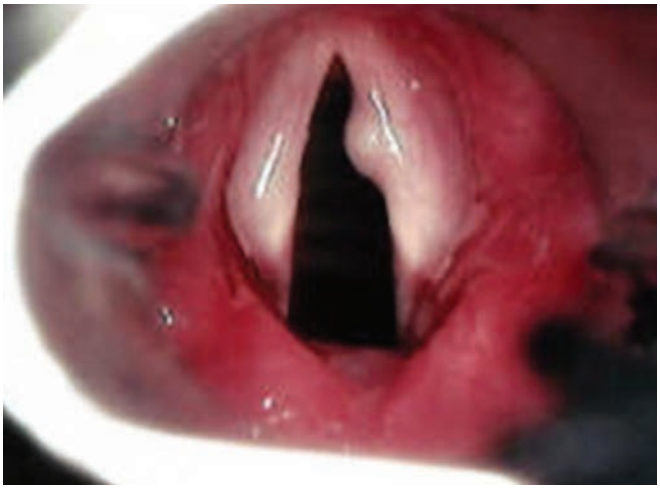


Fig. 2: Vocal cord cyst

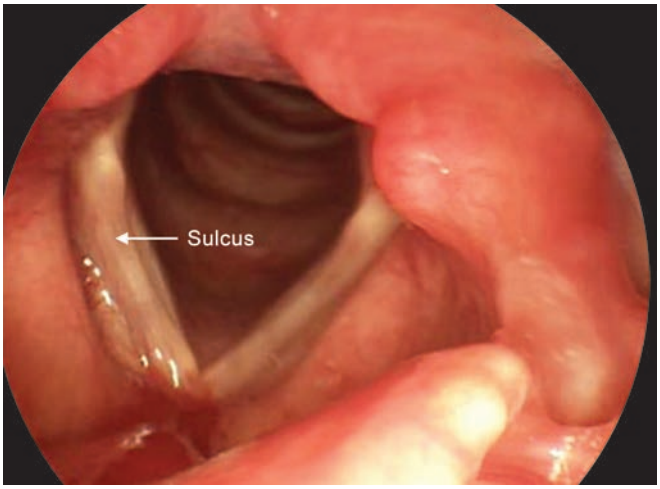


Fig. 3: Sulcus vocalis

Juvenile Laryngeal Papillomatosis

Juvenile laryngeal papillomatosis (recurrent respiratory papillomatosis) is a benign infectious condition of larynx due to human papilloma virus infection of serotype mainly 6 and 11. It is the most common benign neoplasm of larynx and second most common cause of dysphonia or hoarseness in children. It is more aggressive in childhood, often requiring multiple surgical intervention. Most common age of presentation is from 2 to 4 years, with youngest reported age is at 1 day. It has an incidence of 4.3 per 100,000 among the children with an equal male and female distribution. It usually presents as dysphonia in early stage of disease, but may be presented with breathing difficulty and stridor when compromises the glottic airway and may require tracheotomy. The most common sites involved in larynx are midzone of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricle, the undersurface of the vocal folds, the carina with a common histologic feature of a squamociliary junction sites (Fig. 4).

Congenital or Acquired Vocal Fold Paresis

In children it may present as dysphonia, resulting from birth trauma or congenital anomaly involving the central nervous system. Vocal fold paralysis may have a unilateral or bilateral vocal cord involvement and should be differentiated from cricoarytenoid joint dislocation. Unilateral vocal fold paresis may remain undiagnosed, but bilateral vocal fold paresis may present with stridor, requiring tracheostomy. It may have spontaneous recovery, otherwise may need corrective surgical intervention later on.

Laryngopharyngeal Reflux

It can present as hoarseness, which is more aggressively being evaluated in recent era. Although confirming the diagnosis is difficult, reflux laryngitis with dysphonia may be reversible with antireflux proton pump inhibitors and prokinetic drug treatment.

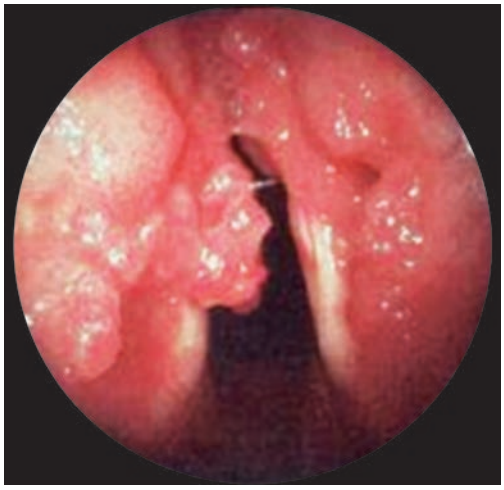


Fig. 4: Juvenile papilloma (endoscopic view)

Acute or Chronic Laryngitis

It may present as dysphonia causing vocal fold edema. Although it has a viral etiology, may be bacterial or fungal also. Symptoms may worsen more with vocal abuse. It should be differentiated from acute laryngotracheobronchitis or croup, caused by parainfluenza virus I and II.

Foreign Body Inhalation

It can cause hoarseness of acute onset with or without breathing difficulty. On evaluation patient may have stridor along with change in voice, which may need immediate intervention.

Malignant Tumors

Malignant tumors of larynx although rare, but should be ruled out in a pediatric patient presented with progressively worsening hoarseness with dysphagia or breathing difficulty. Embryonal rhabdomyosarcoma is the most common variant, others are squamous cell carcinoma, lymphoma, muco-epidermoid carcinoma or metastatic carcinoma variant. Long standing recurrent respiratory papillomatosis is known risk factor in the development of malignant transformation with an incidence of 2–3%.

Iatrogenic

patient may present with change in voice following surgery. It may be due to vocal fold paresis following cardiothoracic surgery or may be due to cricoarytenoid dislocation.

Clinical Pearl

- Laryngopharyngeal reflux, despite being common, in children is still an underdiagnosed entity
- Neonates and infant with unilateral cord paralysis have a weak cry whereas bilateral vocal cord paralysis presents with stridor.

EVALUATION

Approach to a child with hoarseness needs a multidisciplinary approach involving otolaryngologist, speech language therapist for detailed evaluation of medical history, physical examinations, laryngoscopic vocal cord assessment and acoustic and aerodynamic evaluation of voice with stroboscopic examination if needed.

History

Patient should be thoroughly studied regarding the age of onset, i.e., since birth or later, duration of hoarseness. Congenital lesions usually present at birth, whereas neurological illnesses may present from birth or later on. It may be intermittent as in reflux laryngitis or vocal abuse or persistent as in structural laryngeal pathology. Progressively worsening dysphonia may be because of neoplastic lesions and juvenile papillomatosis.

When associated with noisy breathing, it should be evaluated seriously; otherwise it may progress in to a life threatening condition. Stridor may be inspiratory, expiratory or biphasic, depending upon the site of involvement in the larynx. The etiology may be laryngeal papillomatosis or neoplastic lesion.

Difficulty in swallowing may be associated, when laryngeal involvement because of neurologic disorder or large structural abnormality that hampers the swallowing physiology. It may be associated with aspiration, especially in cases of neurological disorders and laryngeal clefts.

Significant gastroesophageal reflux may present as hoarseness, but it is a difficulty entity to diagnose or ruled out reflux. Some physicians prefer an antireflux trial response for the diagnosis of the entity.

Examination

It includes thorough otolaryngological examination, examination of endolarynx and voice analysis. Endolarynx is examined using 90 degree telescope or fiberoptic 2.7 or 4.0 mm laryngoscope. This provides information regarding structural vocal cord abnormality and its functional aspects also. Although awake laryngoscopy is superior to laryngoscopic evaluation under general anesthesia, in infants for proper evaluation some surgeon prefer evaluation under anesthesia without muscle relaxant. Video stroboscopic examination provides better clinical details regarding the detail mucosal vibratory function (Fig. 5).

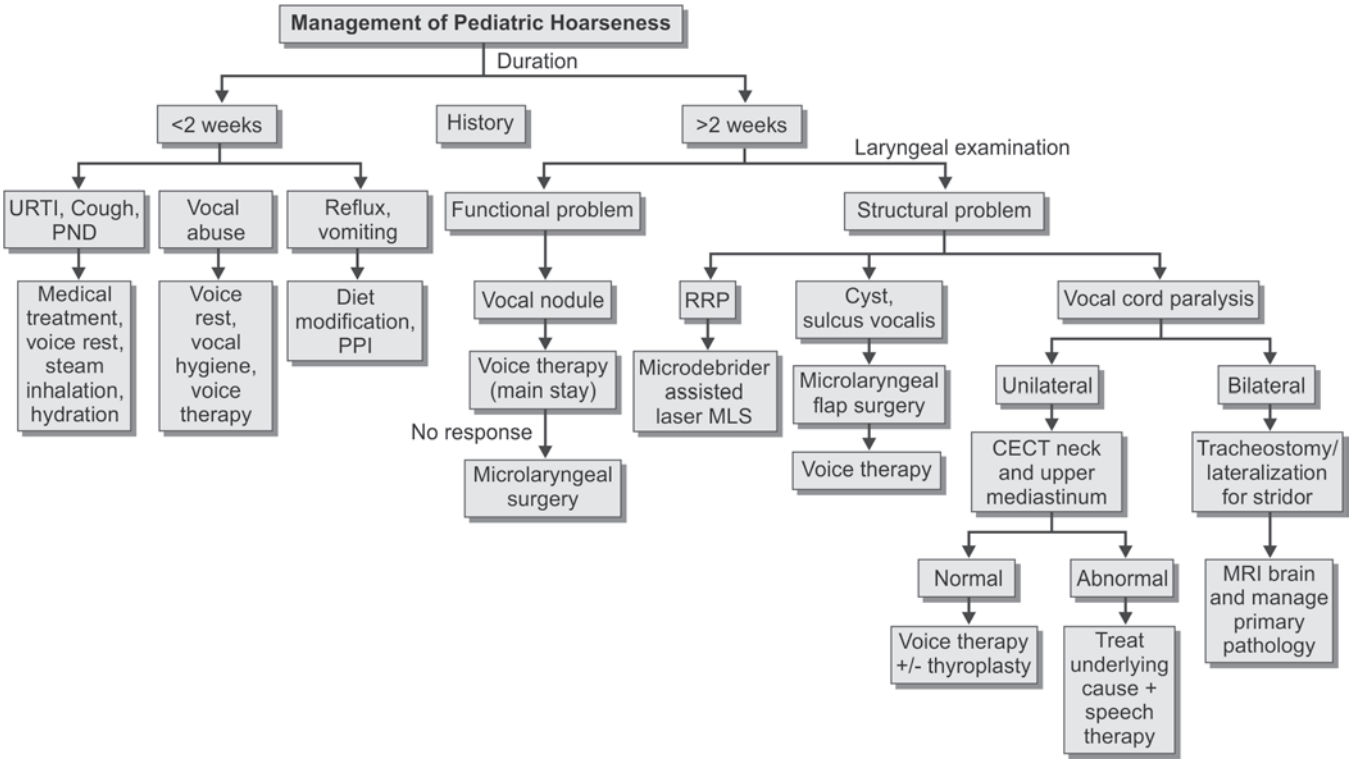
Subjective evaluation with pediatric voice handicap index (pVHI) and objective voice evaluation with acoustic and aerodynamic analysis plays an important role in evaluation and examining response to treatment.

Clinical Pearl

- With patience, counseling, and parental cooperation good examination of larynx are possible in most cases either by indirect laryngoscopy or flexible laryngoscopy
- Direct laryngoscopy for examination under anesthesia, without muscle relaxant, is required only in select few.

Fig. 5: Videostroboscope for examination of the vibratory edge of the vocal fold

ALGORITHM 1



URTI, upper respiratory tract infection; PND, paroxysmal nocturnal dyspnea, PPI, proton pump inhibitor, RRP, recurrent respiratory papillomatosis, MLS, microlaryngeal surgery; CECT, contrast-enhanced computed tomography.

Additional test laryngeal electromyography, pH probing may be done when there is any clinical suspicion and requirement.

TREATMENT

Voice therapy: Usually it is the initial and most common form of treatment used in treatment of dysphonia in pediatric age group. Voice therapy for children is usually behavioral in nature and includes family orientation, vocal hygiene and vocal training. In children specific voice therapy techniques are associated with drawing, body movements, and hand gestures to make them understand the goals of therapy. Computer games and software's like the voice therapy segment in Doctor's Speech etc. especially designed to provide visual and audio feedbacks related to respiration, voice quality, pitch, loudness, resonance, and articulation are used to make voice therapy for children more interesting and concrete.

General voice therapy techniques include body relaxation, breathing exercises, laryngeal manipulation, and repositioning in the neck. Whereas the specific techniques include resonance and vibration technique, chanting of poems and rhymes reduces the compression of laryngeal forces and increases reverberation in oral and nasal cavities.

Clinical Pearls

- Voice therapy is mainstay of treatment for vocal nodules in children
- It is very important to involve the family for voice therapy in children.

Surgery

It is done in specific conditions. Vocal polyps need microscopic laser or cold instrument excision while vocal nodules respond most of the times to voice therapy. It is only vocal nodules which do not respond to voice therapy that need surgery. Vocal cord cysts mucus retention or epidermoid needs surgical excision. This may be done by laser or flap phonomicrosurgery.

Recurrent respiratory papillomatosis (Juvenile papillomas) needs surgical excision. Nowadays a combination of debrider debulking using a skimmer blade and CO_2 laser is used for removal of juvenile papillomas. Papillomas can recur and need multiple surgical sittings.

Bilateral abductor cord paralysis may need surgical intervention if stridor is severe. The commonly done procedures are posterior laser cordectomy, Kashima procedure (disjunction of vocal process from the vocal cord) and endoscopic laser arytenoidectomy.

Unilateral cord paralysis not responding to voice therapy may need injection or medialization thyroplasty.

Clinical Pearls

- Removal of vocal nodule without a good and adequate speech therapy is not advisable. Surgery reserved only for rare refractory cases
- Repeated frequent removal of juvenile onset recurrent respiratory papillomatosis is required to prevent airway obstruction and tracheotomy
- The aim of surgery in recurrent respiratory papillomatosis is to provide adequate airway, functional voice with minimal scarring.

KEY POINTS

- ☞ Hoarseness in pediatric age group needs proper evaluation including detailed history of duration, infection, vocal abuse, trauma, etc.
- ☞ As it is difficult to get child's cooperation so examination of larynx in children may be challenging
- ☞ Vocal nodules occur due to vocal abuse or overuse and management includes voice therapy with or without surgery
- ☞ Vocal polyps are less common in children
- ☞ Vocal cysts do not respond to voice therapy and require surgical correction
- ☞ Sulcus vocalis may be congenital or acquired requires prolonged voice therapy, and the surgical results are not very dramatic thus requiring postoperative speech therapy also
- ☞ Recurrent respiratory papillomatosis presents in early childhood with weak cry, hoarseness, and may progress on to stridor if not treated. Surgery is treatment of choice but there is high chance of recurrence
- ☞ Cause of Vocal fold paralysis in a child should be evaluated radiologically with imaging of brain, neck and upper mediastinum
- ☞ Laryngopharyngeal reflux in children is more common in children than thought of
- ☞ Malignant tumors in children are less common so may get diagnosed late because of delay in laryngeal examination
- ☞ Voice therapy may be helpful in majority of lesions causing hoarseness in children.

SUGGESTED READINGS

1. Akif Kilic M, Okur E, Yildirim I, G zelsoy S. The prevalence of vocal fold nodules in school age children. Int J Pediatr Otorhinolaryngol. 2004;68(4):409-12.
2. Chen X. Comparative research on vocal polyps and nodules. Zhonghua Er Bi Yan Hou Ke Za Zhi. 1989;24(1):53-5, 63.
3. Derkay CS. Task force on recurrent respiratory papillomas. Arch Otolaryngol Head Neck Surg. 1995;121:1386-91.
4. Ferlito A, Rinaldo A, Marioni G. Laryngeal malignant neoplasms in children and adolescents. Int J Pediatr Otorhinolaryngol. 1999;49(1):1-14.
5. Gaylis B, Hayden R. Recurrent respiratory papillomatosis: progression to invasion and malignancy. Am J Otolaryngol. 1991;12:104-12.
6. Kashima H, Mounts P, Leventhal B, Hruban RH. Sites of predilection in recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol. 1993;102(8 Pt 1):580-3.
7. Kleinsasser O. Pathogenesis of vocal cord polyps. Ann Otol Rhinol Laryngol. 1982;91(4 Pt 1):378-81.
8. Merati AL, Keppel K, Braun NM, Blumin JH, Kerschner JE. Pediatric voice-related quality of life: findings in healthy children and in common laryngeal disorders. Ann Otol Rhinol Laryngol. 2008;117(4):259-62.
9. Morgan AH, Zitsch RP. Recurrent respiratory papillomatosis in children: a retrospective study of management and complications. Ear Nose Throat J. 1986;65:19-28.
10. Silverman EM. Incidence of chronic hoarseness among school-age children. J Speech Hear Disord. 1975;40(2):211-5.
11. Zur KB, Cotton S, Kelchner L, Baker S, Weinrich B, Lee L. Pediatric voice handicap index (pVHI): a new tool for evaluating pediatric dysphonia. Int J Pediatr Otorhinolaryngol. 2007;71(1):77-82.

CHAPTER 147

Otitis Media with Effusion

Anurag M Srivastava, Anil K Monga, Uday Monga

INTRODUCTION

Otitis media with effusion (OME) is the chronic accumulation of mucus within the middle ear and sometimes the mastoid air cell system. It is characterized by a nonpurulent effusion of middle ear that may be either mucoid or serous. Symptoms usually involve hearing loss or aural fullness but typically do not involve pain or fever. Otitis media with effusion can occur during the resolution of acute otitis media once the inflammation has resolved. Middle ear infections are most common medical problem in infants and children of pre-school age. Tympanostomy tube insertion is preferred initial procedure. Adenoidectomy should not be performed, unless a distinct indication exists (e.g., nasal obstruction, chronic adenoiditis). Medical Therapy to manage the mucosal aspect of the disease will be required regardless of surgical intervention. The otolaryngologist should monitor patients until the conditions resolves with medical or surgical intervention. Thereafter, if the patient's hearing is normal, the paediatrician can provide care.

DEFINITION

Otitis media with effusion is the chronic accumulation of mucus within the middle ear and sometimes the mastoid air cell system. The time that the fluid has to be present for the condition to be chronic is usually taken as 12 weeks.

SYNONYMS

Serous otitis media is also known as nonsuppurative otitis media, exudative otitis media or simply "glue ear". Other terms are serous otitis media, secretory otitis media and chronic non-purulent otitis media (Table 1).

TABLE 1: Definition for otitis media

Middle ear condition	Definition
MEE	Fluid in the middle ear space
AOM	MEE with symptoms and signs of inflammation (i.e., otalgia, fever, irritability)
OME	MEE without symptoms or signs of inflamation
RAOM	Three or more episodes of AOM in 6 months
Persistent OME	MEE without symptoms for more than 3 months

AOM, acute otitis media; MEE, middle ear effusion; OME, otitis media with effusion; RAOM, recurrent acute otitis media.

SUBJECTIVE COMPLAINTS

Otitis media with effusion is characterized by a non-purulent effusion of the middle ear that may be either mucoid or serous. Symptoms usually involve hearing loss or aural fullness but typically do not involve pain or fever. In children, hearing loss is generally mild and is often detected only with an audiogram.

In many children, OME may be preceded by an episode of acute otitis media (AOM) with otalgia and fever. These secretions then become secondarily infected with bacteria—AOM. Once the infection has resolved, it takes time for the epithelium to recover. So, OME will be present temporarily in many children after an episode of AOM.

CLINICAL AND FUNCTIONAL ANATOMY

Middle ear cleft is a continuous space that extends from the nasopharyngeal orifice of the eustachian tube to the furthermost mastoid air cells. Three main segments are the eustachian tube; middle ear (tympanum); and the air cells of

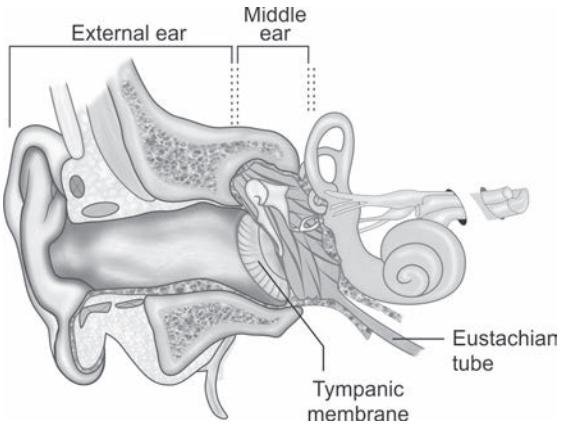


Fig. 1: Anatomy of the external and middle ear

the mastoid, petrosa, and related areas. Tympanic membrane facilitates sound transfer also allow it to serve as a clinical window into the middle ear cleft, one that permits inferences about the condition of the tympanum based on visible changes in the color, mobility, or position (Fig. 1).

Mucosal lining of the middle ear cleft varies from the thick, ciliated, respiratory epithelium of the eustachian tube and anterior tympanum to the thin, relatively featureless cuboidal epithelium in the mastoid cells.

OBJECTIVE FINDINGS

Otoscopic findings of inflammation in AOM may include decreased mobility of the tympanic membrane that is manifested by difficulty in assessing the ossicular landmarks, yellowness and/or redness with hypervascularity, purulent middle ear effusion (MEE), and, occasionally, bullae. This appearance clearly contrasts with that of OME.

Findings that suggest the presence of OME include observable air-fluid levels (which may be vertically oriented), serous middle ear fluid, and a translucent membrane with diminished mobility.

Otitis media with effusion can also be associated with negative pressure in the middle ear. This negative pressure is suggested by the prominence of the lateral process, a more horizontal orientation of the malleus, and movement only with negative pneumatoscopy.

Occasionally, tonsillar hypertrophy can accompany findings of OME. More commonly, adenoid hypertrophy is present. Additional findings may include turbinate bogginess, postnasal drip, rhinorrhea, and watery and/or erythematous eyes consistent with a concurrent upper respiratory tract infection (URTI) or environmental allergies.

PATHOPHYSIOLOGY

Otitis media with effusion can occur during the resolution of AOM once the acute inflammation has resolved. Among children who have had an episode of AOM, as many as 45% have persistent effusion after 1 month, but this number decreases to 10% after 3 months.

Classic Theory

The classic explanation proposes that eustachian tube dysfunction is the necessary precursor. If eustachian tube dysfunction is persistent, a negative pressure develops within the middle ear from the absorption and/or diffusion of nitrogen and oxygen into the middle ear mucosal cells. If present for long enough and with appropriate magnitude, the negative pressure elicits a transudate from the mucosa, leading to the eventual accumulation of a serous, essentially sterile effusion.

Newer Theories

The newer models describe the primary event as inflammation of the middle ear mucosa caused by a reaction to bacteria already present in the middle ear. Indeed, Bluestone and others have shown (using radiographic evidence) that reflux up the eustachian tube is demonstrable in children prone to otitis media. Furthermore, Crapko et al. demonstrated the presence of pepsin in the middle ear space of 60% of children with OME. This reflux certainly may also occur in otherwise healthy individuals. Yilmaz et al. published a study that documented significant changes in oxidative stress in patients with OME. The investigators demonstrated a significantly improved but not normalized level of oxidants following the placement of ventilation tubes.

ETIOLOGY

Clinical Pearl

- OME and AOM—still one of the most researched area in otology.

Same flora found in AOM can be isolated in OME. With OME, the inflammatory process has clearly resolved, and the volume of bacteria has decreased. However, because of the similarity of these two conditions, reviewing the pathogenic organisms in AOM is worthwhile.

Common Pathogens

The most common bacteria in AOM, in order of frequency, are:

- *Streptococcus pneumoniae* is found in 35% of cases, and the prevalence does not seem to vary with age; the serotypes most commonly isolated, in order of frequency, are 19, 23, 6, 14, and 3
- *Haemophilus influenzae* is found in 20% of cases; of these cases, 25–45% involve beta-lactamase production, with a clear trend of increasing resistance
- *Moraxella catarrhalis* is found in 4–13% of cases of AOM, with a great frequency in winter and autumn; of these cases, 70–100% involve beta-lactamase production.

Additional bacterial pathogens include *Streptococcus pyogenes, Staphylococcus aureus,* Gram-negative enteric bacteria, and anaerobes. When an effusion is present for longer than 3 months, *Pseudomonas* species predominate.

In other more recent studies, viruses have been isolated in conjunction with bacteria in 15–20% of cases of AOM.

Respiratory syncytial virus (RSV) and influenza virus were the most frequent.

The primary difference with the pathogens in OME compared with AOM is that the frequency of *S. pneumoniae* is not as high, and *H. influenzae* and *M. catarrhalis* are moderately more common.

- Allergy has long been recognized as one of the causative factors of OME. Nasotubal mucosal congestion associated with inhalant allergy and obstruction of the ET was mentioned earlier. A significant association has been reported between food allergy and serous otitis media (SOM) and recurrent AOM is more prevalent among children suffering from immunodeficiency.

Some other causes are multiple: Young age, bottle feeding, crowded living conditions (including day-care centers), heredity, and a variety of associated conditions including cleft palate, immunodeficiency, ciliary dyskinesia, Down syndrome and cystic fibrosis. The genetic factors of otitis media have yet to be delineated (Table 2).

EPIDEMIOLOGY

Middle ear infections are the most common medical problem in infants and children of preschool age.

Clinical guidelines from a joint commission of specialties document that screening surveys of healthy children between infancy and age 5 years show 15–40% point prevalence in MEE. Furthermore, among children examined at regular intervals for 1 year, 50–60% of child care attendees and 25% of school-aged children were found to have an MEE at some point during the examination period, with peak incidence during the winter months.

Between 84% and 93% of all children experience at least 1 episode of AOM. Furthermore, approximately 80% of children have had an episode of OME when younger than 10 years. The prevalence of OME is highest in those aged 2 years or younger, and it sharply declines in children older than 6 years.

Otitis media is more frequent in the winter months regardless of climate, presumably due to crowding in schools during the upper respiratory infection (URI) season. Henderson et al. (1982) confirmed the chronologic proximity of otitis media to URI in a day-care setting, which held regardless of time of year.

TABLE 2: Risk factor potentially incresing incidence otitis media

Intrinsic	Extrinsic
Patient age	Fall/winter season
Male gender	Upper respiratory infection
Atopic disease	Daycare
Immune deficiency	Older sibling
Palate anomaly	Passive smoke exposure
Craniofacial anomalies	Pacifier use in daycare
Genetic predisposition	Bottle feeding

PHYSICAL EXAMINATION

Otoscopic findings of inflammation in AOM may include decreased mobility of the tympanic membrane (which has a bulging contour) manifested by difficulty in assessing the ossicular landmarks, yellowness and/or redness with hypervascularity, purulent MEE, and, occasionally, bullae. This appearance clearly contrasts with that of OME.

Findings that suggest the presence of OME are observable air-fluid levels (which may be vertically oriented), serous middle ear fluid, and a translucent membrane with diminished mobility. Extensive inflammation and purulent MEE should not be evident.

Occasionally, tonsillar hypertrophy can accompany findings of OME. More commonly, adenoid hypertrophy is present, especially in patients with prolonged or recurrent condition. Other findings are turbinate bogginess, postnasal drip, rhinorrhea, and watery and/or erythematous eyes consistent with a concurrent URTI or environmental allergies (Fig. 2).

DIAGNOSTIC CHALLENGES

In adults, recognizing unilateral otitis media (OME) with effusion is crucial. It must be considered a nasopharyngeal mass until definitively proven otherwise. Indirect mirror examination or flexible nasopharyngoscopy should be performed. Imaging studies and possibly even biopsies may be indicated. Other neglected areas include:

- Failure to note hearing loss
- Failure to recognize a delay in language development in children.

The following are conditions that should be considered when evaluating patients with suspected OME:

- Benign nasopharyngeal masses
- Nasopharyngeal carcinoma

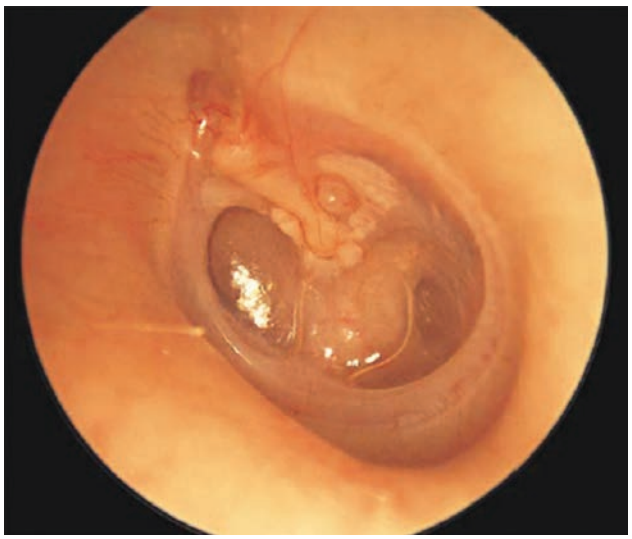


Fig. 2: Thin tympanic membrane showing fluid level

- Acute otitis media
- Adenoid hypertrophy
- Congenital defects affecting the eustachian tube and its egress
- Ciliary dyskinesia
- Immunoglobulin G (IgG) subclass deficiencies.

Differential Diagnoses

- Cleft palate
- Eustachian tube malfunction
- Malignant tumors of the nasal cavity
- Malignant tumors of the temporal bone
- Middle ear inflammation/infection
- Patulous eustachian tube
- Sinonasal manifestations of cystic fibrosis.

Assessment

Laboratory tests have rarely been used:

- History taking and physical examination are sensitive and specific enough to facilitate accurate diagnosis and treatment of the disease
- Obtaining cultures is not routine for this condition but is in tympanocentesis
- Complete blood cell (CBC) count is assessed to rule out active infection.

Radiologic Studies

Plain radiography of the nasopharynx is needed to identify enlarged adenoids.

Computed Tomography

Computed tomography (CT) scanning is extremely sensitive but done only in rare situations.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) useful in the workup for soft-tissue masses.

Pneumatic Otoscopy

American clinical practice guidelines have strongly advocated the use of pneumatic otoscopy as the primary diagnostic method for OME. The sensitivity of pneumatic otoscopy is 85–93% and its specificity from 71% to 89%. This can be carried out with a closed system in a handheld otoscope or with a Siegle's pneumatic speculum, viewed with headlight illumination or microscope. Acceptable to most children, the inability to gain a seal with the available speculum can occur in up to 20% of children aged over 18 months.

Video Otoscopy

Video recordings of otoscopy, including pneumatic otoscopy, can be documented and used to monitor changes with time. It can also be used for teaching and research purposes.

Free-field Testing

In primary care, audiometry is seldom available, particularly for younger children. Under these circumstances, the practitioner could perform free-field voice testing of hearing.

Tympanometry

Tympanometry is perhaps the most useful of all tests in association with OME. This test reveals a type B result in 43% of cases of OME and a type C result in 47% of cases.

Though an acoustic seal is sometimes difficult to achieve, bilateral tympanograms should be obtainable in the majority (98%) of children between the ages of 3.5 and 7 years, in a slightly lower percentage (90–94%) of infants 2–11 months of age and 78–88% of infants 12–24 months of age are included.

According to American Academy of Family Physicians (AAFP), the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), and the American Academy of Pediatrics (AAP) subcommittee on OME, audiology is a necessary component of the evaluation of certain patients with this condition.

The committee not only stated that initial hearing testing can be done in a primary care setting for children aged 4 years or older, but it also stated that conventional audiometry with earphones is performed with a fail criterion of more than 20 dB HL at 1 or more frequencies (500, 1000, 2000, 4000 Hz) in either ear.

Language Testing

Language testing has also been advised for children with hearing loss (pure tone average greater than 20 dB HL on comprehensive audiometric evaluation). Testing for language delays is important, because communication is integral to all aspects of human functioning (Box 1).

Box 1: Host factor that potentially increase the risk of language delay with otitis media

- Eustachian tube dysfunction
  - Over cleft palate
  - Submucous cleft palate
  - Craniofacial anomaly
- Congenital conductive hearing loss
  - Aural stenosis/atresia
  - Ossicular malformation
- Neuro-developmental/behavioral issues
  - Attention deficit disorder
  - Autism, pervasive developmental delay
  - Global developmental dealy
  - Mental retardation
  - Chromosomal anomalies
- Sensorineural hearing loss
- Primary language delay

Tympanocentesis and Myringotomy

Tympanocentesis involves aspiration of effusion from the middle ear. Tympanocentesis can serve as both a therapeutic procedure and a diagnostic procedure.

The criterion for documentation of an MEE is myringotomy, which has the advantage of increased exposure and better suctioning relative to tympanocentesis. Only disadvantage

is a larger incision with a greater, although small, chance of persistent perforation or otorrhea.

OVERVIEW OF MEDICAL AND SURGICAL APPROACHES

Clinical Pearls

- Modification of risk factors is also a form of definitive management
- Reasonable primary intervention
- Avoidance of passive smoking
- Breastfeeding is associated with a lower incidence of otitis media
- No feeding in supine position
- Avoidance of exposure to large number of children
- Avoidance of Allergens.

Summary of Medical Intervention

The American Academy of Family Physicians (AAFP), the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), and the American Academy of Pediatrics (AAP) subcommittee on OME published clinical guidelines for OME:

- Document the laterality, duration of effusion, and presence and severity of associated symptoms at each assessment of the child with OME
- Distinguish the child with OME who is at risk for speech, language or learning problems from other children with this condition, and more promptly evaluate hearing, speech, language and need for intervention in children at risk
- Manage the child with OME who is not at risk with watchful waiting for 3 months from the date of effusion onset (if known), or from the date of diagnosis (if onset is unknown)
- Hearing testing should be conducted when OME persists for 3 months or longer, or at any time that language delay, learning problems, or a significant hearing loss is suspected in a child with OME
- Children with persistent OME who are not at risk should be reexamined at 3–6 month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Autoinflation

Many studies have reported mixed results when attempting to determine if autoinflation, compared with no intervention, improves effusion clearance rates. However, it is not routinely practiced.

Summary of Surgical Intervention

The following is a verbatim summary of the AAFP, AAO-HNS, and AAP clinical guideline recommendations:

- When a child becomes a surgical candidate, tympanostomy tube insertion is the preferred initial procedure
- Adenoidectomy should not be performed, unless a distinct indication exists (e.g., nasal obstruction, chronic adenoiditis)
- Repeat surgery consists of adenoidectomy plus myringotomy, with or without tube insertion
- Tonsillectomy alone or myringotomy alone should not be used to treat OME.

Medication

Pharmacologic management of OME includes administration of antimicrobial agents, steroids, antihistamines and decongestants, and mucolytics.

Antimicrobial Agents

Otitis media with effusion demonstrates viable pathogenic bacteria, treatment with appropriate antibiotics is reasonable, albeit with evidence showing only short-term benefit.

Commonly used drugs are erythromycin, sulfisoxazole, amoxicillin, amoxicillin-clavulanate, and trimethoprim-sulfamethoxazole.

Steroids

Empirical evidence indicates that steroids help in improvement of OME in cases resistant to 2 weeks of antibiotics. It may be beneficial to add intranasal steroids.

Antihistamines and Decongestants

Nasal obstruction, rhinorrhea, and sinusitis often accompany otitis media, and antihistamines and decongestants may be considered for the relief of these associated symptoms.

Mucolytics

Used in antibiotic resistant cases.

Indications for Surgical Intervention

Surgical intervention is indicated in cases of developmental delays, particularly in the areas of speech and language development.

Children who need aggressive intervention include any of the following:

- Children with permanent hearing loss independent of OME
- Those with suspected or diagnosed speech and language delay or disorder
- Those with autism spectrum disorder or other pervasive developmental disorders
- Children with syndromes (e.g., Down syndrome) or craniofacial disorders that include cognitive, speech and language delays
- Those who are blind or have uncorrectable visual impairment
- Children with cleft palate, with or without an associated syndrome
- Children with developmental delay.

MYRINGOTOMY

This section will briefly review myringotomy and aspiration of effusion and myringotomy with pressure equalization tube (PET) insertion.

Myringotomy and Ventilation Tubes

Introduced in 1954 by Armstrong, ventilation tube insertion has become the criterion standard and most common therapy for chronic otitis media with effusion (COME). Improved hearing and decreased rates of AOM are absolute benefits of myringotomy with placement of ventilation tubes; these have been documented multiple times. Typically, the tubes self-extrude 9–12 months after placement.

Pressure equalization tubes are available in a variety of sizes, shapes and materials. All are designed to permit ventilation of the middle ear and mastoid system. Prolonged aeration of the middle ear has been shown to reverse the mucosal hyperplasia and metaplasia that accompany OME.

Complications

Overall complication rate of ventilation tubes are 11%.

- Persistent otorrhea is the most common complication, occurring in 15% of patients and persisting as long as 1 year in 5%
- Second in frequency is tympanosclerosis, which is not clinically significant unless it is extensive
- Persistent perforation is seen in approximate 2% cases, where it is in place longer than 18 months. This complication is also known to increase with the placement of tympanostomy tubes (T-tubes) that are designed to stay in the tympanic membrane longer than the typical grommet tube
- Other lesser known complications are granulation tissue formation, cholesteatoma and sensorineural hearing loss.

Clinical guidelines summarize a number of studies and state that tympanostomy tubes are recommended for initial surgery, because randomized trials show a mean 62% relative decrease in effusion prevalence and an absolute decrease of 128 effusion days per child during the next year. Hearing levels improve by a mean of 6-12 dB while the tubes remain patent (Table 4) (Fig. 3).

Adenoidectomy

Although adenoidectomy was once the principal treatment for OME, easy and low-risk placement of PETs is now favored.

TABLE 4: Otitis media with effusion duration and tympanostomy tube

OME duration	Probability of spontaneous resolution	TT
<3 months	High	No
3–6 months	Intermediate	Placed on individuaized basis
>6 months	Low	Yes

TT, tympanostomy tube placement.

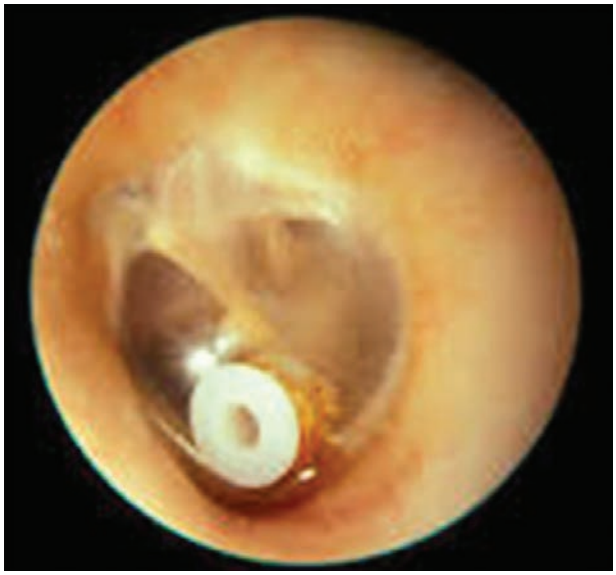


Fig. 3: Showing a tympanic membrane with grommet *in situ*

Three rationales exist for the removal of the adenoids in the treatment of OME and are discussed below.

Removal because of Enlargement

Enlarged adenoids occlude the nasopharynx and choanae. This potentiates eustachian tube reflux. However, multiple studies have revealed that the result of adenoidectomy is independent of adenoid size. This finding suggests that processes other than simple adenoid mass are involved.

Removal for Improvement of Eustachian Tube Function

Improvement in the equilibration of positive middle ear pressure after adenoidectomy has been documented. In addition, extremely large adenoids may physically occlude the eustachian tube orifice, although Bluestone and others have shown that this is rare. The obstruction is nearly always functional.

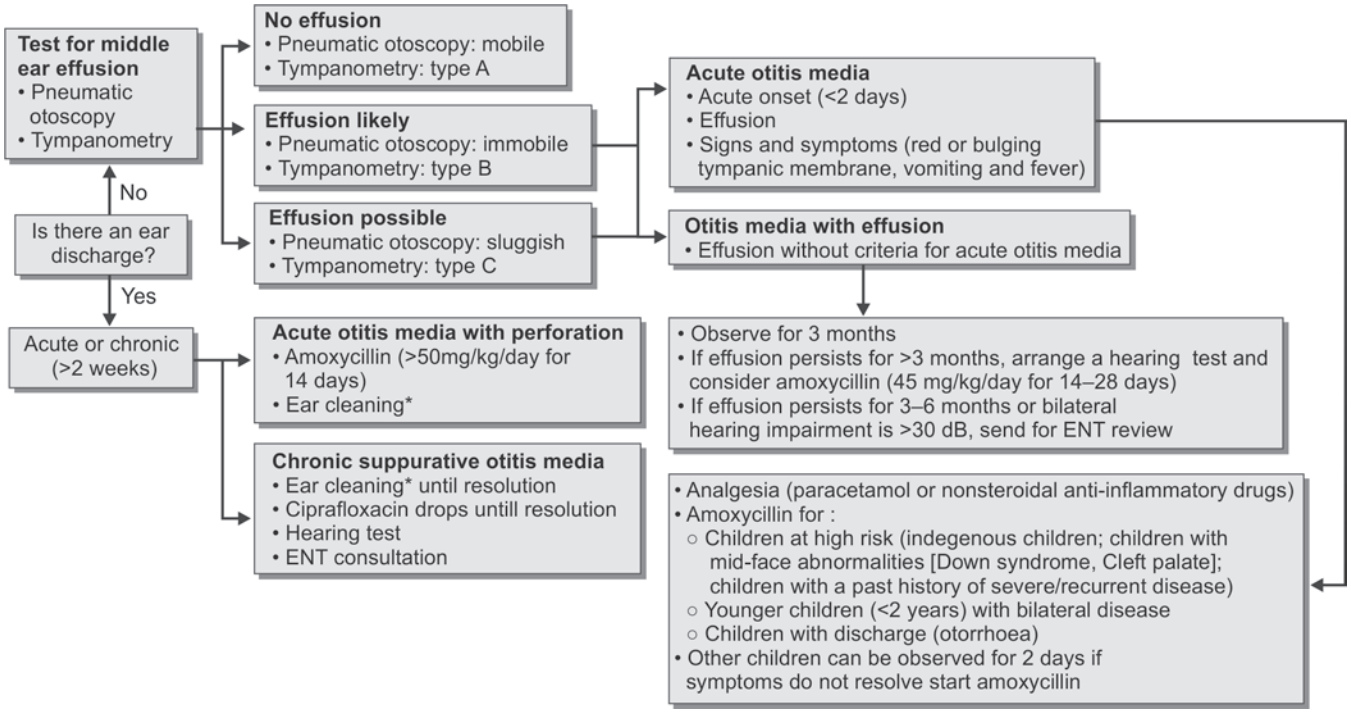
Removal of a Potential Source of Inflammation and Infection at the Eustachian Tube Orifice

The third and most recent rationale for adenoidectomy is to remove a potential inflammatory source and the presence of infection at the orifice of the eustachian tube. When performed correctly, adenoidectomy can be used to create a smooth nasopharyngeal mucosa, which decreases the colonization of bacteria that can occur in the crypts of adenoid tissue.

Complications of adenoidectomy include bleeding (0.4%), velopalatal insufficiency (usually temporary), and a patulous eustachian tube.

ALGORITHM 1

Management of otitis media with effusion



*Gentle suction cleaning

Long-term Monitoring

No standard of care for the follow-up of patients with OME has been established.

Most ventilation tubes stay in situ for 6–9 months and are extruded naturally through ear canal. Patient should be followed after 3 weeks after the placement of the tubes and then every 6 months thereafter, until the tubes extrude or are removed.

Patients are instructed that if more than two episodes of otorrhea occur before the 6-month follow-up is scheduled, they should see their otolaryngologist (ENT) instead of or in addition to their primary care physician (PCP)/pediatrician. We recommend the removal of ventilation tubes that have not spontaneously extruded between 18 and 24 months after placement due to the increasing risk of persistent tympanic membrane perforation.

The otolaryngologist should monitor patients until the conditions resolves with medical or surgical intervention. Thereafter, if the patient's hearing is normal, the primary physician/pediatrician can provide care. If a documented hearing loss is present, it should be reevaluated for severity and type of management.

A multidisciplinary team should rigorously follow and aggressively treat language-related developmental delays. Interventions should include the use of hearing aids, if justified.

Clinical Pearls

To treat or not to treat, that is the question

- Significant associated conductive hearing loss
- Occurrence in young infants, as they are unable to communicate about their symptoms and may have suppurative disease
- An associated acute suppurative URTI
- Concurrent permanent conductive/sensorineural hearing loss
- Presence of speech/language delay associated with effusion and hearing loss
- Tinnitus, vertigo or disequilibrium
- Alterations of tympanic membrane, such as a retraction pocket
- Middle-ear changes, such as adhesive otitis media or ossicular involvement
- Previous surgery for otitis media (e.g., tympanostomy tube placement or adenoidectomy)
- When episodes of acute otitis media recur frequently (5–6 episodes/year)
- Effusion that persists for 3 months or longer (i.e. chronic otitis media with effusion, before consideration for tympanostomy tube placement)
- Difficult as it is each patient has to be taken up for surgery at his own merit considering a holistic global understanding of the extent of the problem, the effect on quality of life and above all possibility of sequelae and complications in later life.

PITFALLS

Thorough investigations required for persistence of OME as in children with craniofacial abnormalities.

Medical Therapy to manage the mucosal aspect of the disease will be required regardless of surgical intervention.

Limitations of surgical management of tube placement, i.e., persistent otorrhea, tympanosclerosis, persistent perforation (2%), others—focal atrophy, granulation tissue formation, cholesteatoma, and SNHL.

KEY POINTS

- ☞ Secretory otitis media is non-inflammatory middle ear effusion usually following acute otitis media (AOM)
- ☞ Diagnosis is clinical; adults and adolescents must undergo nasopharyngeal examination to exclude malignant or benign tumors
- ☞ Antibiotics and decongestants are not helpful
- ☞ If unresolved in 1–3 months, myringotomy with tympanostomy tube insertion may be needed
- ☞ Myringotomy and ventilation tube insertion is a safe and effective way to relief middle ear dysfunction and audition loss, it should be considered to be a basic principle of therapy
- ☞ Xylitol chewing gum appears to decrease rates of AOM secondary with otitis media effusion in children going to daycare by 25%.

SUGGESTED READINGS

1. American Academy of Pediatrics. Otitis media with dysfunction in young children: a comparison of 1412-29. OME guidelines.
2. Bluestone CD. State of the art: definitions and classifications. In: Liu DJ, Bluestone CD, Klien JO, Nelson JD (Eds). Recent Advances in Otitis Media with Effusion. Proceedings of the 3rd International Conference. Ontario: Decker and Mosby; 1984.
3. Cavanaugh RM. Obtaining a seal with otic specula: must we rely on an air of uncertainty? Pediatrics. 1991;87:114-6.
4. Crapko M, Kerschner JE, Syring M, Johnston N. Role of extra-esophageal reflux in chronic otitis media with effusion. Laryngoscope. 2007;117(8): 1419-23.
5. Engel J, Anteunis L, Chenault M. Otoscopic findings in relation to tympanometry during infancy. European Archives of Otorhinolaryngology. 2000;257:366-71.
6. Henderson FW, Collier AM, Sanyal MA, Watkins JM, Fairclough DL, Clyde WA Jr, et al. A longitudinal study of respiratory viruses and bacteria in the etiology of acute otitis media with effusion. N Eng J Med. 1982;306:1377-83.
7. Kaleida PH. Evidence assessment of the accuracy of methods of diagnosing middle ear effusion in children with otitis media with effusion. J Pediatr. 2004; 145(1):138.
8. Medical Research Council Multicentre Otitis Media Study Group. Sensitivity, specificity and predictive value of tympanometry in predicting a hearing impairment in otitis media with effusion. Clinical Otolaryngology. 1999;24: 294-300.
9. Palmu A, Puhakka H, Rahko T, Takala AK. Diagnostic value of tympanometry in infants in clinical practice. International Journal of Pediatric Otorhinolaryngology. 1999;49:207-13.
10. Pichichero ME, Poole MD. Assessing diagnostic accuracy and tympanocentesis skills in the management of otitis media. Arch Pediatr Adolesc Med. 2001;155(10):1137-42.
11. Preston K. Pneumatic otoscopy: a review of the literature issues in comprehensive pediatric nursing. Good Literature Review. 1998;21:117-28.
12. Rosenfeld RM, Culpepper L, Doyle KJ, Grundfast KM, Hoberman A, Kenna MA, et al. Clinical practice guideline: otitis media with effusion. Otolaryngol Head Neck Surg. 2004;130(5 Suppl):S95-118.
13. Tracy JM, Demain JG, Hoffman KM, Goetz DW. Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion. Ann Allergy Asthma Immunol. 1998;80(2):198-206.
14. Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. A meta-analytic attempt to resolve the brouhaha. JAMA. 1993;270(11):1344-51.
15. Yilmaz T, Koan EG, Besler HT, Yilmaz G, G rsel B. The role of oxidants and antioxidants in otitis media with effusion in children. Otolaryngol Head Neck Surg. 2004;131(6):797-803.

CHAPTER 148

Pediatric Sinusitis

Devinder Rai

INTRODUCTION

The paranasal sinuses in childhood are difficult to evaluate because of the variability in size, shape, and patterns of development. However, the child's sinuses are affected by a wide spectrum of conditions including congenital abnormalities, inflammatory, traumatic and neoplastic conditions.

At birth, both the maxillary and ethmoid sinuses are present; however, they are diminutive in size. Thus, they may appear to be opacified in infants in good health. As sinus development proceeds, opacification or mucous membrane thickening continues to be physiological till about 6 years of age.

The sphenoid sinus is underdeveloped and non-pneumatized at birth and only starts to aerate at about 3 years of age. The varying degrees of pneumatization of the sphenoid sinus results in three types:

1. Conchal
2. Presellar
3. Sellar.

The last sinus to develop is the frontal sinus, which starts appearing at the age of 6 and only completes its aeration by the age of 15. Depending upon the extent of aeration of the frontal recess, which is the narrow hourglass shaped doorway leading to the frontal sinus, Kuhn divided the cells in the recess into four types:

1. Kuhn Type 1—Single cell above an agger nasi cell
2. Kuhn Type 2—Two or more cells above and behind agger nasi cell
3. Kuhn Type 3—Single large cell above agger nasi, pneumatized into frontal sinus (<50% the height of frontal sinus)
4. Kuhn Type 4—Single large cell above agger nasi, pneumatized into frontal sinus (>50% the height of frontal sinus).

SINUSITIS

The common predisposing events that set the stage for acute bacterial sinusitis are acute viral upper respiratory infections that result in a viral rhinosinusitis (a diffuse mucositis that predisposes to approximately 80% of bacterial sinus infections) and allergic inflammation (that predisposes to 20% of bacterial sinus infections). Children have 6–8 viral upper respiratory infections each year; it is estimated that 5–13% of these infections may be complicated by a secondary bacterial infection of the paranasal sinuses.

Sinusitis in children is also associated with an increased risk of complications. The complications of sinusitis may be divided into orbital, intracranial and local complications. The increased risk may be attributed to the low immunity of the children as well as the low bone density of the lamina and the fovea ethmoidalis.

CLASSIFICATION

According to duration of sinusitis:

1. Acute Sinusitis (7 days to 4 weeks)
2. Subacute sinusitis (4–12 weeks)
3. Chronic sinusitis (persistence of symptoms beyond 3 months).

According to etiology or the causative factors:

1. Bacterial
2. Fungal; Fungal sinusitis is usually seen in children who are immunocompromised. Thus, the cause of immunocompromise if any should be searched for in any child suffering from fungal sinusitis. The cause could be uncontrolled Type 1 diabetes, children undergoing steroid therapy, HIV infection, or those suffering from neoplastic conditions of the blood cells
3. Allergic sinusitis without polyposis: children are inherently prone to allergies, which is manifested as nasal discharge and nasal obstruction leading to obstructive sleep apnea symptoms
4. Allergic sinusitis with nasal polyposis: nasal polyposis, being relatively common in adults is rarely seen in children. Any child with polyposis should be further examined to rule out ciliary dyskinesia syndromes, cystic fibrosis and other similar diseases.

BACTERIOLOGY

The usual bacteria implicated in sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella catarrhalis*. Other lesser common bacteria isolated were *Staphylococcus aureus*, *Bacteroides*, *Peptostreptococcus*, *Fusobacterium*, and *Prevotella*.

In immunocompetent children the usual fungal species responsible are *Aspergillus* and *Candida*. However, in immunocompromised individuals, there is a greater incidence of invasive fungal sinusitis with *Rhizopus* and *Mucor spp*.

NATURAL HISTORY

Usually, bacterial sinusitis occurs as sequelae of viral sinusitis. Every child on an average has about 5–7 attacks of allergic rhinitis per year. The most common causative factor is viral.

Due to viral rhinitis there is increased nasal discharge or rhinorrhea along with nasal congestion and edema of the nasal mucosa. Another effect of viral infection is that there is ciliary dysfunction leading to impaired clearance of secretions particularly in the sinuses. This leads to stasis, which over a period of time undergoes secondary infection leading to bacterial sinusitis along with all its signs and symptoms.

Due to the bony immaturity of the pediatric skeleton and thin intervening septa between the eye and the ethmoid sinuses there is an increased incidence of complications in pediatric sinusitis.

SYMPTOMOLOGY

The typical symptoms of nasal obstruction, nasal discharge and headache as seen in the adult population are rarely seen among young children. Thus indirect signs are considered as pointers to a possible sinusitis in infants and young children.

The diagnosis of pediatric rhinosinusitis is usually based on a combination of history, physical examination, laboratory investigation and radiological findings.

The first and perhaps most common clinical indicator of sinusitis in children is similar to that of a viral upper respiratory tract infection which is refractory to supportive therapy. According to Lusk, it is virtually impossible to differentiate between an upper respiratory tract infection and rhinosinusitis during the first 7–10 days of symptomatology. Symptoms may include:

1. Rhinorrhea which may be serous or mucopurulent
2. Nasal congestion
3. Cough
4. Low grade fever, malaise and irritability
5. Dental pain.

However, in more advanced cases, there may be high-grade fever and a profuse purulent nasal discharge. Always this should also raise the suspicion of a nasal foreign body in infants. Once excluded, this may be the sign of acute sinusitis. Several warning signs point to an impending complication of acute sinusitis like:

1. Periorbital pain and swelling
2. Double vision in more advanced cases leading to loss of vision in extreme cases
3. Signs indicating intracranial involvement like meningismus and altered sensorium.

COMPLICATIONS

There is an increased incidence of complications in pediatric sinusitis due to the following reasons:

1. Thinner bony septa and sinus walls
2. Greater porosity of bones
3. Larger vascular foramina
4. Open suture lines.

The complications occurring in sinusitis can be divided into orbital, intracranial or local complications. The incidence of orbital complications is higher with about 75% of pediatric sinusitis cases presenting with an orbital complication. This greater incidence of orbital complications can be attributed to the close relationship between the sinuses and the orbit, which are separated only by a thin bone, the lamina papyracea, which has congenital dehiscences.

Chandler et al., divided the orbital complications into five stages:

1. Stage of preseptal cellulitis
2. Stage of orbital cellulitis
3. Stage of subperiosteal abscess
4. Stage of orbital abscess
5. Stage of cavernous sinus thrombosis.

PRESEPTAL CELLULITIS

This is the first stage of orbital complications of sinusitis. About 30% of children with sinusitis have preseptal cellulitis as the initial presentation. The signs include eyelid edema and erythema. There is normal extraocular muscle movement and normal vision. The diagnosis of preseptal cellulitis is based upon the characteristic clinical picture and radiological finding. The radiologic findings include diffuse thickening of the lids and conjunctiva.

Medical therapy is usually sufficient in preseptal cellulitis which consists of IV antibiotics, head end elevation and warm compresses. Decongestant therapy consisting of mucolytics, topical and systemic decongestants should be instituted to facilitate drainage of sinuses.

ORBITAL CELLULITIS

This stage consists of post-septal infection, which is characterized by eyelid edema and erythema. On external examination, chemosis and proptosis may be present. Extraocular muscle movement may or may not affect in this stage. Vision is normal though blurring may be present due to proptosis. There is no discrete abscess however localized inflammation signs are positive. Radiologically there is a low attenuation next to lamina papyracea.

Orbital cellulitis stage may be managed the same as the stage of preseptal cellulitis. However, due to advanced stage

frequent visual acuity testing and extraocular movement testing is warranted. Surgical drainage is indicated if no improvement or worsening of symptoms is seen after 48 hours of medical therapy.

SUBPERIOSTEAL ABSCESS

The stage of subperiosteal abscess is characterized by pus formation between the periorbita and the lamina papyracea. This displaces the orbital contents downward and laterally. On local examination there is proptosis, chemosis, and total ophthalmoplegia. There is thus and increased risk of residual visual sequelae. The pus may rupture through the septum and present in the eyelids. On CT scanning there is a rim enhancing hypodensity with mass effect adjacent to lamina.

Treatment consists of combined medical and surgical approaches. Only medical therapy has a success rate of about 50–67%. Combined approach is successful in 95–100% of the cases. Due to the morbidity associated with loss of eye function, we advocate an aggressive approach consisting of surgical drainage along with medical therapy consisting of IV antibiotics, systemic and topical decongestants and supportive therapy.

The surgical approach depends upon the location and extent of the abscess in question. In case of medical abscesses and endoscopic orbital decompression is preferred. However, in case of lateral abscesses an external ethmoidectomy via lynch incision or a transcaruncular approach is considered best.

ORBITAL ABSCESS

Orbital abscess is characterized by pus formation within orbital tissues. On local examination there is exaggeration of signs seen in subperiosteal abscess. There is visual impairment, which may range from blurring of vision to total visual loss. Vision loss constitutes an emergency and according to studies, the surgeon has about 100 minutes to save the vision before the loss becomes irreversible. On CT scanning there is a rim enhancing hypodensity within the orbital tissue, which may extend to the intraconal region.

Orbital abscess with its ominous complication of irreversible vision loss must be treated aggressively with surgical drainage the primary modality of treatment in addition to medical therapy.

CAVERNOUS SINUS THROMBOSIS

This dreaded complication of sinusitis is characterized by formation of clots in the cavernous sinus secondary to infection because of activation of the coagulation cascade. This condition is associated with chemosis, exophthalmos, decrease or loss of vision, headaches or paralysis of the cranial nerves 3, 4, 5, 6. Other common signs include signs of raised intracranial tension and sepsis. Infection can spread to contralateral sinus within 24–48 hours.

Clinical acuity and testing is paramount to diagnosis as the signs and symptoms of cavernous sinus thrombosis are characteristic. However, imaging used in confirming diagnosis consists of MRI Venogram in addition to CT scan. Cerebral angiography is invasive and not very sensitive to the diagnosis of cavernous sinus thrombosis.

Treatment includes early diagnosis and prompt medical therapy consisting of IV antibiotics. Drainage of sinuses to remove the source of infection is a must and should be done as soon as possible. The role of anticoagulants like heparin is controversial. Heparin should be used only if diagnosis is made within a few hours. In more delayed cases anticoagulants like warfarin may be tried.

LOCAL COMPLICATIONS

The basic premise of sinusitis is that it is always rhinologic in origin. The ideology being that rhinitis causes the nasal mucosa to undergo inflammation leading to edema and blockage of the sinus prechambers leading to accumulation of secretions in them which undergo secondary infections leading to sinusitis. The local complications of sinusitis are particularly more common in children as compared to adults due to the immature bony skeleton and incompletely closed foramina.

In an acute case there is an incidence of frontal bone osteomyelitis, which is termed as Potts Puffy Tumor. This is a misnomer as there is no actual tumor but a subperiosteal collection of pus in the frontal bone usually secondary to frontal sinusitis.

The other local complications of sinusitis in children are mucoceles and pyoceles. Pyocele is a collection of pus within a walled cavity usually present in the ethmoid or the sphenoid sinus leading to a myriad of symptoms depending on the sinus involved and its surrounding structures. A similar presentation but when the walled cavity contains sterile fluid it is termed as a mucocele. Sphenoidal mucoceles are considered more dangerous due to the close proximity of the optic nerve, which passes in the posterolateral wall of the sphenoid sinus, which invariably gets compressed due to the mucocele leading to visual deficits. According to various studies once the optic nerve gets involved or compressed, the surgeon has about 60 minutes to decompress the nerve in order to save its function before irreversible functional deficits occur, leading to the concept of the "golden hour".

INTRACRANIAL COMPLICATIONS

Due to the bony immaturity, thin fovea ethmoidalis and numerous foramina that remain open in children till full ossification takes place there is an increased incidence of intracranial complications as compared to adults. The signs and symptoms that the children present with are also subtle, thus a high degree of suspicion is needed to diagnose the intracranial complications.

There are five types of intracranial complications of sinusitis in children:

1. Meningitis
2. Epidural abscess

3. Subdural abscess
4. Brain abscess
5. Cavernous sinus thrombophlebitis.

These complications can also be considered as a spectrum of progression of disease. Thus the symptoms can be quite overlapping and confusion to the surgeon and the final diagnosis is often made radiologically. The common symptoms include general symptoms like fever, irritability, vomiting, seizures, and altered sensorium. Specific symptoms include hemiparesis, visual disturbances and other neurological deficits. Thus ruling out sinusitis is an important part of working up a child with such symptoms even with no preceding complaints of nasal discharge or obstruction.

The most common microorganisms isolated in children include *S. pneumoniae, S. aureus*, Gram-negative rods, and anaerobes.

Meningitis: Acute bacterial meningitis follows sinusitis and presents with all the general malaise symptoms in the child. In addition the child may have neck rigidity on examination and photophobia. The child may also present with cranial nerve palsies. Upon examination, the various tests done are the Kernig's sign and Brudzinki's sign. Radiologically there may be enhancement along the meninges but with no abscess formation.

EPIDURAL AND SUBDURAL ABSCESS

Due to the usual ambiguity between the two types of abscesses, which are close to one another, they may be considered together. They present with fever with chills and rigors, headache and vomiting. Due to raised intracranial tension there may be features of papilledema upon fundoscopic examination. Epidural and subdural abscess are differentiated from one another radiologically. Epidural abscess presents with a rim shaped enhancement on CT scanning, whereas subdural abscess presents with biconvex or crescentic enhancing lesions. Subdural abscess also have a higher rate of residual neurological sequelae, which are present in 35–55% of the cases.

INTRACEREBRAL ABSCESS

In the present antibiotic era, brain abscesses have become extremely rare. However, if present they present the surgeon as an emergency with symptoms of altered sensorium, focal neurological deficits, seizures, and papilledema. There is also a grave prognosis as there is a 20–30% risk of mortality associated with it. On CT scanning there is hypodense lesion in the brain, usually in the frontal or temporoparietal lobe with peripheral rim enhancement.

DIAGNOSIS

A high clinical suspicion and rapid diagnosis is a must for pediatric sinusitis due to rapid progression of infection. A detailed history and clinical examination including anterior rhinoscopy is a must in every case. Flexible fibreoptic nasendoscopy is an invaluable tool in order to better assess the nasal cavity and the sinus prechambers. Laboratory investigations include nasal smears for bacteriology, blood work for leukocytosis, culture and for diagnosis of sepsis. The gold standard for the diagnosis of acute bacterial sinusitis is the recovery of bacteria in high density ($\geq 10^4$ colony-forming units/mL) from the cavity of a paranasal sinus. Blood investigations may also rule out immunodeficiency conditions and ciliary dyskinesia.

In children below 6 years of age with uncomplicated sinusitis radiography is generally not indicated. However, the American College of Radiology has taken the position that the diagnosis of acute uncomplicated sinusitis should be made on clinical grounds alone. They support this position by noting that plain radiographs of the paranasal sinuses are technically difficult to perform, particularly in very young children. Correct positioning may be difficult to achieve and therefore the radiographic images may overestimate and underestimate the presence of abnormalities within the paranasal sinuses.

CT scans of the paranasal sinuses should be reserved for patients in whom surgery is being considered as a management strategy (strong recommendation based on good evidence and strong panel consensus).

In complicated cases, radiography is invaluable in assessing the extent of disease as well as differentiating the type of complications present. In case of a suspected intracranial complication MRI may be considered as it has greater sensitivity and specificity as compared to a CT scan.

Lumbar puncture maybe considered to confirm the presence of meningitis; however, an ophthalmology consult must be sought prior to this invasive procedure to rule out raised ICT, as it may be fatal in such cases.

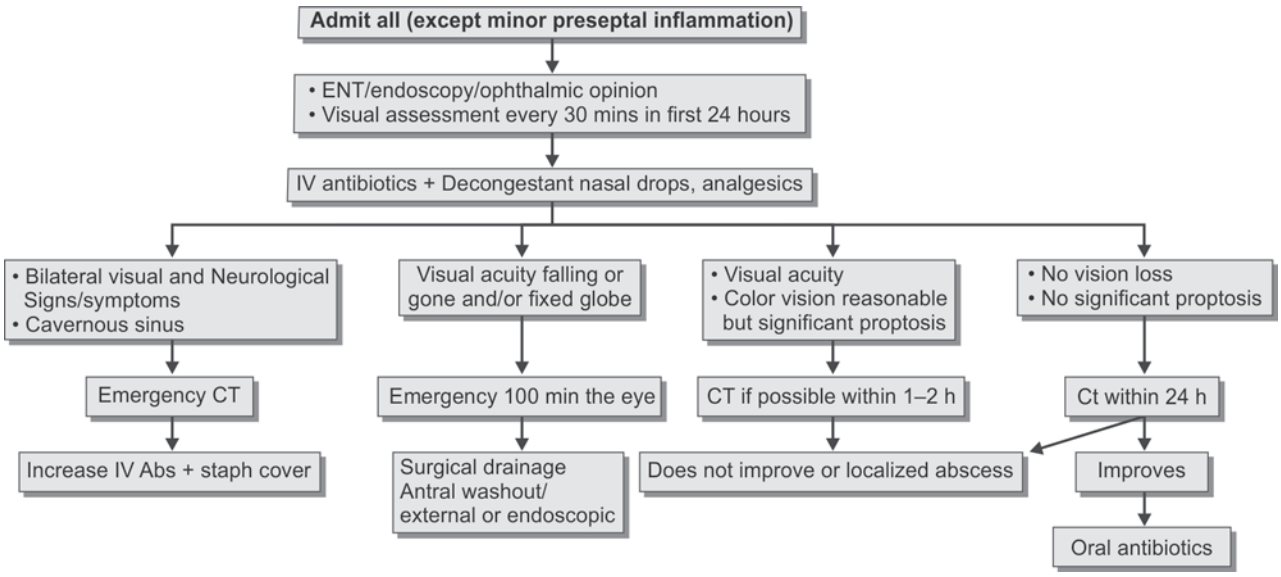
TREATMENT

For the sake of discussion, treatment of pediatric sinusitis can be divided into uncomplicated cases and cases with complications. However, treatment strategies are aimed to be aggressive due to the fulminant and rapid progression of infection in children.

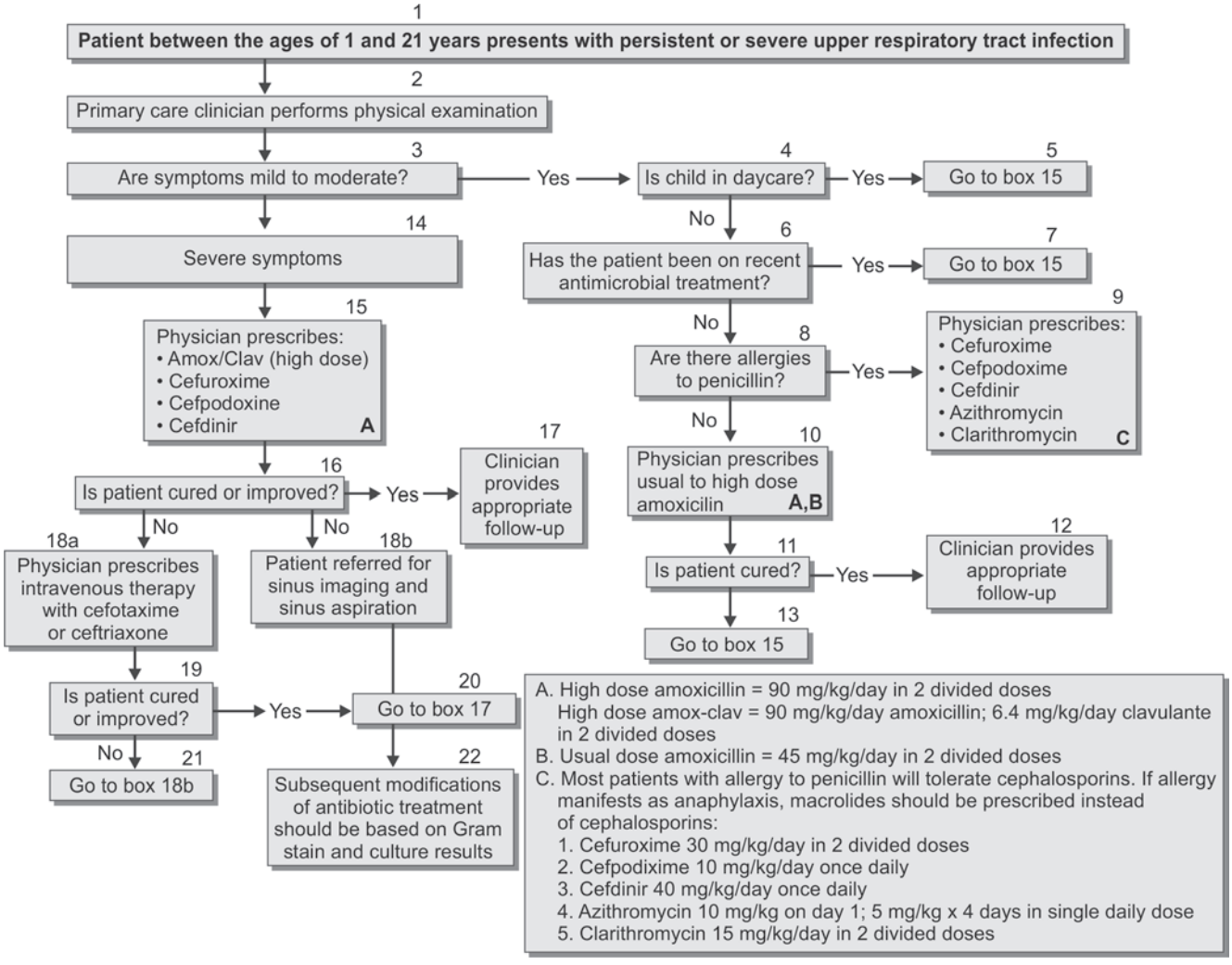
The mainstay of treatment of acute uncomplicated bacterial sinusitis is antibiotics, which may be parenteral or oral depending upon variables like severity, general condition of the child. In all suspected cases of complications hospital admission and IV antibiotics are a must. Supportive therapy including systemic and topical decongestants is controversial once sinusitis has set in. A short burst of corticosteroids may be given in atopic children to manage the symptoms but should be used with caution in fungal sinusitis. The following treatment algorithm has been recommended by the Subcommittee on Management of Sinusitis and Committee on Quality Improvement Paediatrics in 2001.

In complicated cases of sinusitis the treatment is more aggressive as compared and involves prompt radiography to diagnose the complication. In cases of orbital complication,

ALGORITHM 1



ALGORITHM 2



prompt surgical drainage of sinuses in addition to IV antibiotics is recommended except in Stage 1, where the role of surgery is debatable. In Stage 3 and above surgery is a must to prevent further complications. The norm is to do an endoscopic drainage of the sinuses and also to do an orbital decompression and remove the lamina papyracea.

The treatment in intracranial complications is to first differentiate between meningitis and frank abscess formation. This can be done by ruling out raised ICT through a retinal fundoscopy. In case of an abscess formation, surgical drainage is a must and should be done as early as possible. Drainage consists of removal of pus from the abscess as well as drainage of the paranasal sinuses. Thereafter antibiotic therapy and supportive management should continue.

In cases of mucocele and pyoceles, surgical drainage and decompression of the surrounding structures is the only option as supportive therapy has no role it the management. In cases of Sphenoidal lesions, which compress the optic nerve decompression of the nerve, must be carried out in the same sitting.

Clinical Pearls

- Antibiotics in all cases of sinusitis in children less than 2 years of age or in those who have had a complication in the past
- Early recognition of warning signs a must for successful treatment and prevention of complications
- Limited role of antihistaminics and systemic decongestants, IV antibiotics is the mainstay of treatment
- Multidisciplinary team to successfully diagnose and treat sinusitis and its complications
- Early radiography may remove doubt in most cases
- Prompt surgical intervention is a must in case of visual deficit and threatening complications.

KEY POINTS

- ☞ Bacterial sinusitis in children is usually preceded by viral rhinitis, which is one of the most common diseases in children
- ☞ Usual bacteria implicated are *S. pneumoniae, H. influenzae,* and *M. catarrhalis*
- ☞ The symptoms include runny nose, nasal obstruction, fever and cough
- ☞ High index of suspicion, anterior rhinoscopy and nasendoscopy is a must to diagnose pediatric sinusitis
- ☞ Increased rate of complications of sinusitis in children, which may be local, orbital or intracranial
- ☞ In case of complications IV antibiotics, prompt management and imaging is a must
- ☞ Surgery may be needed on an emergent basis to prevent vision loss in advanced orbital complications.

SUGGESTED READINGS

1. American Academy of Pediatrics. Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. Pediatrics 2001;108(3):798-808.
2. Chandler JR, Langerbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute rhinosinusitis. Laryngoscope. 1970;80:1414-28.
3. Kuhn FA. Chronic frontal sinusitis: the endoscopic frontal recess approach. Operative Techniques Otolaryngol Head Neck Surg. 1996;7:222-9.
4. Lusk RP, Stankiewicz JA. Pediatric rhinosinusitis. Otolaryngology—Head and Neck Surgery. 1997;117(3):S53-7.
5. Mackay IS, Lund VJ. Classification and differential diagnosis of rhinosinusitis. In: Michael Gleeson (Ed). Scott Brown's Otorhinolaryngology, 7th edition. pp. 2008;1380-6.
6. Miller AJ, Amedee RG. Sinus anatomy and function. In: Bailey BJ et al. (Eds). Otolaryngology—Head and Neck Surgery. 1(31): 413-21.
7. Ott NL, O'Connell EJ, Hoffman AD, Beatty CW, Sachs MI. Childhood Sinusitis. Mayo Clin Proc. 1991;66:1238-47.
8. Stammberger H, Lund VJ. Anatomy of the nose and paranasal. In: Gleeson M (Ed). Scott Brown's Otorhinolaryngology, 7th edition. pp. 2008;1315-43.

CHAPTER 149

Stridor in Children

Arvind S Bais

INTRODUCTION

It is not uncommon to come across many young anxious parents seeking advice for their child's problem of noisy breathing.

It is believed that less than 10% of the new born babies have some kind of noisy breathing and all of them do not fit into the category of congenital laryngeal stridor.

Clinical Pearl

- It is important to know that no clinical entity as congenital laryngeal stridor existing pathology in the upper airway and needs evaluation.

In clinical practice, a variety of terms are frequently used to describe the noisy breathing which are given in table 1.

It is essential to know that there are some basic differences between the larynx of an infant and adult larynx. A proper understanding which helps in treatment planning.

Infant larynx:

- Situated higher up in the neck close to the base of the tongue
- The size is small
- Epiglottis is infolded
- The aryepiglottic folds are large
- The internal diameter of the larynx is small
- The mucous membrane of the larynx is loosely attached especially in the subglottic region
- The entire cartilaginous framework of the larynx is soft.

TABLE 1: Terms frequently need to describe noisy breathing

	Site of origin
Wheeze	Intrathoracic airways
Stridor	Extrathoracic airways
Rattle	Either of the above or both
Snuffle	Nose and nasopharynx

Clinical Pearl

- As the internal diameter of the infant larynx is small even 1 mm of edema in the subglottic area narrows the airway to approximately 50% as compared to adults in whom no significant change occurs.

The gravity of the situation is enormous in infants. The causes of stridor can be divided into: (A) Congenital and (B) Acquired.

CONGENITAL CAUSES

- Laryngo tracheal stenosis
- Laryngeal atresia
- Laryngomalacia
- Tracheomalaci
- Laryngeal webs
- Laryngeal cysts
- Vascular abnormalities such as:
  - Aberrant left subclavian artery
  - Innominate artery compression
  - Double aortic arch
- Vocal cord palsy.

ACQUIRE CAUSES

- Laryngeal trauma
- Fixation of the arytenoid
- Epiglottitis
- Croup
- Multiple laryngeal:
  - Papilloma
- Bilateral abductor palsy of the vocal cords
- Cystic hygroma
- Hemangioma may be congenital or acquired
- Foreign bodies in the airway, i.e., larynx, trachea, and the bronchus

- Reflux laryngitis.

Laryngo-tracheal Stenosis

- Adopt the policy of wait and watch if the symptoms are mild. Allow the time for growth.
- If severe stridor is present do tracheostomy.
- Laryngo-tracheal reconstruction can be done at a later date.

Laryngeal Atresia

- It is usually incompatible with life.

Laryngomalacia

It is most common condition the clinical findings are as follows:

- Type I—The epiglottis is omega shaped
- Type II—The aryepiglottic folds are foreshortened
- Type III—The arytenoids have loosely attached mucous membrane or one may see a combination of both.

Diagnosis

Use flexible endoscope to assess the status of the larynx in spontaneous respiration. It is a self-limiting disease. No need for tracheostomy:

- Occasionally supraglotto
- Plasty in from of trimming of the soft tissues of the larynx may be required
- Symptoms usually subside by 2-3 years of age.

Clinical Pearl

- Genetic or familial incidence does occur. Reassure the parents regarding clinical improvement over a period of time.

Tracheomalacia

- The incidence ranges between 1 in 1,500 and 1 in 2,000 children. Diagnosis is by CT and MRI.
- Bronchoscopy reveals flattening of the trachea anteriorly or at the junction of middle and lower third of the trachea use of antibiotics is recommended to prevent bronchitis.
- In severe cases surgery is indicated.

Clinical Pearl

- The parents should be advice to bring their child for regular check-up in order to minimize unnecessary usage of antibiotics and overcome anxiety.

Laryngeal Webs

In the third month of gestation if the larynx fails to get recanalized web forms. In majority of cases webs are located anteriorly and are usually thick and complete:

- Patient presents with severe stridor
- Immediate measure requires tracheostomy following endoscopy.
- Abalation of the web by CO_2 laser.

Laryngeal Cysts

True congenital cysts of the larynx are extremely rare. There is severe stridor endoscopy reveals cystic swilling completely distorting the view of the larynx, originating from the aryepiglottic folds. Manage by Aspiration of fluid from the cyst, allow it to collapse and then followed by complete excision of the cyst wall. The procedure is known as deroofing and excision.

ACQUIRED CAUSES

Epiglottitis

Inflammation of the supraglottic Larynx caused by *H. influenzae* type B and rarely by streptococci and pneumococci. Asses by:

- Postural inspiratory stridor
- Drooling
- Thick mucus secretion
- High temperature.

Recommended:

- Pulse oximetry
- Monitor arterial blood gas (ABGS)
- Humidification
- Oxygenation
- Tracheostomy rarely done.

Clinical Pearl

- There is no evidence to show that the systemic corticosteroid is useful yet it is widely administered by pediatricians and otolaryngologists.

Croup

Most common between 6 months and 5 years of age. Commonly occurs in winter and is viral in origin.

Symptoms

- Inspiratory stridor
- Fever
- Barking cough.

Diagnosis

Lateral X-ray of the neck in extended position will reveal enlarged edematous epiglottis, called as Thumb sign or a tapered subglottic area called "steeple sign" is seen.

Management

Always admit the child. Humidification does not give much relief. Administer nebulized adrenaline. For moderate to severe cases systemic or nebulized corticosteroids is recommended.

Clinical Pearl

- Repeated clinical examination is most desired intervention as the clinical condition may worsen.

Foreign Bodies in the Airways

History of aspiration of foreign bodies in most of the cases occasionally no history of aspiration yet the child may have violent cough, breathing difficulty, difficulty in swallowing and inspiratory stridor.

Management:

- Ensure adequate airway
- Oxygenation in severe stridor
- Prophylactic antibiotics and systemic corticosteroids to be given on need based cases
- Plan for quick intervention in form of pan endoscopy, i.e., laryngoscopy bronchoscopy and in few cases esophagoscopy is required because foreign bodies in the upper end of esophagus is a common cause of unsuspected partial airways obstruction
- Endoscopic procedure requires good team work between pediatrician otolaryngologist and anesthetist
- Premedication is always by Atropine injection.
- Spontaneous anesthesia by use of nitrous oxide, oxygen and halothane
- Rarely muscle relaxant may be given.

Instruments:

- All types of rigid pediatric laryngoscopes including anterior commissure laryngoscope rigid bronchoscopes with internal diameter of 2.5 mm, 3 mm, 4 mm or 6 mm with facility for ventilation telescopes with an angle of 0, 30, and 70 degree and all types of foreign body removal forceps and powerful suction apparatus is a must.
- Tracheostomy tray should be kept ready one may need it at times.

Clinical Pearls

- In foreign bodies in the airway cases there is no viral prodrome.
- Always prefer to use rigid endoscopes as a flexible bronchoscope fails to give the depth of the field.

SUBGLOTTIC HEMANGIOMA

- May be congenital or acquired.
- Large hemangioma produces inspiratory stridor.
- Removal by CO_2 laser.
- Radiotherapy is contraindicated.
- Always look for cutaneous.

HEMANGIOMA IN SUCH CASES

In all cases of stridor the essential broad principles of approach is as follows:

- Proper history taking and clinical observation followed by auscultation
- Note the type of stridor
- Any relationship with change of posture. Note does it gets aggravated or stops by change of posture or while feeding
- Note the duration of stridor
- Is it continuous, regular or intermittent
- Any change in the pattern of stridor while crying
- Is there any aspiration while taking feeds
- Asses the neurodevelopmental status of the infant. It is very helpful in cases of laryngomalacia.

Clinical Pearls

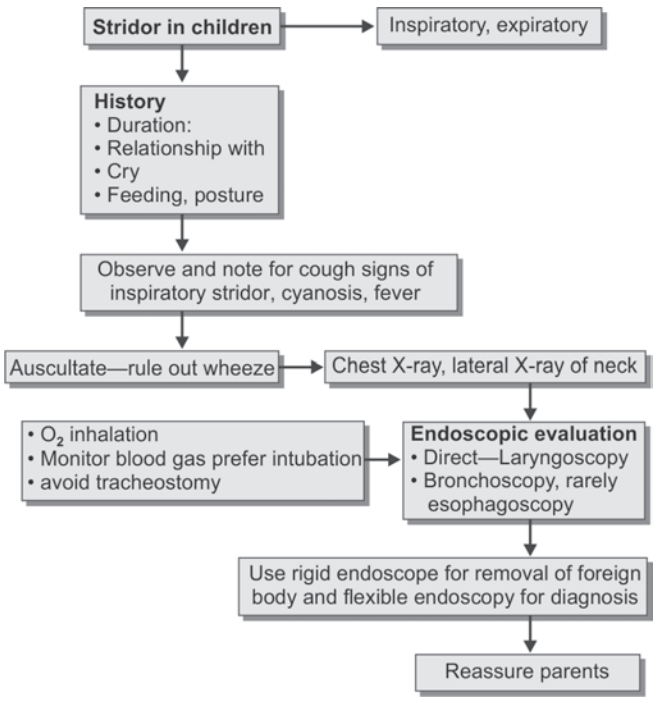
- Do not classify stridor as wheeze as one may miss upper airway obstructive pathology.
- Always look for respiratory distress, at times even slow respiratory rate. There may be evidence of Hypoxia, Hypercarbia and even cyanosis.

Abnormalities of the Cry

- In unilateral vocal cord palsy weak cry but obstructive airway symptoms are missing
- In bilateral vocal cord palsy the cry is weak but clear
- In tracheomalacia barking cough with or without stridor is present
- Absent or Muffled cry is noted in laryngeal web.

ALGORITHM 1

Workup of a child with stridor



Physical Signs

Inspiratory stridor:

- Breathing is rapid
- Recession of the suprasternal and Intercostal spaces
- In drawing of the epigastric region
- Flaring of the nostrils.

Nasal Patency Test

Put a small piece of cotton in front of the baby's nostril and observe for to and fro movement of cotton. Less movement on one or both sides gives an idea of nasal block. It helps in ruling out nosal causes of noisy breathing.

Radiology

- Lateral skiagram of neck in extended position is a must
- CT and MRI is very helpful in cases of stenosis and tracheomalacia
- Contrast radiography is not indicated except in cases of suspected vascular abnormalities
- Chest X-ray PA and lateral view should always be done.

KEY POINTS

- ☞ Supraglottic lesion causes inspiratory stridor while subglottic pathology may cause biphasic stridor
- ☞ Clinical evaluation of the patient cannot be overemphasised, it is a must
- ☞ Follow the principle of observation, palpation, and auscultation of the chest and neck also for any tracheal thud
- ☞ Never hesitate to consult anesthetist for proper management of airway, i.e., intubation, oxygenation tracheostomy and for endoscopy anesthesia
- ☞ Monitor oxygen saturation and arterial blood gas estimation
- ☞ Ultrasonography may be needed in vocal cord palsy
- ☞ Prefer laryngeal intubation than tracheostomy as much as possible
- ☞ In severe cases of stridor shift the patient to OT where all facilities for anesthesia, ventilator support, tracheostomy and endoscopy are available
- ☞ Flexible endoscopy is helpful for screening, but for removal of foreign bodies form the airway rigid endoscopy is preferred
- ☞ Never use jet ventilation anesthesia in cases of surgery of multiple papilloma of the larynx because of seedling and recurrence
- ☞ Autogenous vaccine and acyclovir do not give any benefit in laryngeal papilloma cases
- ☞ If there is delay in setting up OT trolly always intubate the child and oxygenate
- ☞ For laryngoscopic evaluation with a rigid laryngoscope in infants never try to lift the epiglottis with the tip of laryngoscope as severe laryngeal spasm may occur. Just wait for few seconds spontaneous visualization is possible because in infants the larynx is very close to the base of the tongue
- ☞ If foreign body such as seed of any such object has been removed piecemeal then always do a check bronchoscopy before discharging the patient from the hospital as a small foreign bodies if left in the bronchus may cause serious complications later on
- ☞ Be careful in bronchoscopy as one may override a foreign body and nothing may be found
- ☞ Carina is the thinnest part of tracheobronchial tree respect it while doing the endoscopy. A small tear may lead to spontaneous pneumothorax
- ☞ Never waste time in removing a foreign body especially in demonstrating its location as it may slip deeper down and make the whole procedure difficult and time consuming
- ☞ Gastroesophageal reflux may play a major role in acquired abnormalities in older children. In cases of laryngeal stenosis be treated first.

SUGGESTED READINGS

1. Cummings CW, Richardson MA, et al., Stridor and airway management. In: David Albert, Susanna Leighton (Eds). Otolaryngology Head and Neck surgery, 3rd edition. pp. 285-8.
2. Cummings CW. Congenital disorders of the Larynx. Otolaryngology Head and Neck surgery. pp. 262-84
3. Ear Nose and Throat Disorders. Mosbys Clinical Nursing Series, pp. 190-5.
4. Seiden AM, Gluckman JL, et al. Congenital disorders. In: Padhya TA, Wilson KM (Eds). Otolaryngology the Essentials. pp. 247-51.

CHAPTER 150

Upper Airway Obstruction and Sleep Related Breathing Disorders

Girish Raheja

INTRODUCTION

Habitual snoring during sleep, the hallmark indicator of increased upper airway resistance, is an extremely frequent occurrence during childhood, with a median incidence of about 10% among preschool and school-aged children, with subsequent declines in frequency after 9 years of age. The exact polysomnographic criteria that differentiate between innocent snoring (i.e., habitual snoring that does not lead to gas exchange abnormalities, sleep disruption and/or to any morbid consequences), and snoring that is associated with adverse consequences, have yet to be defined. Nevertheless, a consensus statement has been generated, and defines a set of empiric criteria, on the basis of which we currently estimate that of the many children with habitual snoring; approximately 2–3% will have clinically relevant disease. Therefore, the ratio between symptomatic habitual snoring and obstructive sleep apnea is usually between 3:1 and 5:1.

Whenever lymphoid tissue in a child occupies a disproportionate amount of space in the oropharyngeal region, it causes a compromise airway. The problem can be made more intense by associated anatomic conditions such as craniofacial abnormalities, obesity, laryngomalacia and conditions with diminished neuromuscular tone as in Down syndrome and cerebral palsy.

Tonsilar adenoid hyperplasia is often associated with upper airway obstruction in children. During daytime these children demonstrate an altered muffled "Hot Potato" closed voice with mouth breathing, rhinorrhea and hyponasal speech.

It is however during sleep they exhibit signs of the full spectrum of airway obstruction. This is due to the relaxation of the oropharyngeal relaxation leading to further obstruction. These children may usually snore loudly with cessation of breathing for intermittent periods with sternal retraction and paradoxical movement of the chest. The negative physiological outcome includes hypoxemia, hypercapnia and acidosis which leads to arousals, awakenings and a poor quality sleep. These children demonstrate a variety of behavioral problems including hyperactivity, lack of stamina, poor attention spans and daytime sleepiness or tiredness (Box 1).

Box 1: Clinical indicators of childhood obstructive sleep apnea

- Symptoms and signs anatomical and physiological characters
- Snoring underweight or overweight
- Witnessed apnea tonsillar hypertrophy
- Labored breathing adenoidal hypertrophy
- Restless sleep allergic rhinitis
- Mouth breathing micrognathia/retrognathia
- Impaired behavior high-arched palate
- Nasal blockage laryngomalacia
- Sweating during sleep neuromuscular disorder
- Cyanosis prematurity
- Daytime sleepiness failure to thrive
- Family history hypertension
- Obstructive sleep apnea

These disturbances in sleep are collectively called sleep related breathing disorders (SRBD). One such syndrome is called upper airway resistance syndrome (UARS) where a child with a significantly obstructive nose causes snoring, mouth breathing without significant apneas but a significant increase in respiratory effort related arousal giving rise to daytime fatigue and poor performance. This is now considered akin to mild obstructive sleep apnea (Box 2).

CLINICAL PRESENTATION

Children with significant obstructive sleep apnea if not treated may land up with cor pulmonale, right ventricular hypertrophy, congestive heart failure, pulmonary hypertension and edema, failure to thrive and are at a definitive risk for permanent neurologic damage and even death.

Box 2: Symptoms and signs of obstructive sleep apnea syndrome

- History:
  - Frequent snoring (≥3 nights/week)
  - Labored breathing during sleep
  - Gasps/snorting noises/ observed episodes of apnea
  - Sleep enuresis (especially secondary enuresis)*
  - Sleeping in a seated position or with the neck hyperextended
  - Cyanosis
  - Headaches on awakening
  - Daytime sleepiness
  - Attention-deficit/ hyperactivity disorder
  - Learning problems
- Physical examination:
  - Underweight or overweight
  - Tonsillar hypertrophy
  - Adenoidal facies
  - Micrognathia/retrognathia
  - High-arched palate
  - Failure to thrive
  - Hypertension

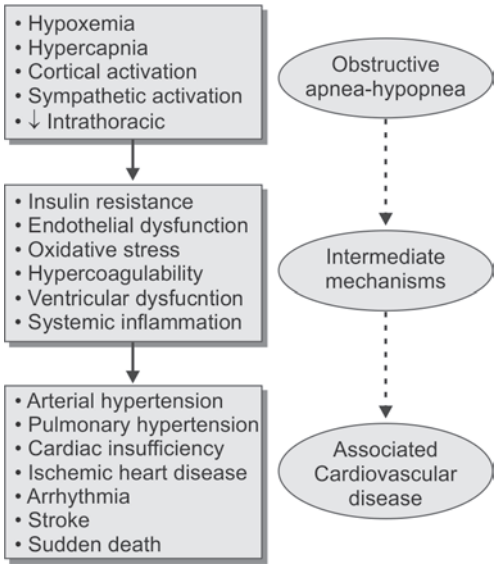
*Enuresis after at least 6 months of continence.

The prevalence of obstructive sleep apnea in children is 1–4% and surprisingly up to 10% of children may present with primary snoring. Physical examination should include the patient's weight, height, and body mass index. Detailed examination should be of heart and lung, head, and neck with special emphasis to adenoids, tonsils, mandible, and mid facial development. Adenoid facies is perhaps the most common observation.

Tonsil size should ideally be scaled from 1–4. Scale 1 being mild hypertrophy and Scale 4 would compromise more than 75% of the oropharyngeal airway. The adenoid size is best evaluated with a soft tissue lateral neck radiograph to assess the anteroposterior dimension of the nasopharynx. However, the correlation to the clinical symptoms is still effected by subjectivity.

ALGORITHM 1

Sleep related breathing disorders



Clinical Pearl

- Evaluation of the nasopharynx is only possible with a high quality radiograph requiring an experienced radiology technician.

The full extent of the problem can only be diagnosed with a full night polysomnography; however, in practical life the availability of pediatric sleep labs and the ability of the parent to conduct the study with a small child in a new environment is wrought with errors and therefore most clinicians find it convenient with clinical examination to interpret signs and symptoms as explained in literature to determine the presence or absence of obstructive sleep apnea in children. In a large majority this clinical decision-making is shown to be accurate. However, it may benefit a child with severe problems to consult with a pulmonologist and a cardiologist to rule out the ore significant and dangerous complications of obstructive sleep apnea.

Clinical Pearl

- Polysomnography is the gold standard for the diagnosis of obstructive sleep apnea and disordered breathing; however, in the absence of availability the clinician will need to relay on his clinical judgment for management of patients presenting with signs and symptoms as listed in the tables 1 and box 3 text.

In behavioral studies these children demonstrate a high prevalence of altered behavior such as withdrawal, anxiety, emotional lability, impulsivity, hyperactivity, aggressiveness,

TABLE 1: Symptoms and signs suggestive of sleep apnea hypopnea syndrome in children

Nighttime	Daytime
Continuous snoring (not only in exacerbation)	Normal
Observed respiratory pauses	Daytime oral breathing, nasal vioce, adenoid facies
Noisy breathing	Tonsillar hypertrophy
Oral breathing	Facial dysmorphia (retrognathia, micrognathia, marcoglosia, midfacial hypoplasia)
Increased respiratory effort (supra-sternal and intercostal retraction)	Difficulty to wake up, tiredness upon getting up, morning headaches, daytime sleepiness
Nocturnal sweating	Alterations in behavior (hyperactivity, aggressiveness, irritability, low school performance level)
Abnormal sleep posture (hyper-extension of the neck)	Delayed growth and low height/ weight development
Restless nocturnal sleep	Obesity
Cyanosis	Strong second heart sound
Nocturnal enuresis	Systemic arterial hypertension Presence of metabolic syndrome

Box 3: Symptoms and signs of obstructive sleep apnea syndrome

History:

- Frequent snoring (≥3 nights/week)
- Labored breathing during sleep
- Gasps/snorting noises/observed episodes of apnea
- Sleep enuresis (especially secondary enuresis)*
- Sleeping in a seated position or with the neck hyperextended
- Cyanosis
- Headaches on awakening
- Daytime sleepiness
- Attention-deficit/hyperactivity disorder
- Learning problems

Physical examination:

- Underweight or overweight
- Tonsillar hypertrophy
- Adenoidal facies
- Micrognathia/retrognathia
- High-arched palate
- Failure to thrive
- Hypertension

*Enuresis after at least 6 months of continence.

psychosomatic presentations, social problems, etc., in comparison with their peers.

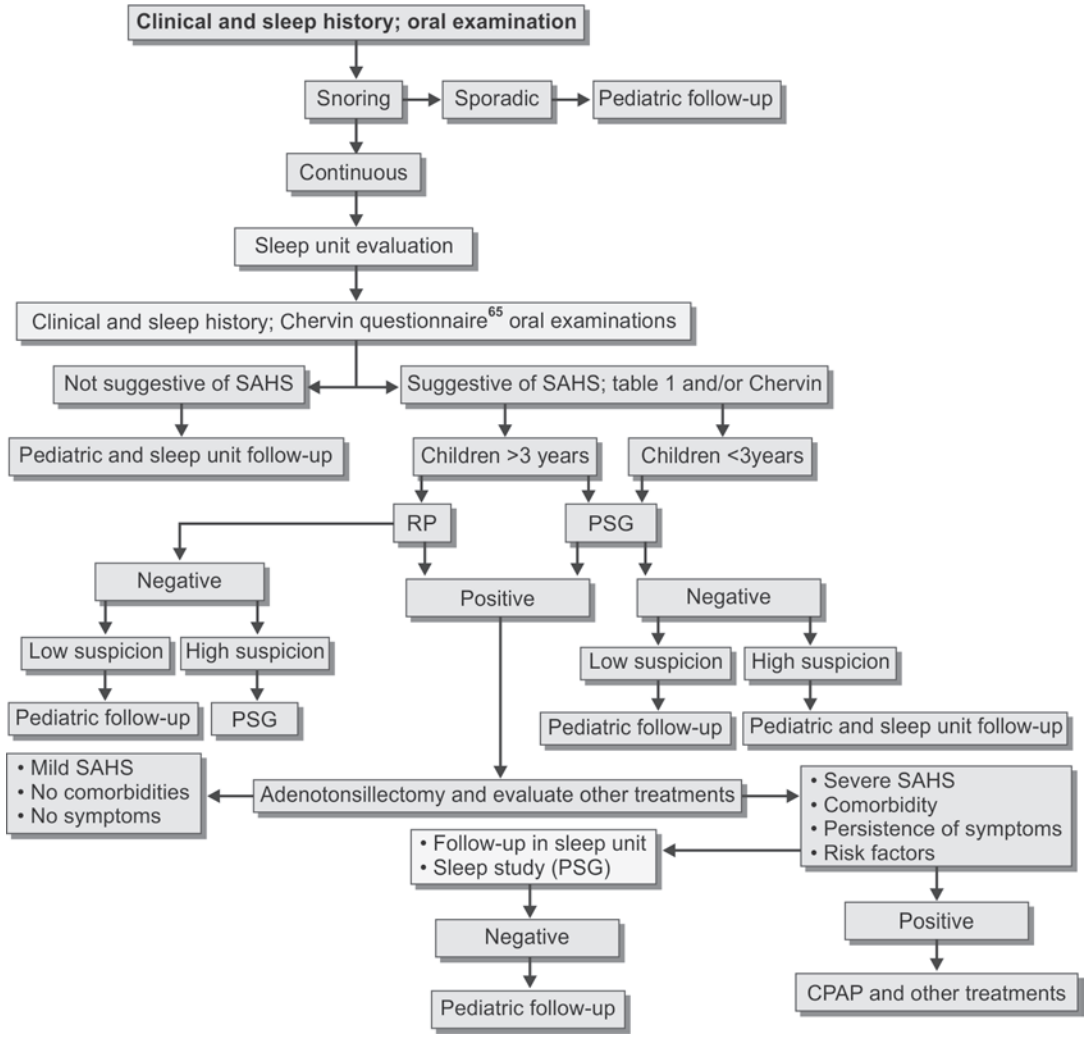
There is some suggestion that behavioral patterns may also be associated with reduced verbal abilities and language scores possibly a result of hypoxemia induced dysfunction of the frontal lobe. However, this supposition needs to be substantiated with research in future.

ADENOID AND TONSIL SURGERY FOR OBSTRUCTIVE SLEEP APNEA

Unfortunately there are few randomized studies in the efficacy of the tonsillectomy and adenoidectomy for children with obstructive sleep apnea. The most have concluded that Adenotonsillectomy should be considered first line of therapy for obstructive sleep apnea provided adenotonsillar hyperplasia is present. Outcomes appear to improve regardless of the measure used and show a definite improvement of

ALGORITHM 2

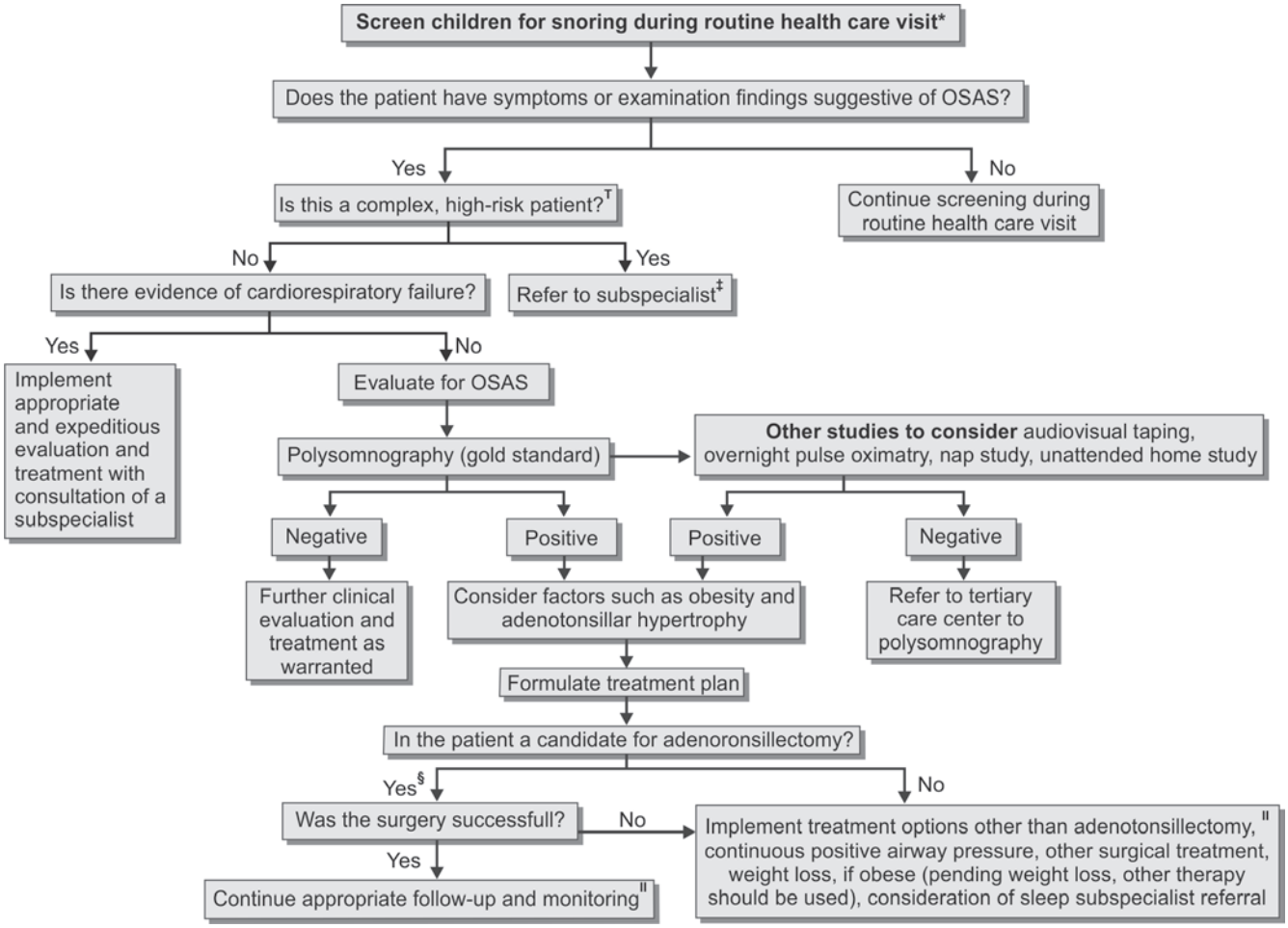
Dignosis and management of disordered sleep in a child



SAHS, sleep apnea hypopnea syndrome; PSG, polysomnography; CPAP, continuous positive airway pressure; RP, respiratory polygraphy.

ALGORITHM 3

Diagnosis and management of uncomplicated obstructive sleep apnea syndrome in children



OSAS, obstructive sleep apnea syndrome.

*Historical findings associated with OSAS include habitual snoring with labored breathing, observed apnea, restless sleep, daytime neurobehavioral abnormalities or sleepiness, and others. Physical findings may include growth abnormalities, signs of nasal obstruction, adenoidal facies, enlarged tonsils, increased pulmonic component of second heart sound, and others. Note that patients may have no abnormalities on examination.

†Complex, high-risk patients include infants younger than 12 months and children with craniofacial disorders, Down syndrome, neuromuscular disorders (including cerebral palsy), chronic lung disease, sickle cell disease, central hypoventilation syndromes, or genetic, metabolic, or storage disease.

‡Subspecialist refers to a physician with expertise in sleep disorders in children. This physician may be a pulmonologist, neurologist, or other physician with experience in the management of sleep-disordered breathing in children.

§High-risk patients should be monitored as inpatients postoperatively.

‖All patients should undergo clinical reevaluation. High-risk patients should undergo objective testing.

quality of life and severity of obstruction and there related size and symptoms.

Clinical Pearls

- Tonsil size does not always correlate with severity of obstructive sleep apnea as determined by polysomnography
- Primary care physician can assess adenoid size by ordering a soft tissue lateral radiograph of the nasopharynx from a good center

Children with other comorbidities such as craniofacial, neuromuscular, genetic, allergic abnormalities are at a higher risk for persistent postoperative obstructive sleep apnea and also at a higher risk of postoperative complication such as respiratory embarrassment and residual airway obstruction.

Long-term follow-up shows a dramatic improvement in the quality of life scores after adenotonsillectomy with reduction in the number of upper respiratory episodes, and hospital visit and admissions. A reduction in problem behaviors and

cognitive impairment was seen after adenotonsillectomy. Studies suggested that in a majority of children enuresis resolves or improves after the surgery.

Clinical Pearls

- Adnotonsillectomy is effective in reducing physiological, behavioral, and cognitive sequelly in patients with adenotonsillar hypertrophy and obstructive sleep apnea
- Some patients with obesity develop recurrent obstructive sleep apnea after adenotensillectomy. The primary care physician must emphasize weight reduction and continue to monitor the signs and symptoms of obstructive sleep apnea after surgery.

ADENOTONSILLECTOMY

Adenoidectomy and adenotonsillectomy remain the most commonly performed operations in children. However, they are also the most discussed, appreciated, denounced and least studied procedures in the history of ENT surgery. While the indications have changed over the decades. The essential surgery remains the same with the advent of laser, coblation, high frequency diathermy, etc. The intraoperative bleeding has reduced dramatically; however, the traditional surgery with blunt dissection and snare still seems to have a large number of favorable references.

Adenoidectomy however has become more effective and definitive with the introduction of nasal endoscopy coupled with powered instrumentation like shavers made by Zomed. The operative and postoperative complications of hemorrhage remain the most common serious problems of the surgery. The incidence is reported from 0.2 to 0.22% from primary hemorrhage and from 0.1 to 3% for secondary hemorrhage. Fever in the first 36 hours is considered "normal". It is important to maintain hydration in hospital and immediate postoperative period. Mortality from tonsillectomy is estimated at 1/16,000–35,000 tonsillectomies. About one-third attribute to primary bleeding and the majority to anesthetic mishaps.

The American Academy of Pediatrics recommends adenotonsillectomy as the first line treatment in any child with obstructive sleep apnea and enlargement of the tonsils and adenoids. A lot of parents are worried about the surgery, but it is actually quite safe and the benefits are significant. In some kids, however, there is residual obstructive sleep apnea after surgery. Thus, all children with obstructive sleep apnea who have surgery need to be followed up to see if there symptoms resolve and to make sure that they do not return. If symptoms persist, a sleep study may be helpful. Alternative treatments are available if sleep apnea persists. Weight loss will help in obese kids, and allergy treatments, intranasal steroids, orthodontic work, and continuous positive airway pressure (CPAP) can benefit some kids.

Clinical Pearl

- There are no studies to date that demonstrate significant negative clinical effect of tonsillectomy on the immune system.

What Are the Signs and Symptoms of Obstructive Sleep Apnea for the Mother to See?

- Loud or noisy breathing, snoring or mouth breathing during sleep
- Brief pauses in breathing during sleep or difficulty breathing during sleep
- Restless sleep (i.e., lots of tossing and turning)
- Sweating heavily during sleep
- Bedwetting
- Sleeping in odd positions (e.g., neck hyperextended)
- Inattentiveness and lack of focus at school
- Excessive daytime sleepiness (e.g., child regularly falls asleep in school)
- Poor academic performance
- Irritable mood, aggressiveness, other behavioral problems
- Morning headaches.

KEY POINTS

- ☞ Screening for snoring should be part of routine health maintenance visits in all children; if snoring is present, a more detailed evaluation should follow (good evidence; strong recommendation). Note: Obstructive sleep apnea syndrome is unlikely in children who do not have habitual snoring.
- ☞ Complex, high-risk patients should be referred to a subspecialist (good evidence for increased surgical risk in these patients and consequent need for more complex management; strong recommendation).
- ☞ Patients who have cardiorespiratory failure cannot wait for elective evaluation. These patients are not covered in the AAP guideline because it is expected that they will be in an intensive care setting and managed by a subspecialist.
- ☞ The diagnostic evaluation should be thorough. The history and physical examination have been shown to be poor in differentiating between primary snoring and obstructive sleep apnea syndrome (strong evidence). Polysomnography is the diagnostic method of choice; it is the only test that quantifies sleep and ventilatory abnormalities. Other screening techniques, such as videotaping, audiotaping, nocturnal pulse oximetry, and daytime nap polysomnography, may be helpful if the results are positive. However, these tests have high false-negative rates, and they do not assess the severity of the syndrome (disease severity is useful in determining treatment and follow-up). When the results of other diagnostic tests are negative, polysomnography should be performed; additional audiotaping is necessary (strong evidence; strong recommendation).
- ☞ In most children, adenotonsillectomy is a first-line treatment for obstructive sleep apnea syndrome; continuous positive airway pressure is an option in patients who are not surgical candidates or do not respond to surgical treatment (strong evidence; strong recommendation). Note: Potential complications of adenotonsillectomy include anesthetic-related medical problems, pain and poor oral intake in the immediate postoperative period, and hemorrhage. Patients with obstructive sleep apnea syndrome may have respiratory complications (e.g., worsening of the syndrome, pulmonary edema); death attributable to severe

respiratory complications has been reported in patients with severe obstructive sleep apnea syndrome. Risk factors for complications after adenotonsillectomy in children with obstructive sleep apnea syndrome include age younger than 3 years, cardiac complications of the syndrome (e.g., right ventricular hypertrophy), severe obstructive sleep apnea syndrome determined by polysomnography, failure to thrive, obesity, prematurity, recent respiratory infection, craniofacial anomalies, and neuromuscular disorders (the last two risk factors are not discussed in the AAP Guideline).

SUGGESTED READINGS

1. **AAO-HNS Position Statement—Treatment of Obstructive Sleep Apnea.
2. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. Am J Respir Crit Care Med. 1996;153(2):866-78.
3. Beebe DW. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. Sleep. 2006;29(9):1115-34.
4. **Bhattacharjee 2010—Adenotonsillectomy Outcomes in Treatment of obstructive sleep apnea in children.
5. Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. Otolaryngol Head Neck Surg. 2004;131(6):827-32.
6. Brietzkes SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. Otolaryngol Head Neck Surg. 2006;134(6):979-84.
7. **Brieztke 2006—The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: A meta-analysis.Epstein 2009—Clinical Guidelines for Evaluation, Management and long-term care of obstructive sleep apnea in adults.
8. Brown KA, Laferriere A, Lakheeram I, Moss IR. Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. Anesthesiology. 2006;105(4):665-9.
9. Carroll JL, McColley SA, Marcus CL, Curtis S, Loughlin GM. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest. 1995;108(3):610-8.
10. Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics. 2002;109(3):449-56.
11. Chervin RD, Ruzicka DL, Giordani BJ, Weatherly RA, Dillon JE, Hodges EK, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. Pediatrics. 2006;117(4):e769-78.
12. Cohen SR, Simms C, Burstein FD, Thomsen J. Alternatives to tracheostomy in infants and children with obstructive sleep apnea. J Pediatr Surg. 1999;34(1):182-6.
13. De Serres LM, Derkay C, Sie K, Biavati M, Jones J, Tunkel D, et al. Impact of adenotonsillectomy on quality of life in children with obstructive sleep disorders. Arch Otolaryngol Head Neck Surg. 2002;128(5):489-96.
14. Farber JM. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2002;110(6):1255-7.
15. Gozal D, Crabtree VM, Sans CO, Witcher LA, Kheirandish-Gozal L. C-reactive protein, obstructive sleep apnea, and cognitive dysfunction in school-aged children. Am J Respir Crit Care Med. 2007;176(2):188-93.
16. Gozal D, Kheirandish-Gozal L. Sleep apnea in children—treatment considerations. Paediatr Respir Rev. 2006;7(Suppl 1):S58-61.
17. Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics. 1998;102(3 Pt 1):616-20.
18. Kheirandish L, Goldbart AD, Gozal D. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. Pediatrics. 2006;117:e61-6.
19. **Kribbs 1993—Objective Measurement of Patterns of Nasal CPAP Use by Patients with obstructive sleep apnea.
20. Marcus CL, Ward SL, Mallory GB, Rosen CL, Beckerman RC, Weese-Mayer DE, et al. Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea. J Pediatr. 1995;127(1):88-94.
21. Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol. 2000;119(2-3):143-54.
22. McColley SA, April MM, Carroll JL, Naclerio RM, Loughlin GM. Respiratory compromise after adenotonsillectomy in children with obstructive sleep apnea. Arch Otolaryngol Head Neck Surg. 1992;118(9):940-3.
23. Monasterio FO, Drucker M, Molina F, Ysunza A. Distraction osteogenesis in Pierre Robin sequence and related respiratory problems in children. J Craniofac Surg. 2002;13(1):79-83.
24. Richards W, Ferdman RM. Prolonged morbidity due to delays in the diagnosis and treatment of obstructive sleep apnea in children. Clin Pediatr (Phila). 2000;39(2):103-8.
25. Rosen CL, D'Andrea L, Haddad GG. Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. Am Rev Respir Dis. 1992;146(5 Pt 1):1231-4.
26. Rosen GM, Muckle RP, Mahowald MW, Goding GS, Ullevig C. Postoperative respiratory compromise in children with obstructive sleep apnea syndrome: can it be anticipated? Pediatrics. 1994;93(5):784-8.
27. Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr. 2006;149(6):803-8.
28. Waters KA, Everett FM, Bruderer JW, Sullivan CE. Obstructive sleep apnea: the use of nasal CPAP in 80 children. Am J Respir Crit Care Med. 1995;152(2):780-5.
29. **Weaver 2004—Survival of Veterans with Sleep Apnea—CPAP vs Surgery.
30. **Weaver 2008—Adherence to CPAP Therapy—The Challenge to Effective Treatment.

Note: **Articles recommended by the American Academy of Ophthalmology-Head and Neck Surgery

CHAPTER 151

Septic Arthritis

Viraj Shingade, Mandar Agashe

INTRODUCTION

Septic arthritis continues to be one of the major causes of orthopedic disability in pediatric population. Although the management is not very difficult, it usually needs a multidisciplinary approach. Most of the neonates are either missed in diagnosis in early stages or they are managed by a medical person single-handed and they lead to outcomes like deformity and limb shortening. If diagnosis is made timely and management is done by the team including neonatologist, pediatrician, pediatric orthopedic surgeon, microbiologist, and radiologist, most of these cases can be cured completely without any remnant deformity or disability. This chapter gives useful information about how to diagnose it at the earliest and what should be the approach for the treatment.

HOW COMMON IS THE PROBLEM?

Septic arthritis refers to bacterial invasion of the joint space and the subsequent inflammatory response.

The incidence of septic arthritis in India is approximately 1 in 1,500 live births. Although bone and joint infections are quite common, the diagnosis of septic arthritis is not always straightforward.

MECHANISM/PATHOPHYSIOLOGY OF THE PROBLEM

Septic arthritis usually is of hematogenous origin, but can arise through direct inoculation. It can occur from the primary seeding of the synovial membrane, secondarily from infection in the adjacent metaphyseal bone or directly from infection in the adjoining epiphysis.

When septic arthritis occurs, bacteria rapidly gain access to the joint cavity and within a matter of hours cause synovitis and formation of fibrinous exudates followed by areas of synovial necrosis. Endotoxins are released. This leads to destruction of the synovium and cartilage matrix. Proteases, peptidases, and collagenases are released from the leukocytes and synovial cells. These enzymes breakdown the cellular and extracellular structures of the cartilage. The loss of glycosaminoglycans is the first measurable change in articular cartilage, occurring as early as 8 hours after bacteria are introduced into the joint. Loss of glycosaminoglycans softens the cartilage and may cause it to be susceptible to increased wear. Collagen destruction follows and is responsible for visible change in cartilage appearance. Elevation of the intracapsular pressure, thrombosis causes impairment of the intracapsular vascular supply which causes articular destruction. Destruction of the joint space leads to long-term sequelae in a significant percentage of patients. In certain joints like hip, infection distends and softens joints capsule and may cause joint subluxation or dislocation.

WHICH ARE THE SUSCEPTIBLE GROUPS IN NEONATES?

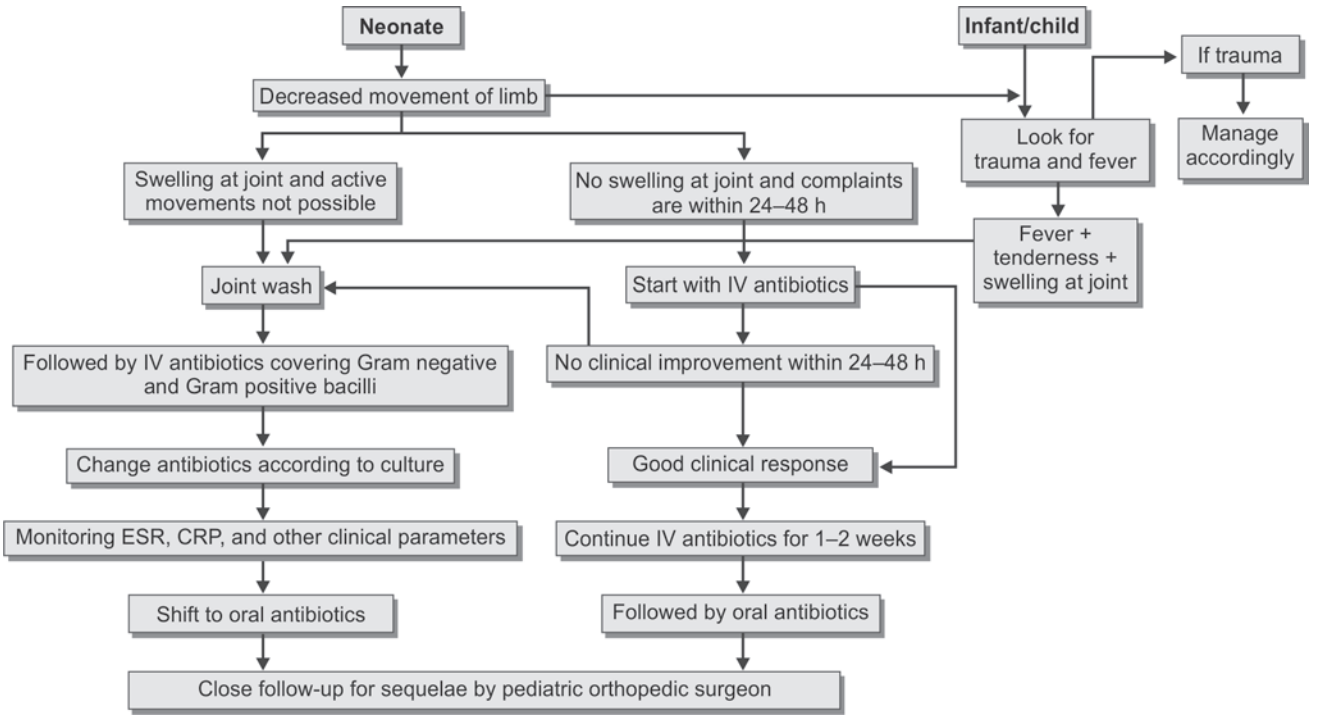
Septic arthritis in the neonates is seen in two distinct groups. One is the neonate, who is sick, premature, and needs intensive care. The other group is healthy neonate, who has been discharged from the hospital and then presents 2–3 weeks later with bone and joint infection.

When to Suspect (Algorithm 1)?

Clinically, septic arthritis usually presents with obvious swelling of one or more joints. Symptoms include edema, erythema, joint effusion, and tenderness. Patients tend to keep the affected joint in a position that maximizes intracapsular volume and comfort. Refusal to move an affected joint is referred to as pseudoparalysis and even passive movement may be painful. Systemic symptoms, such as fever, malaise, and poor appetite, are also seen in most patients. If the infection involves a lower extremity, the child will often have a limp or will be unable to bear weight on the limb. A history of antecedent trauma is quite common. Trauma rarely results in a delayed limp. The clinician should elicit specific details

ALGORITHM 1

How to diagnose and treat a baby with septic arthritis



ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IV, intravenous.

regarding any traumatic event. Did the child cry and limp or refuse to bear weight immediately after the trauma? If the answers to these questions are no and there was a period of time between the injury and time symptoms appeared, the suspicion of infection should increase.

WHICH ARE THE MOST COMMON JOINTS INVOLVED?

Knees and the hips being most commonly affected (80%), other commonly affected joints include the ankles, wrists, elbows, and shoulders.

What Are Clinical Clues for Diagnosis in Neonate?

The initial presentation is with swelling of a limb or joint and reluctance to move the limb. There may be irritability on handling, e.g., when changing the nappies. Sometimes, the reluctance to move a limb is so severe as to cause a pseudoparalysis. Septic arthritis of the hip may cause the baby to hold the leg flexed, abducted, and externally rotated.

In the fulminant form of septic arthritis, signs of bone and joint involvement may occur at the time of, or some times after the signs of, sepsis. The babies are lethargic with or without fever, do not tolerate feeds, and may have abdominal distension and jaundice. Multiple bones or joints may be involved.

What are Clinical Clues in Infants and Older Children?

Typical symptoms like high grade fever, and warmth or hot extremity may not be present. Limping, refusal to walk, and refusal to bear weight may be the earliest symptom.

CHALLENGES IN DIAGNOSING SEPTIC ARTHRITIS

Many immunocompromised children fail to have fever and may show lowered white blood cell count. X-rays may be reported as normal in early phase of the disease. Ultrasound, bone scan, or magnetic resonance imaging (MRI) suggest a process of inflammation and effusion, but cannot diagnose septic arthritis confirmatively in the early stage of disease. The damage to the cartilage, growth plate, and bone due to avascularity and enzymatic destruction sets in very early. The cartilage destruction starts as early as 8 hours following the onset of infection. The avascularity sets in within 24–48 hours of the tamponade. The biggest challenge is, therefore, to control the infection and drain the joint before the damage takes place. Understanding the limitations of investigations for confirmation of diagnosis, it is important that physician should have high index of suspicion and should start treatment as earliest as possible.

WHICH ARE OTHER DIFFERENTIAL DIAGNOSES?

It includes hemarthrosis, traumatic effusion, transient synovitis, reactive arthritis, Lyme arthritis, juvenile rheumatoid arthritis, arthritis of acute rheumatic fever, and slipped capital femoral epiphysis.

WHICH ARE THE MOST COMMON CAUSATIVE ORGANISMS?

In the neonatal period, *Staphylococcus aureus* remains a common organism, but Group B β-hemolytic streptococcus and Gram-negative enteric bacilli are also frequently identified. No bacteria are grown from the blood or joint fluid of 50% cases of typical septic arthritis.

Other contributing organisms could be methicillin-resistant *S. aureus* (MRSA), Gram-negative organisms (Enterobacteriaceae) fungal species like *Aspergillus* and *Candida*. Tuberculosis and syphilis must be considered in atypical case contexts.

WHAT INVESTIGATIONS ARE SUPPORTIVE TO CONFIRM THE DIAGNOSIS?

The most important diagnostic test is clinical acumen. Positive changes on X-ray suggest that the disease is already in its advanced stage. Hence to diagnose the condition in its early stage, optimum use of investigations like ultrasound and MRI can be done.

Radiographs

The role of plain X-ray film in the diagnosis of early bone and joint sepsis is often undervalued. It is because the most sought after change is osteopenia or bone lysis, which takes 7–10 days to develop. Actually, deep soft tissue swelling with obliteration of fat plane is the earliest radiographic evidence of infection. Unlike older children, radiographic changes appear early in neonatal age group. The thin periosteum ruptures easily, and osteolytic lesions, soft tissue swelling, and periosteal elevation are often seen within 7 days of onset of infection. Erosion of the cortex, cavitation in the metaphysic or epiphysis can be seen as early as 3 days of onset of infection.

Ultrasonography

Ultrasonography (USG) is very useful to detect any joint effusion and subperiosteal edema. Although USG cannot clearly differentiate between pus and synovial fluid, in experienced hands USG-guided aspiration may be very useful to confirm the diagnosis.

Bone Scan

Bone scans are both sensitive and specific. They are often abnormal within 2–3 days of onset of symptoms.

Magnetic Resonance Imaging

In selected cases, an MRI is the most sensitive. It shows changes of marrow edema and helps to differentiate between transient synovitis, inflammatory arthritis, and septic arthritis by virtue of changes in marrow edema and synovial lining.

Hematological Investigations

A routine hemogram (complete blood count) with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually required and helpful to diagnose and monitor the course of treatment. In the community setting, CRP is useful parameter and is highly sensitive for infection. In an immunocompromised child, it may not be very reliable. Rather than a single value, changing trend in a CRP is more informative.

Erythrocyte sedimentation rate is not very useful in neonates, but with chronicity of infection, a decreasing trend in ESR usually indicates subsidence of infection.

Blood culture must be routinely performed and sometimes it can identify the pathogen. However, the blood sample must be promptly analyzed after collection and any contamination must be prevented.

Organism identification is extremely important for both confirmation of the diagnosis and guiding antimicrobial selection. Needle aspiration is likely to grow an organism in almost 50–60% of cases whereas blood cultures yield positive results in one-third to little more than half of specimens.

HOW TO PROCEED FOR THE MANAGEMENT ONCE DIAGNOSIS IS MADE (ALGORITHM 1)?

Early diagnosis and treatment of septic arthritis is usually highly effective and usually achieves a clinically normal joint. Consequently, it is essential that children with septic arthritis are urgently referred to treatment centers and it is essential that the latter centers commence treatment as soon as possible. Prompt diagnosis and treatment of septic arthritis is not only rewarding, but also saves the child from a lifelong disability.

The treatment is a team approach which involves pediatrician, pediatric orthopedic surgeon, pediatric intensivist (particularly in sick neonates), microbiologist, and radiologist.

Treatment is directed towards obtaining a rapid cure as the sequelae of septic arthritis can be quite devastating (Figs 1 and 2). Any suspicion of the infection in a neonate should initiate prompt investigation to identify the site and source of the infection. Ideally, a joint or bone aspirate or positive blood culture must be obtained before commencing antimicrobial therapy. However, often this is not the case, and many neonates have received oral or intravenous antibiotics before they reach the definitive treatment center. In any case, if there is no improvement in clinical parameters within 48–72 hours of antimicrobial administration, then surgical intervention is mandatory.

Prompt surgical drainage and thorough wash of the joint is necessary. Open surgical drainage of the certain joints is essential to prevent necrosis (e.g., head of the femur or

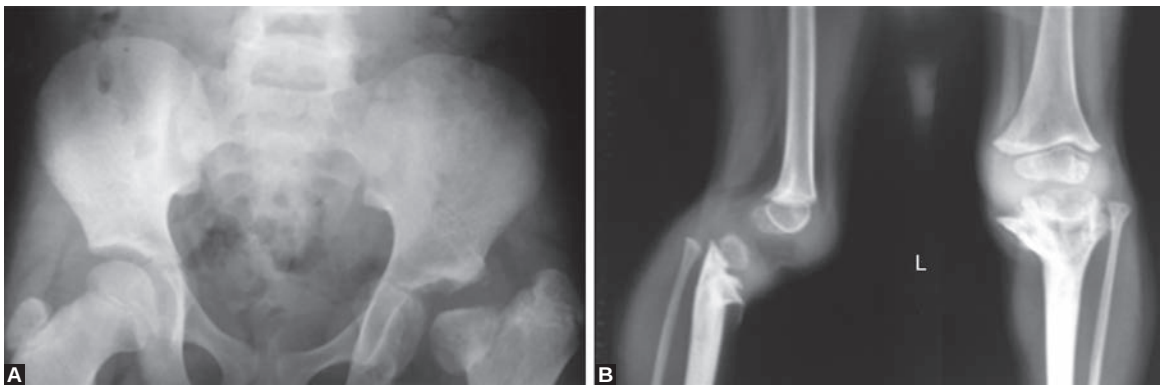


Fig. 1: A, An X-ray pelvis in an 8-year-old child who suffered septic arthritis of left hip in neonatal age group. Left femoral head shows growth arrest and gross collapse and incongruity. **B,** An X-ray of knee in a 5-year-old child who suffered septic arthritis in neonatal period. There is gross deformity and growth arrest of proximal tibia. Child had gross shortening of limb and deformity

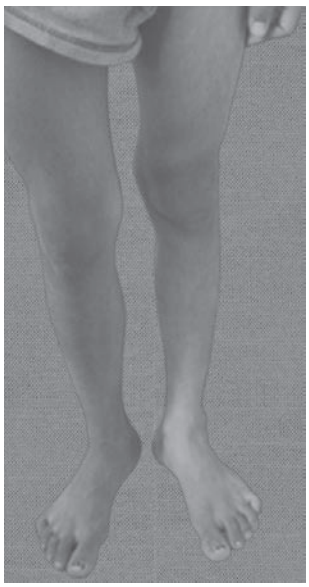


Fig. 2: Clinical photograph of the same child whose X-ray is shown in figure 1A suggesting gross shortening of left lower limb

humerus). The current trend is towards mini-invasive surgeries (Figs 3 and 4), particularly in neonates; or arthroscopic joint lavage rather than big incisions. Smaller joints can usually be effectively treated by regular aspiration and rarely need open surgical drainage.

Drainage of pus by a pediatric orthopedic surgeon decompresses the joint with drainage of pus leading to increased vascularity and healing. The antibiotics which were not able to reach the local site due to tight compartment like pressure are able to reach the infection site after drainage of pus. This ultimately results in rapid healing of bone and joint due to clearance of tissue-destroying fluid and also due to decrease in the tamponade effect on the delicate circulation around the growth plate.

Pus or fluid obtained during surgery must be sent for Gram staining and appropriate culture which helps in selection of proper antibiotics. Involvement of pediatric orthopedic surgeon at the onset of treatment itself is important as he or she is the person who is going to manage the sequelae in future. These children need long-term follow-up.

Antimicrobial therapy should commence immediately after drainage of pus. Antimicrobial therapy is guided by Gram stain on the aspirated pus. Up to 50% of joint aspirates are sterile in septic arthritis, possibly because joint fluid is bacteriostatic or because the organisms are limited to the synovium.

WHICH ANTIBIOTICS NEED TO BE GIVEN?

Since Gram-positive organisms are most frequently responsible for the infection, an antibiotic that is effective against these organisms should be started empirically. In infants and children, a third-generation cephalosporins (e.g., cefotaxime, ceftriaxone) are the drug of choice combined with amikacin or gentamicin which provide coverage against many *S. aureus* (methicillin-sensitive *S. aureus*), most streptococci, *Haemophilus influenzae,* and *Kingella kingae*.

Linezolid, vancomycin, teicoplanin, and tobramycin are reserved until there is a positive report to support their use. Once an organism has been identified, coverage can be narrowed based on results of susceptibility testing.

WHICH IS THE PREFERRED ROUTE OF ANTIBIOTICS?

The initiation of treatment should be with intravenous antibiotics only. The oral route is preferred for maintenance phase.

HOW LONG ANTIBIOTICS NEED TO BE GIVEN?

The duration of parenteral antimicrobial therapy is a matter of debate. While the final choice is decided by the prevalent pathogen in the bacteriological and culture report, the duration of intravenous treatment varies from 7 days to 5 weeks.

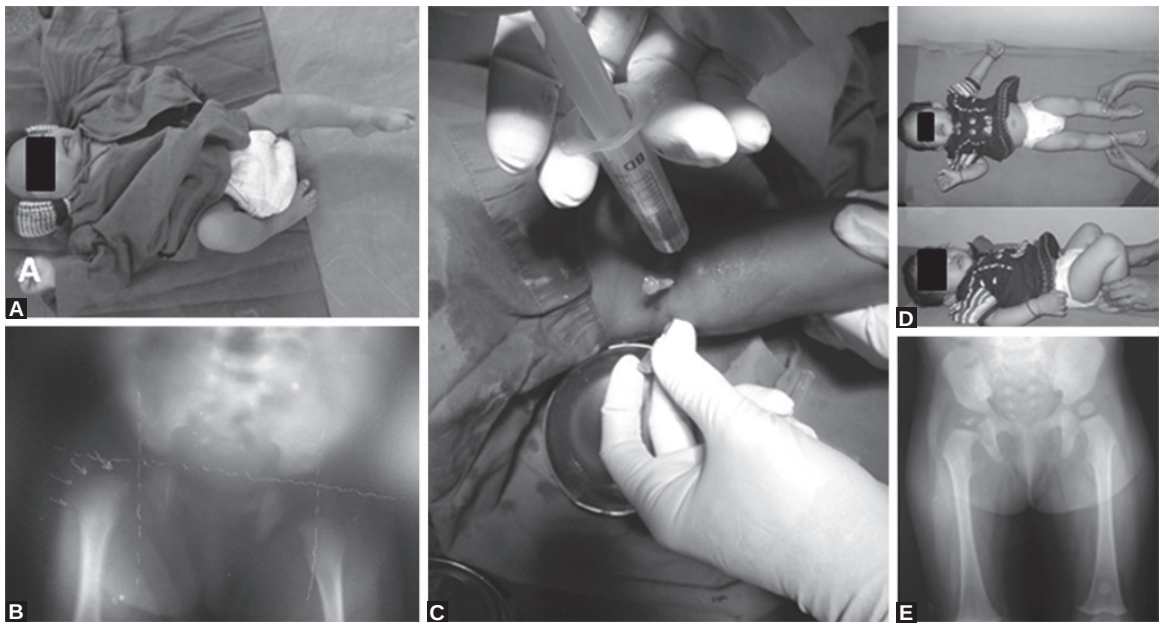


Fig. 3: **A,** Clinical photograph of a 25-day-old neonate with septic arthritis right hip. There is fixed flexion deformity at right hip and baby refuses to move the right lower limb. **B,** An X-ray shows right hip dislocation, which is due to inflamed synovium pushing the head outside the acetabulum. **C,** Joint wash of the right hip was done by mini-invasive technique using 16 G needles through multiple ports. This was followed by course of intravenous and then oral antibiotics. **D,** Clinical photographs showing one and half year follow-up with full range of movement at right hip joint and no limb length discrepancy. **E,** X-ray done at 15 months suggests growth is getting affected and small-sized epiphysis of right hip

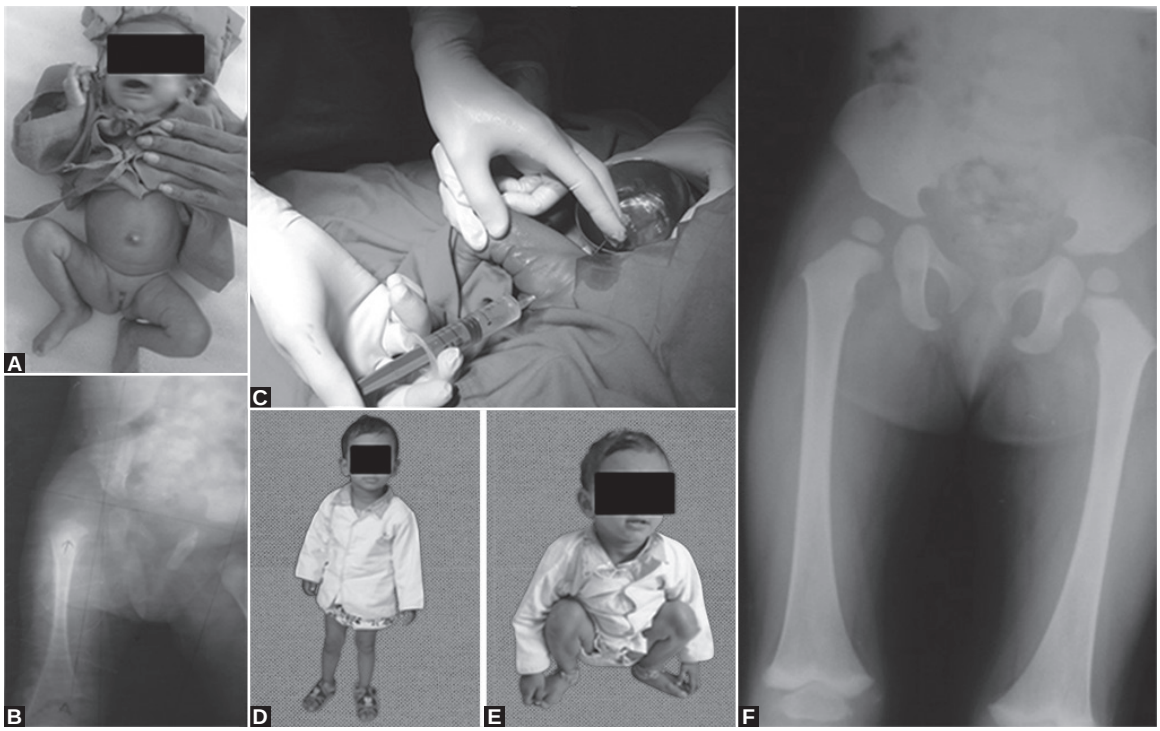


Fig. 4: **A,** Clinical photograph of a 28-day-old neonate with septic arthritis right hip. There is fixed flexion deformity at right hip and painful movements of right lower limb. **B,** X-ray shows right hip dislocation as well as lytic changes in proximal femur. **C,** Joint wash of the right hip was done by mini-invasive technique using 16 G needles through multiple ports. This was followed by course of intravenous and then oral antibiotics. **D,** and **E,** Clinical photographs showing two and half year follow-up with full range of movement at right hip joint and no limb length discrepancy. **F,** X-ray done at two and half years suggests normal recovery; no growth arrest, no limb length discrepancy

There are many studies which has proven efficacy of minimum 3 weeks of intravenous antibiotics followed by 2–3 weeks of oral therapy (total 4–6 weeks). The author follows the regimen of 2–3 weeks of intravenous antibiotics followed by oral antibiotics for 2–3 weeks at our center. Few studies have indicated a shortened course of appropriate antibiotics for 3 weeks is as efficacious as 6 weeks of parenteral therapy.

Close monitoring of the clinical, blood, and radiological parameters is required to ensure that the treatment is effective and the outcome satisfactory. Antibiotics can usually be stopped by 6 weeks if the child has improved. Radiographs must be taken 6 monthly to see for any sequelae which develop in future.

Based on the latest review of literature, use of intravenous antibiotics till child improves clinically and starts weight bearing, followed by oral antibiotics for 4–6 weeks seems to be a standard regimen. The duration of antibiotics depends on the clinical recovery rather than a fixed time frame. To start with, an intravenous route is preferred. Once the clinical signs improve and CRP levels touch baseline, the antibiotic may be given orally.

WHERE AND WHO SHOULD PERFORM THE JOINT ASPIRATION?

Although older literature mentions about drainage in the emergency room, recent guidelines suggest to be done under aseptic atmosphere like operation theater or sterile neonatal intensive care unit/pediatric intensive care unit room. It should be done by a person well worse with anatomy of particular joint (preferably by pediatric orthopedic surgeon).

Clinical Pearls

- Suspect septic arthritis in all neonates with decreased movements of limb or painful movements of limb
- Suspect septic arthritis in all toddlers or children having gait disturbance with history of fever
- Give joint lavage as earliest as possible
- Joint lavage should be given in aseptic conditions preferably in operation theater or sterile neonatal intensive care unit/ pediatric intensive care unit room (preferably by pediatric orthopedic surgeon who will keep follow-up of the case managing sequelae in long term)
- Send joint fluid for microbiological evaluation
- X-rays and ultrasonography are helpful in diagnosis
- Empirical antibiotics should be commenced after prompt drainage of joint collections
- Start antibiotics with intravenous route only
- Further choice of antibiotics will depend on culture report and clinical course
- Once clinical course is better shift to oral route of antibiotics
- Keep patient in long-term follow-up for observation of sequelae and their subsequent management.

Is Simple Joint Aspiration Sufficient or a Joint Wash Need to Be Done?

Joint wash gives an additional advantage of reducing the bacterial load and thereby better chances of healing. Hence, whenever a pediatric orthopedic surgeon is available he should be involved in the management and a thorough joint wash should be done rather than simple aspiration.

What is the Role of Plaster Cast/Splints/Traction?

Plaster cast/splints help in immobilization of the joint and better healing particularly initial 1–2 weeks of treatment. Hip spica is needed in cases of septic hip dislocations to achieve the containment. Joint should not be immobilized for prolonged time to avoid stiffness. In children, traction helps in reducing the pain as well as correcting the deformity. On traction, movements need to be started as earliest as possible.

KEY POINTS

- ☞ Septic arthritis is a surgical as well as medical emergency
- ☞ Prevention of sequelae by starting treatment urgently is the key to success
- ☞ The treatment needs a team approach by pediatrician, pediatric orthopedic surgeon, neonatologist, microbiologist, and radiologist
- ☞ Small setups where facilities are not available should refer the patient urgently to tertiary center where treatment needs to be started by the team on emergency basis
- ☞ Septic arthritis if untreated will cause growth plate disturbances or damage, subsequent shortening of affected limb and lifelong deformity. Hence, the need for urgent diagnosis and treatment.

SUGGESTED READINGS

1. Curtiss PH, Klein L. Destruction of articular cartilage in septic arthritis. II. In vivo studies. J Bone Joint Surg Am. 1965;47(8):1595-604.
2. Fox L, Sprunt K. Neonatal osteomyelitis. Pediatrics. 1978;62(4):535-42.
3. Narang A, Kumar PK. Bone and joint infection in neonates. Indian J Pediatr. 1988;62:535-42.
4. Pääkkönen M, Kallio MJ, Kallio PE, Peltola H. Sensitivity of erythrocyte sedimentation rate and C-reactive protein in childhood bone and joint infections. Clin Orthop Relat Res. 2014;468(3):861-6.
5. Rutz E, Brunner R. Septic arthritis of the hip-current concepts. Hip Int. 2009;19(Suppl 6):S9-12.
6. Sultan J, Hughes PJ. Septic arthritis or transient synovitis of the hip in children: the value of clinical prediction algorithms. J Bone Joint Surg Br. 2010;92(9):1289-93.
7. Syriopoulou VP, Smith AL. Osteomyelitis and septic arthritis. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SD, editors Textbook of Pediatric Infectious Diseases, 2nd ed. Philadelphia, PA: WB Saunders; 1987. pp. 759-79.

CHAPTER 152

Angular and Rotational Deformities in Children

Taral V Nagda, Venkatadass Krishnamoorthy

INTRODUCTION

Any deviation from the normal alignment of the limb in coronal plane is termed as angular deformity and that in transverse or axial plane is termed as rotational (torsional) deformity. While angular deformities are obviously seen as outward or inward deviation of legs, children with rotational deformities often present with either in-toeing or out-toeing walking. This chapter discusses in brief the common causes of these abnormalities and an algorithmic approach to each of this clinical scenario.

ANGULAR DEFORMITIES IN CHILDREN

Genu varum (bow legs) and genu valgum (knock knees) are the most common angular deformities for which the child is brought to the pediatric orthopedic clinic.

Normal Variation During Growth

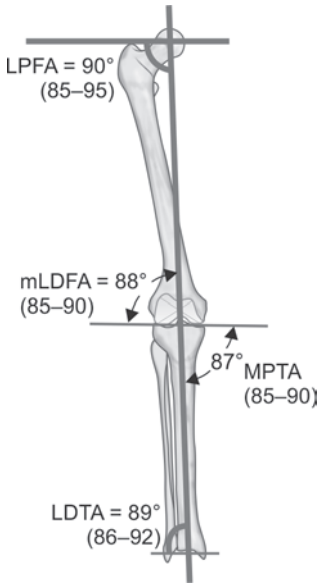
Before going to the pathological genu varum and valgum, it is important to know the normal variation during growth. Most newborns have bow legs, with 10–15° of varus angulation. This gradually corrects until 18–24 months of age. After 2 years, there is valgus angulation with maximum valgus occurring around 4 years of age. The limb usually reaches normal adult alignment of 6–7° of valgus by around 11 years of age.

Radiological Assessment of Alignment of Lower Limb

Full length standing radiograph of both lower limbs covering from both the hip joints to ankle joints with patellae facing anteriorly is the standard radiograph needed for analyzing the angular deformities of lower limbs. This should be standardized as management decisions are made based on this radiograph. Mechanical axis is drawn by the line joining the center of the femoral head to the center of tibial plafond. Usually, it passes through the center of the knee joint. Medial deviation of mechanical axis is seen in genu varum and lateral deviation is seen in genu valgum. The measure of the deviation of mechanical axis of lower limb from the center of knee joint is called as "mechanical axis deviation (MAD)". The other angles which needs to routinely measured are mechanical lateral-distal femoral angle, medial proximal tibial angle, modified tibiofemoral angle (TFA), and joint line convergence angle (Fig. 1).

Genu Varum (Algorithm 1)

Causes of genu varum are given in box 1.

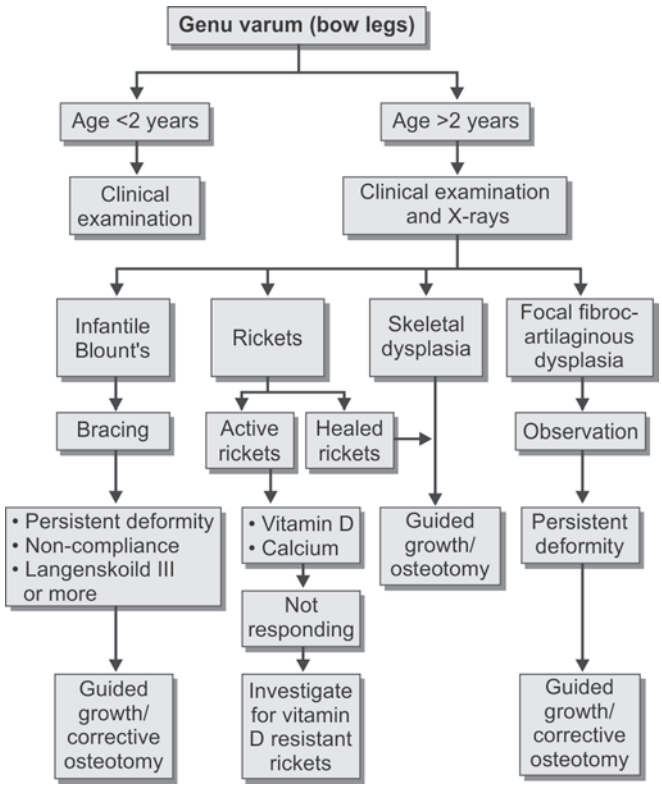


LPFA, lateral proximal femoral angle; mLDFA, mechanical lateral-distal femoral angle; MPTA, medial proximal tibial angle; LDTA, lateral-distal tibial angle.

Fig. 1: Mechanical axis of lower limb

ALGORITHM 1

Approach to a child with genu varum (bow legs)



Box 1: Causes of genu varum

- Physiological genu varum
- Infantile Blount's disease
- Metabolic disorders
- Skeletal dysplasias
- Focal fibrocartilaginous dysplasia

Physiological Genu Varum

Bow legs usually become prominent when the child starts walking and the parents get concerned about the deformity. Physiological genu varum is common in early walkers and in obese children. In physiologic genu varum, there may be associated tibial intorsion. There are no other significant positive findings on clinical examination. X-rays of the knees may show an apparent delay in the ossification of the medial side of the distal femoral and proximal tibial epiphyses or flaring of the medial distal femoral metaphysis. The physes are normal. Majority of children less than 2 years of age have physiological genu varum, which needs reassurance to parents and follow-up evaluation. The genu varum that persists after 2 years of age is considered to be pathological and needs to be investigated further.

Nutritional Rickets

Nutritional rickets is one of the most common causes for bowed legs in developing countries. The typical clinical scenario would be a child presenting with bowed legs and on clinical examination will have other signs of active rickets. The X-rays show cupping and flaring of the metaphysis with widening of the physis. Active rickets will have to be treated with vitamin D supplements and the deformity needs to be observed. The children with active rickets who are not responding to vitamin D supplements are likely to have vitamin D resistant rickets and they need to be investigated preferably by a pediatric endocrinologist and managed accordingly.

It is not uncommon to see children presenting with bowlegs after the active rickets has healed. The persistent deformity needs to be corrected to get the mechanical axis of the lower limb to normal. Guided growth in the form of temporary hemiepiphysiodesis with a tension band plate (8 plate) applied on the lateral side is the preferred form of treatment when the physes remains open. The parents must be counseled well about the need for regular follow-up X-rays at 3–4 monthly intervals and the need for 8-plate removal once the deformity is corrected. In children for whom the physes are closed or those with sick physis not responding to guided growth, the deformity is corrected by osteotomy.

Blount's Disease

Blount's disease also called as tibia vara is classified into three types based on the age of onset of the deformity.

- Infantile tibia vara: less than 3 years
- Juvenile tibia vara: 4–10 years
- Adolescent tibia vara: more than 10 years.

Infantile Blount's disease is considered to be a disorder on the other end of the spectrum of physiological bowing.

Clinical Features

The two major features which helps in differentiating physiologic genu varum from infantile tibia vara is that the child is usually obese (>95th percentile) and the presence of lateral thrust while walking. This sudden lateral knee movement with weight bearing is caused by varus instability at the joint. This sign, though not pathognomonic of infantile tibia vara, increases the level of suspicion and is an indication for radiography, regardless of the age of the patient.

Radiographic Findings

A standardized standing anteroposterior view of the lower extremities from hip to ankle with both patellae facing forwards must be obtained. The diagnosis is based on radiographic changes in the proximal end of the tibia as follows (Fig 2):

- A sharp varus angulation in the metaphysis
- A widened and irregular physeal line medially
- A medially sloped and irregularly ossified epiphysis
- Prominent beaking of medial metaphysis with lucent cartilage islands within the beak
- Lateral subluxation of the proximal end of the tibia.

Infantile Blount's disease in early stages and young patients can be managed by Blount's brace, which needs to be worn 23 hours a day. Though the compliance rates are very poor with brace treatment, there is good evidence in the literature that in early stages of the disease just braces could normalize the mechanical axis of the limb. Persistent and severe deformities

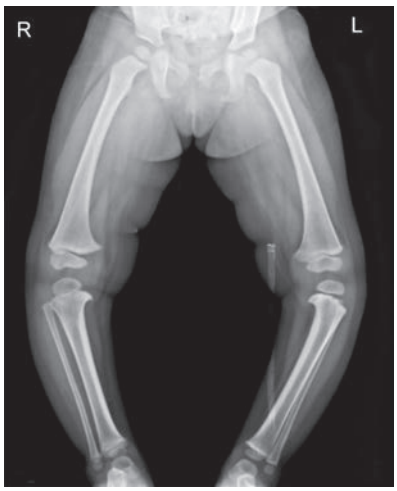


Fig. 2: An X-ray of a child with bilateral Blount's disease

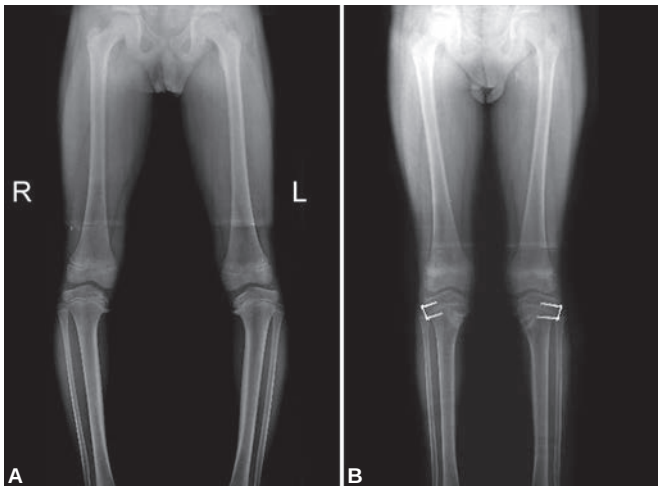


Fig. 3: A, Preoperative X-ray of a 7-year-old boy with bilateral Blount's disease and **B,** 2 years follow-up X-ray after osteotomy showing normal alignment of the lower limbs

in late stages will require surgical correction in the form of corrective osteotomy (Fig. 3).

Skeletal Dysplasia

Children with genu varum secondary to skeletal dysplasia usually have associated short stature. The dysplasia could be either at the epiphysis, metaphysis or the diaphysis. The common dysplasias which present with genu varum are achondroplasia, pseudochondroplasia and metaphyseal-chondrodysplasia (Schmid/McKusick) and hereditary multiple exostosis. Genu varum in these children will need surgical correction to restore the mechanical axis. It is worthwhile considering growth modulation or guided growth in these patients while the physes are open. Those children who are not ideal for growth modulation will need corrective osteotomy.

Focal Fibrocartilaginous Dysplasia

Focal fibrocartilaginous dysplasia is a rare cause of unilateral genu varum in an infant or toddler. Careful clinical examination reveals that the deformity is slightly more distal than the knee joint. On weight bearing and walking, the child may have a lateral thrust along with associated hyperextension of the knee which is not a feature of Blount's disease.

Radiographic Findings

X-rays show a characteristic abrupt varus at the metaphyseal-diaphyseal junction of the tibia, clearly not involving the physis. There is cortical sclerosis in and around the area of the abrupt varus on the medial cortex. A radiolucent lesion may be seen just proximal to the area of cortical sclerosis, which probably corresponds to the fibrocartilaginous tissue. The etiology of this defect and the pathogenesis of the deformity are unknown.

The importance of recognizing this variation of infantile tibia vara is that the deformity can resolve without surgery. Surgical treatment may be necessary if the deformity progresses or fails to resolve during a period of observation or orthotic management.

Clinical Pearls

Pointers to pathological genu varum:

- Age more than 2 years
- Lateral thrust on walking
- Hyperextension while standing
- Acute bowing in the tibia
- Unilateral bowing.

Genu Valgum (Algorithm 2)

Causes of genu valgum are given in box 2.

Valgus alignment of the lower extremities is normal in a child between 2 years and 6 years of age. The maximum amount of physiologic valgus occurs between the ages of 2 years and 4 years, after which the alignment of the lower extremity assumes a mild valgus femoral-tibial angle, the normal alignment in an adult.

In a younger child, X-rays are not routinely indicated. Alignment X-rays are indicated in the following situations:

- Presence of short stature
- History of trauma or infection
- Features suggestive of metabolic bone disease
- Asymmetrical genu valgum.

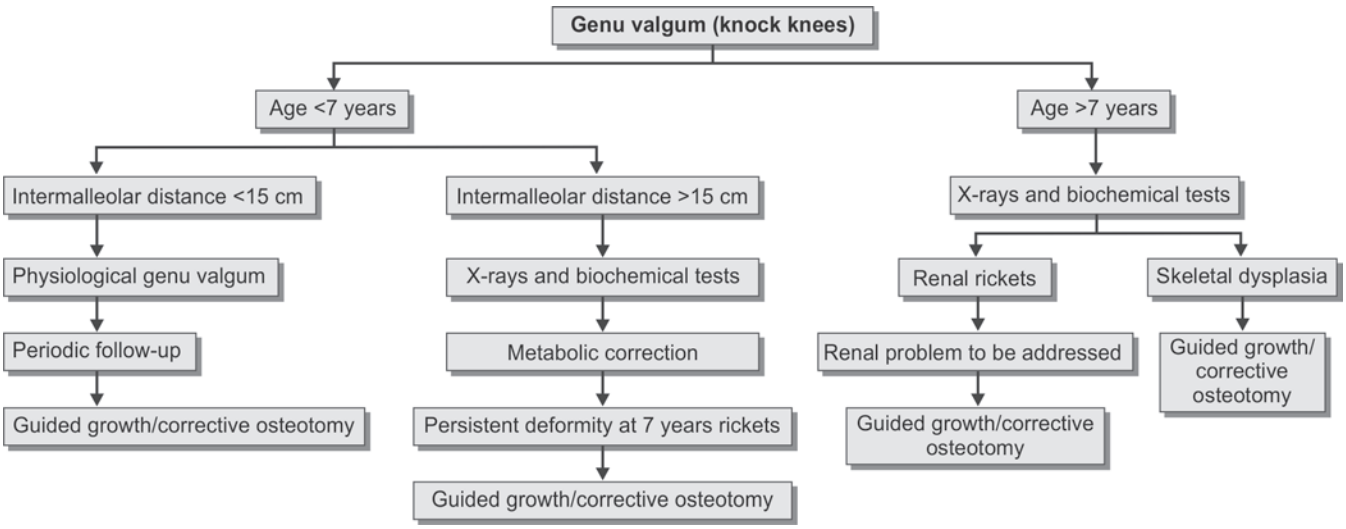
The rotational profile of the extremity must be evaluated carefully because an apparent increase in valgus may result from increased femoral anteversion.

Idiopathic Genu Valgum

Significant genu valgum that persists after 7 years of age without any identifiable underlying cause is usually labeled as idiopathic genu valgum. Surgical correction is indicated when there is significant MAD (the mechanical axis passing lateral to the lateral-tibial plateau). If untreated this may lead to gait

ALGORITHM 2

Approach to a child with genu valgum (knock knees)



Box 2: Causes of genu valgum

- Physiological genu valgum
- Metabolic
- Post-traumatic
- Skeletal dysplasias
- Hereditary multiple exostosis

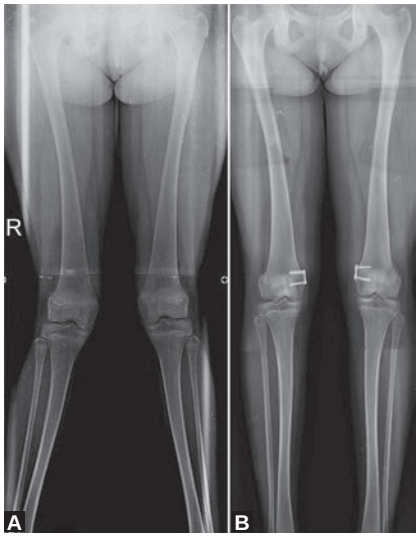


Fig. 4: **A,** 12-year-old girl with idiopathic genu valgum and **B,** 1-year follow-up X-ray after bilateral hemiepiphysiodesis showing complete correction of deformity.

disturbance, difficulty in running, knee discomfort, patellar malalignment, and evidence of ligamentous instability. Growth modulation with medial hemiepiphysiodesis using a tension band plate is currently the preferred method of achieving correction while the physis is open (Fig. 4). However, one must be aware that in genu valgum, correction is rapid and 3-monthly monitoring with X-rays is mandatory to avoid over correction and development of opposite deformity. In children who present late where the physis is fused, corrective osteotomy is indicated.

Metabolic Disorders

Genu valgum may be presenting feature of a child with chronic renal failure. Apart from nutritional rickets, renal rickets must be ruled out in all children presenting with genu valgum by doing renal function tests. Correcting the metabolic abnormality gets the first priority in these children followed by deformity correction later on.

Skeletal Dysplasia

Multiple hereditary exostosis, spondyloepimetaphyseal dysplasia, Ellis-van Creveld syndrome, and focal fibrocartilaginous dysplasia are rare causes of genu valgum. The deformity needs to be corrected when there is severe MAD irrespective of the etiology.

Post-traumatic Genu Valgum

Proximal tibial fracture in toddlers (Cozen's fracture) is known to cause unilateral valgus deformity. Though the etiology of this condition remains undetermined, there is strong evidence in the literature that most of these deformities would correct spontaneously and hence need to be observed periodically for improvement of the deformity.

Clinical Pearl

Beware of unilateral deformity; it is most likely to be pathological.

ROTATIONAL DEFORMITIES IN CHILDREN

Rotational deformities in children manifest as either in-toeing or out-toeing while walking. Parents bring their children

Box 3: Physiologic causes for rotational deformities

In-toeing
- Foot
  - Metatarsus adductus
  - Skew foot
- Leg
  - Internal tibial torsion
- Hip
  - Increased femoral anteversion

Out-toeing
- Foot
  - Pes calcaneovalgus
  - Pes planovalgus
- Leg
  - External tibial torsion
- Hip
  - External rotation contracture
  - Femoral retroversion

seeking opinion for abnormal inward or outward positioning of the feet while walking. Though majority of the rotational deformities in early childhood are benign and gets resolved spontaneously with growth, it is important to do a thorough clinical examination to locate the anatomical site of the deformity. A comprehensive history along with a thorough physical examination helps in differentiating benign from pathologic causes of rotational abnormalities.

Common Causes of Rotational Deformities in Children

Majority of the rotational anomalies in children are physiologic variations (Box 3), which resolve over a period of time. Very rarely physiologic variations may persist or become rigid deformities, which then would warrant a surgical intervention. Pathologic causes of rotational deformities need to be identified and managed appropriately.

Box 4: Pathological causes of rotational deformities

- Cerebral palsy
- Hereditary neurologic disorders—Charcot-Marie tooth disease, Friedrich ataxia
- Mild tibial deficiencies
- Blount's disease
- Metabolic disorders
- Skeletal dysplasia
- Rigid pes planus with or without tarsal coalition
- Slipped capital femoral epiphysis.

Pathologic Causes for Rotational Deformities

Pathological causes for rotational deformities are given in box 4.

Evaluation of Child with Rotational Deformity

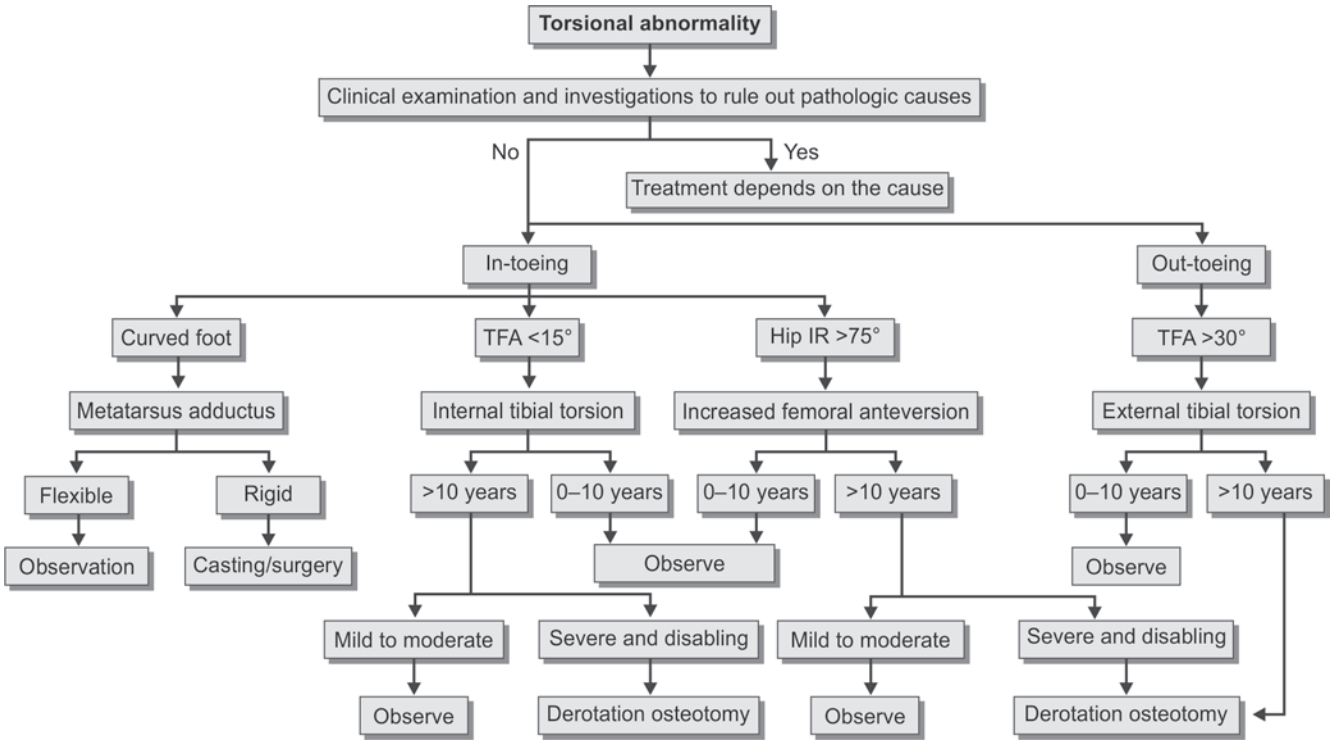
A good history with systematic clinical examination is recommended in all children presenting with in-toeing or out-toeing while walking. The following findings would point towards a pathologic cause of rotational deformity:
- A hypoxic or infective event in neonatal period
- Delayed developmental milestones
- A family history of hip dysplasia or a neurologic disorder
- Spasticity, a neurologic deficit, or signs of muscular dystrophy
- Limping or another abnormality of gait of sudden onset
- Deformities of the foot.

The Three-step Rotational Profile (Algorithm 3)

- Step 1 [foot progression angle (FPA)]: make the child walk in a straight line and look for the FPA. Foot progression angle

ALGORITHM 3

Approach to a child with rotational profile



TFA, tibiofemoral angle; IR, internal rotation.

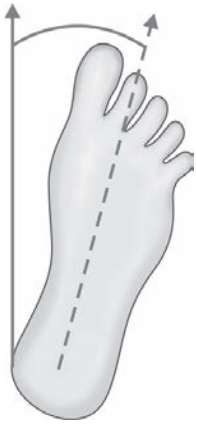


Fig. 5: Foot progression angle

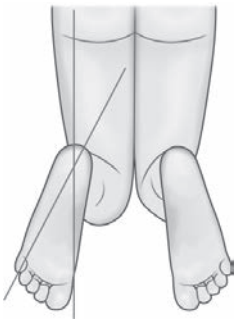


Fig. 6: Thigh foot angle

is the angle between the longitudinal axis of the foot and an imaginary line of progression of the body through space (Fig. 5). A positive or external FPA of 0–20° is considered normal, but the angle varies with age and may necessitate observation over time and correlation with the remainder of the physical examination. A negative FPA indicates that the child is walking with in toeing. Foot progression angle is also an important indicator of dynamic causes of in-toeing such as tibialis anterior overactivity

- Step 2 [external rotation and internal rotation (IR) at both hip joints]: femoral anteversion is diagnosed clinically when a child has more IR than external rotation of the hip. In infants, IR of the hip averages 40°, with a range of 10–60°, and external rotation averages 65° with a range of 45–90°
- Step 3 [thigh foot angle (TFA)]: it is determined in the prone position as the angle between the longitudinal axis of the foot (usually along the second ray) and the longitudinal axis of the thigh, with the knee flexed to 90° and the ankle in neutral position (Fig. 6). Factors influencing the TFA include tibial torsion and any hind foot or forefoot deformities. The average TFA is negative or internal by 5° in infants, and becomes positive or external by 10° by approximately 8 years of age.

In-toeing

The three most common causes of in-toeing are persistent femoral anteversion, internal tibial torsion, and metatarsus adductus. In-toeing is usually the result of metatarsus adductus in an infant, of internal tibial torsion in a toddler, and of femoral anteversion both in children older than 2.5 years and in adolescents.

Among causes for out-toeing, which is less common, are diminished femoral anteversion and, less frequently, femoral retroversion, external tibial torsion, pes calcaneovalgus, and external rotational contracture of the hip. Out-toeing, when seen in newborns, is often a consequence of intrauterine positioning of the foot in dorsiflexion against the shin, or calcaneovalgus. In infants and toddlers, it is often the result of external capsular contracture of the hip, and in older children the consequence of true bone torsion or pes planovalgus.

A comprehensive recording of the patient's history combined with a thorough physical examination are essential for differentiating benign from pathologic causes of rotational abnormalities. Studies present various conclusions in terms of the age beyond which the persistence of in-toeing is abnormal. However, the general consensus is that no natural correction of a rotational malalignment should be expected beyond the age of 10 years, although exceptions to this do occur.

Investigations

As benign variations in the rotational profile of the lower extremities are quite common in children, imaging is not routinely required in the assessment of an in-toeing or out-toeing gait unless indicated by a clinically suspected pathology. It is also important to know that deformities in the rotational or axial plane are difficult to interpret on standard two-dimensional radiographs. Indications for supplemental radiographic imaging include the presence of leg-length discrepancy, asymmetric findings, limp, pain, spasticity, recent changes in gait, persistence of a deformity into adolescence, and cosmetic concerns. Children older than 6 months who present with a leg-length discrepancy, an asymmetric rotational profile, or both should have an anteroposterior radiograph of the pelvis to rule out hip dysplasia or other abnormalities of the hip.

Metatarsus Adductus

In metatarsus adductus, there is inward deviation of the forefoot relative to the hind foot. Metatarsus adductus is the most common congenital foot deformity and it resolves spontaneously in more than 90% of children. A rigid forefoot adduction deformity with a prominent plantar crease, which often requires surgical management, is termed as "metatarsus varus" by some authors. For simplicity, these deformities are now classified as actively correctable, passively correctable or rigid.

The clinical hallmark of the condition is medial deviation of the forefoot relative to the hind foot. When the foot is viewed from the plantar surface, the sole of the foot appears bean shaped.

It is important to establish the degree of flexibility of the deformity. In mild cases, the foot will correct actively when the lateral border of the foot is stimulated. In less flexible cases, the foot will not correct actively but can easily be corrected passively. A rigid deformity has a medial soft-tissue crease at the tarso-metatarsal level and a medial soft-tissue contracture that prevents passive correction of the foot.

If the metatarsus adductus is flexible and spontaneously corrects as the foot is stimulated into active eversion, it does not warrant any treatment. These mild deformities will resolve gradually. Parents should be reassured and shown how to gently stretch the foot and how to stimulate it to achieve active correction. Passively correctable deformities can either be casted or be maintained on a splint. Majority of the rigid deformities will be corrected by serial casting. Surgical intervention is indicated very rarely for those patients with persistent deformity or those presenting late with rigid deformities and in older patients with recurrence of the deformities.

Tibial Torsion

Tibial torsion is defined by the angular difference between the transmalleolar axis and the bicondylar axis of the knee. Medial tibial torsion is most apparent when infants first begin to walk. This contributes to physiologic genu varum, which often presents in toddlers younger than 2.5 years. A slightly externally rotated hip combined with an internally rotated tibia will give the appearance of genu varum even if the knee is normal in the coronal plane. This "apparent genu varum" is frequently confused with true infantile tibia vara (Blount's disease), but can usually be differentiated from the latter by serial physical examinations done over a period of a few months. If torsion alone is present, the knee with the patella facing forward has an orientation that ranges from neutral to slight valgus. Classic tibial torsion usually improves spontaneously, whereas true Blount disease tends to progress to greater varus deformity. External tibial torsion, which is less common than classic tibial torsion, has a greater potential for persistence into adolescence.

Physical examination of the lower extremities is normal or may show physiologic genu varum and negative TFA. Medial tibial torsion resolves spontaneously and hence does not need any treatment. Efforts aimed at changing the torsional profile of a long bone with an orthosis or other splint is generally ineffective. It is better to avoid such devices as there is a possibility of creating a second deformity through the joints.

Due to the benign natural history of the condition and the generally unattractive and ineffective nature of orthotic management, observation and parental education are the main forms of treatment of tibial torsion. A small segment of the population with severe (>2 standard deviation above the mean) medial tibial torsion that does not resolve spontaneously may need treatment. On the other hand, excessive external tibial torsion might not resolve and, therefore, might need treatment at a later age. In either case, moderate-to-severe deformities that fail to resolve should alert the orthopedist to the possibility of an underlying neurologic problem, such as cerebral palsy.

Surgical management by rotational osteotomy may therefore be necessary in the rare situation in which the child has persistent functional or cosmetic problems after 8 years of age. Rotational tibial osteotomies should probably be performed only in a child with a persistent deformity exceeding 15° internal FPA or 30° external FPA at age 8 years or older, thereby ensuring that no other rotational change or gait accommodation is likely to occur, and in whom definite functional and psychological disturbances appear to be present.

Femoral Anteversion

Femoral version is defined as the angular difference between the axis of the femoral neck and the transcondylar axis of the knee. Medial femoral torsion is a common clinical problem during early childhood. It is twice as common in girls as in boys. Normally, children are born with an average femoral anteversion of 40°, which diminishes to approximately 12–16° at skeletal maturity, resolving at a rate of approximately 1.5° per year. This "normalization" with growth is usually achieved by approximately 8–10 years of age.

The child sits with the limbs in the W position, walks with an in-toeing gait with the patella medially rotated and runs in an awkward pattern. The appearance while running is described as egg-beater pattern and the walking is described as pigeon-toed gait. Tripping as a result of crossing the feet may occur in some children.

Clinical examination reveals increased internal rotation and decreased external rotation. Imaging is not routinely indicated, unless there is asymmetrical version. A computed tomography scan or magnetic resonance imaging is needed to exactly measure the amount of version and this is only indicated for surgical planning rather than as a diagnostic aid.

Majority of the children resolve spontaneously and the parents need to be reassured and also counseled to encourage their child sit cross-legged and avoid "W sitting". In a select group of children with persistent increased femoral anteversion (IR >80°) with severe cosmetic and functional limitation de-rotation osteotomy of the proximal femur is indicated to correct the deformity.

Clinical Pearls

- In-toeing is more common than out-toeing
- Majority of rotational anomalies resolve with growth
- No role for orthotics
- Corrective osteotomy only after 10 years of age.

KEY POINTS

- ☞ Many children with angular and rotational deformities can have physiological malpositions which correct over time
- ☞ Angular deformities in a child who has at least 2 years of growth left are treated with guided growth using growth modulation plate
- ☞ Corrective osteotomies may be needed for angular deformities where less than 2 years of growth is remaining or guided growth is contraindicated and for correction of pathological rotational deformities
- ☞ Encourage dual protection for pregnancy and sexually transmitted infection.

SUGGESTED READINGS

1. Herring JA. Tachdjian's Pediatric Orthopaedics: From the Texas Scottish Rite Hospital for Children. 5th ed. Philadelphia, PA: Saunders-Elsevier; 2013.
2. Lovell WW, Winter RB, Morrissy RT, Weinstein SL. Lovell and Winter's Pediatric Orthopaedics. 6th ed. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 2006.
3. Joseph B, Nayagam S, Loder RT, Torode I. Paediatric Orthopaedics: A System of Decision-Making. London, United Kingdom: CRC Press, Taylor & Francis Group; 2009.
4. Staheli LT. Rotational problems in children. J Bone Joint Surg Am. 1993;75:939-49.

CHAPTER 153

Approach to a Child with a Limp

Sandeep A Patwardhan, Anirban Chatterjee, Arjun A Dhawale

INTRODUCTION

A limp is any deviation from the normal gait pattern. The incidence of limping in children is unknown. A child walking with an abnormal gait pattern is a cause of concern for parents and the attending pediatrician. As a number of conditions may be the cause of a limp, a systematic approach is needed for appropriate treatment to be initiated.

DIAGNOSIS

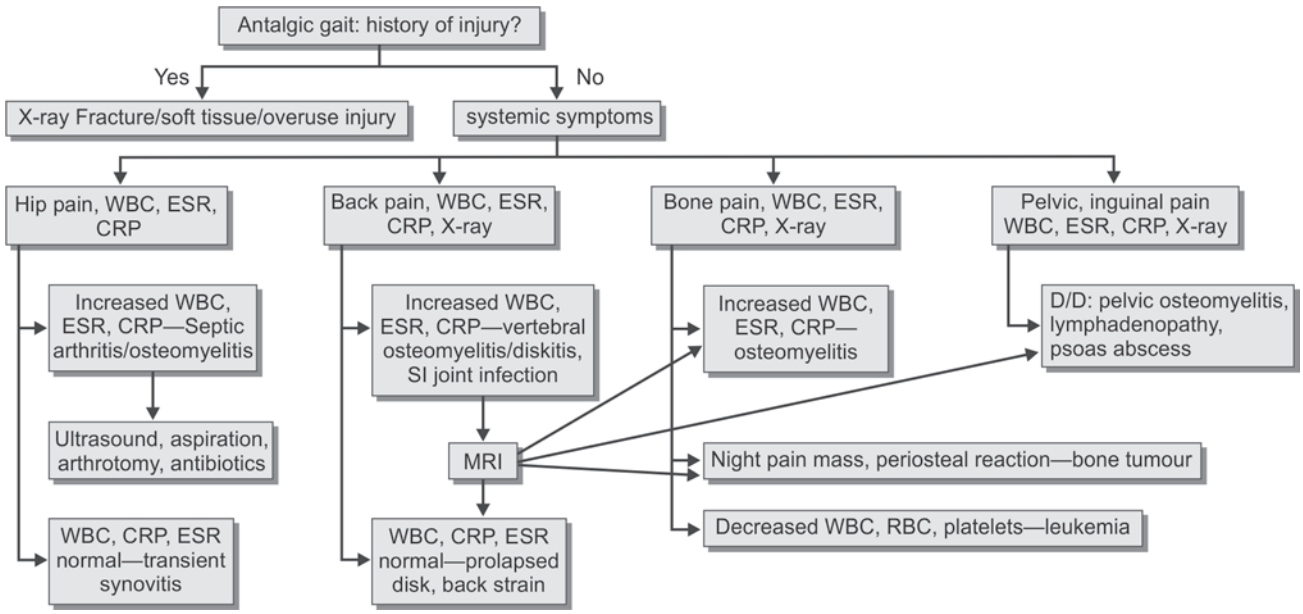
Abnormal gait can be antalgic (Algorithm 1) or nonantalgic. Common abnormal gait patterns are shown in box 1 and common causes of limp in different age groups are shown in box 2. A detailed history, physical examination, laboratory tests, and imaging are necessary for making a diagnosis. Common tests are shown in table 1.

HISTORY

The importance of obtaining a detailed history from the child or parents cannot be overemphasized. Some of the important questions to be answered are: is the onset acute, insidious, or chronic? Is the limp persistent or periodic, static or progressive and if there are any systemic symptoms like fever or weight loss. If there is pain, is it localized and

ALGORITHM 1

Algorithm for antalgic gait



WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RBC, red blood cell; DD, differential diagnosis; MRI, magnetic resonance imaging.

Box 1: Common abnormal gait patterns

Short limb gait
- When limb length discrepancy (LLD) >5%
- Toe walk/shoulder drops on same side
- Compensatory knee bend on contralateral side

Trendelenburg gait
- Weak abductors, abnormal fulcrum
- Pelvis drops on opposite side
- Compensatory leaning on affected side

Antalgic gait
- Short stepping
- Reduced stance time on affected side
- Spine pain
- Slow stiff gradual movement to avoid jarring

Box 2: Common causes of limp in different age groups

Toddlers 1–3 years
- Mild pain
  - Transient synovitis (hip)
  - Toddlers fracture
  - Seronegative spondyloarthropathy
- Severe and night pains
  - Septic arthritis (hip, knee, ankle)
  - Tumors
- Painless
  - Cerebral palsy
  - Muscular dystrophy
  - Coxa vara (hip)
  - Developmental dysplasia of the hip
  - Torsional problems

Child 4–10 years
- Mild
  - Transient synovitis hip
  - Legg-Calvé-Perthes
  - Discoid meniscus (knee)
- Severe
  - Septic arthritis (hip, knee, ankle)
  - Leukemias
  - Tumors
- Painless
  - Limb length discrepancy
  - Tethered cord (spine)
  - Cerebral palsy
  - Muscular dystrophy
  - Coxa vara (hip)
  - Developmental dysplasia of the hip
  - Torsional problems

Adolescents 11–15 years
- Mild to moderate
  - Slipped capital femoral epiphysis
  - Residual hip dysplasia
  - Chondrolysis (hip)
  - Overuse syndromes
  - Osteochondritis dissecans
  - Tarsal coalitions
  - Seronegative spondyloarthropathy
- Severe
  - Sickling crisis
  - Malignant tumors
  - Osteomyelitis
- Painless
  - Tethered cord (spine)
  - Cerebral palsy
  - Other neurological conditions
  - Limb length discrepancy

what its aggravating and relieving factors are. Some examples are:

- Mechanical: pain on loading, relieved by rest
- Inflammatory: continuous pain but relieved by nonsteroidal anti-inflammatory medicines (NSAIDs)

TABLE 1: Tests for diagnosis

Test	Condition
Complete blood count	Polymorphs increased in infective or inflammatory pathologies
C-reactive protein	Level increased in infective or inflammatory pathologies
Erythrocyte sedimentation rate	Level increased in infective or inflammatory pathologies
Synovial fluid analysis	Septic arthritis: leukocyte count increased (>50,000/cmm), turbid synovial fluid; transient synovitis: leukocyte count increased (<15,000/cmm), clear synovial fluid
Synovial fluid culture	Septic arthritis: growth; transient synovitis: no growth
Throat culture	Acute rheumatic fever: group A streptococci
Blood culture	Positive in infective pathologies

- Infective: continuous pain, not relieved by NSAIDs, night pain could be due to chronic granulomatous diseases like tuberculosis
- Tumor: relentless pain, not relieved by medication; night pain—possible tumor, benign or malignant with the exception of osteoid osteoma, where pain relief is known with ibuprofen.

CLINICAL EXAMINATION

It should be noted whether the child walked in or was carried into the consulting room or walked in. If the child walked in then some observation of the gait is possible even before a detailed clinical examination.

To properly analyze the gait, the child should be undressed and made to walk along a corridor, run, and get up from sitting/squatting position, provided it is painless. In case the limp is acute in origin and painful, then such a detailed visual analysis of gait may not be performed. While the child is walking, one needs to observe the trunk, the pelvis, hips, knees, and the ankle foot complex individually. One also needs to observe the shoes, especially the wear characteristics of the heel and sole.

Local Examination

At the end of the history and examination of the gait, one should have narrowed down the differential diagnosis (DD) and also mentally decide which limb, which bone or which joint needs to be examined in more detail. To avoid missing out any subtle signs, examination should include the spine and lower extremities including hip joints, knee joints, and ankle-foot complex with the child suitably undressed. A useful dictum to follow for local examination of a part is look, feel, move, measure, and perform (special tests).

Focal examination should be done if infection or trauma is suspected.

Clinical Pearls

- Onset, duration, and progress of limp and associated or absence of pain must be elicited clearly
- Origin of pathology in a limping child may be from the foot to the spine
- Think of the most common conditions first according to age.

DIFFERENTIAL DIAGNOSIS

Transient Synovitis

Transient synovitis is commonly seen in children aged 3–8 years with acute onset of hip pain and limping with a decreased range of movements. Often, there is a history of a preceding viral illness. Ultrasound findings of joint effusion with no elevation of C-reactive protein and erythrocyte sedimentation rate (ESR) with a normal or slight elevation in white blood cell count help corroborate the diagnosis. Treatment is observation, rest, and analgesics.

Septic Arthritis

Septic arthritis can occur at any age from the neonatal period. There is an acute onset of pain, limping, and fever with restricted hip range of movements. Differentiation from transient synovitis is based on history of fever, inability to bear weight, elevated ESR, and leukocytosis (>12,000 cells/mL). The probability of a diagnosis of septic arthritis increases with the number of criteria present; ultrasound to assess joint effusion and synovial thickening. Radiographs, although not helpful in the early stages, identifies associated osteomyelitis, soft-tissue swelling, or hip subluxation. Early intervention with hip arthrotomy and 6 weeks of antibiotic coverage as per the culture sensitivity is the standard of care.

Osteomyelitis

Osteomyelitis in children usually occurs as a result of hematogenous spread of bacteria. The most common organism is *Staphylococcus aureus*, with incidence of methicillin-resistant *S. aureus* (MRSA) increasing. The child will present with fever, limping, localized swelling, and tenderness. Although metaphyseal involvement is more common, the diaphysis may be involved less often. In acute osteomyelitis, early radiographs may only show soft-tissue swelling and radiographs after a few weeks will show periosteal reaction (Fig. 1) and bone destruction. A 6-week course of appropriate antibiotics is initiated after obtaining blood cultures and local cultures after surgical drainage.

Fracture

Children with trauma to the lower extremity may present with a limp. These could commonly occur while playing or due to motor vehicle accidents. Fractures of the femur and tibia

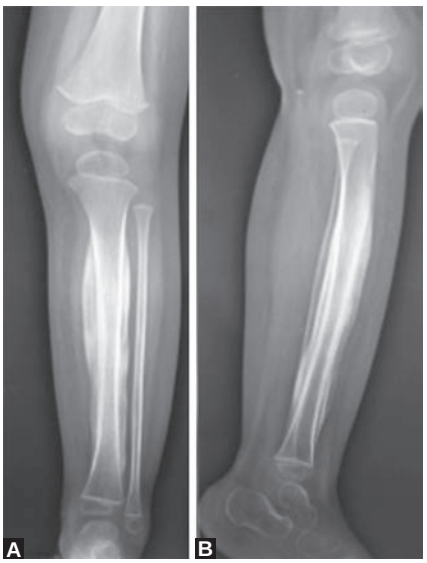


Fig. 1: Periosteal reaction of the tibia, the differential diagnosis could be osteomyelitis, healing fracture, or Caffey's disease.

are common injuries and are diagnosed with appropriate radiographs. Treatment depends on the location and type of fracture and the age of the patient. Closed treatment of long bone fractures with casting or elastic nailing is usually the norm. Epiphyseal injuries and joint injuries should be identified with a thorough local examination and if suspected then an magnetic resonance imaging is useful.

Limb Length Discrepancy

Children with a limb length discrepancy (LLD) will toe walk on the shorter side. The shortening may be due to developmental dysplasia of the hip (DDH), congenital short femur, postinfective physeal growth arrest, or hemimelia (Fig. 2). Apart from treatment of the primary pathology, a lower extremity scanogram will document the LLD. Treatment is usually a shoe raise and observation for a difference of up

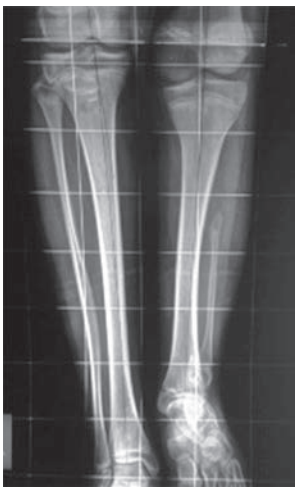


Fig. 2: Limb length discrepancy in a child with fibular hemimelia

to 2 cm. For a greater LLD, lengthening of the short limb with an external fixator or an epiphysiodesis of the contralateral extremity are options after serial documentation of the discrepancy.

Developmental Dysplasia of Hip

Incidence of neglected DDH is higher in India and other developing countries due to the absence of screening programs and unequal distribution of healthcare facilities and personnel in urban and rural areas. This often results in a missed diagnosis of DDH and children present with a limp (Fig. 3). Diagnosis of DDH in a child of walking age can be made clinically on hip examination by eliciting a telescopy sign and restricted abduction with LLD. The pelvis anteroposterior radiograph will confirm the diagnosis of DDH. Treatment depends on the age of the child. After walking age, open reduction is necessary and may be combined with a femoral and acetabular osteotomy to relocate the head into the acetabulum.

Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis is more common in overweight adolescent boys. Onset of limp and pain could be insidious in stable slips or acute with inability to bear weight in unstable slips. Some patients may complain of knee pain (due to referred pain). Patients will have restricted range of hip movements, with obligatory external rotation on flexion and restricted internal rotation. Anteroposterior and lateral hip X-rays are diagnostic of the slip. Bilateral involvement could occur. An endocrinology workup should be completed. Treatment is dependent on the degree of slip and usually involves surgery with *in-situ* pinning for mild-to-moderate slips and management of any underlying endocrinological condition, if present.

Perthes Disease

Legg-Calvé-Perthes disease usually presents with a painful limp with restricted internal rotation of the hip in children between 6 and 11 years. The prognosis is better in younger children due to the better remodeling potential of the capital femoral epiphysis. Although many theories have been postulated, the etiology is not well defined. The pelvis radiograph will show collapse or extrusion depending on the stage of the disease (Fig. 4). Treatment depends on the age of the patient and stage of the disease, the principle being to contain the hip with an abduction cast, femoral varus osteotomy, or an acetabular shelf procedure.

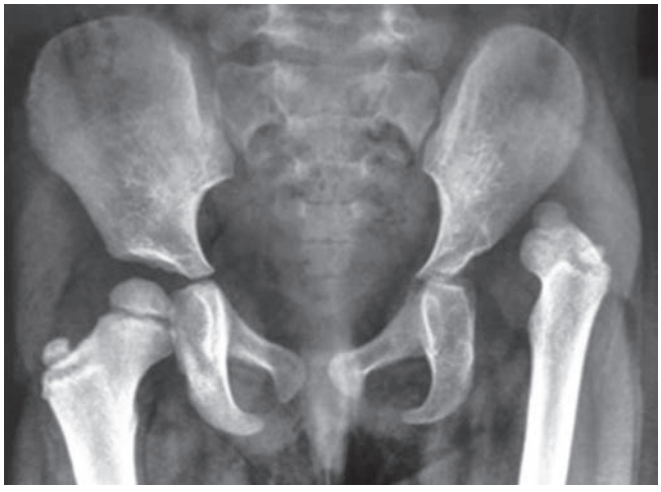


Fig. 3: Developmental dysplasia of the hip

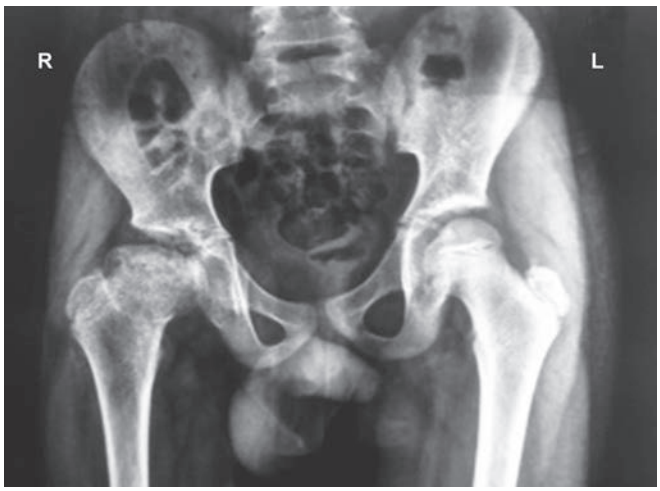


Fig. 4: Perthes disease of the right hip in an 11-year-old male with extrusion and flattening of the head

Osteoid Osteoma

The child will present with boring pain in the extremity with worsening at night and typically NSAIDs will relieve the pain. A computed tomography scan can confirm the diagnosis with a sclerotic ring surrounding a nidus being the classical radiographic appearance. Treatment is image-guided radiofrequency ablation or surgical excision.

Juvenile Arthritis

Juvenile arthritis is an important DD in a child with a limp who presents with pain in the knee, ankle, or subtalar joints. Swelling with some restriction of movement will be present along with an elevated ESR and antinuclear antibody positive titer, although this may often be negative. Orthopedic intervention is rarely needed.

Clinical Pearls

What to tell the parents?

- A limp is often the tip of the iceberg
- Investigations are necessary to prove diagnosis or rule out sinister pathology
- Surgical intervention is very often required, especially in painless limps to prevent future problems.

CONCLUSION

A referral to a pediatric orthopedic specialist is warranted if there is a mild painful limp, not responsive to conservative therapy for more than 10 days; if the limp is associated with severe pain, especially at night; if there is a persistent limp with all basic investigations normal, and if an obvious orthopedic abnormality is diagnosed on investigations.

KEY POINTS

- ☞ Onset, duration, progress, and associated symptoms and age of a limping child are your most valuable diagnostic criteria
- ☞ Supportive and relevant investigations will lead to accuracy in management
- ☞ Early and timely referral significantly affect outcome
- ☞ Unilateral painless limp should never be ignored
- ☞ Bilateral limp usually indicative of as generalized or systemic involvement or bilateral pathology which requires correct prioritization of problems.

SUGGESTED READINGS

1. Aronsson DD, Loder RT, Breur G, Weinstein SL. Slipped capital femoral epiphysis: current concepts. J Am Acad Orthop Surg. 2006;14(12):666-79.
2. Boscainos PJ, Cousins GR, Kulshreshtha R, Oliver TB, Papagelopoulos PJ. Osteoid osteoma. Orthopedics. 2013;36(10):792-800.
3. Flynn JM, Widmann RF. The limping child: evaluation and diagnosis. J Am Acad Orthop Surg. 2001;9(2):89-98.
4. Gill KG. Pediatric hip: pearls and pitfalls. Semin Musculoskelet Radiol. 2013;17(3):328-38.
5. Herring JA. Tachdjian's Pediatric Orthopaedics: From the Texas Scottish Rite Hospital for Children, 5th ed. Philadelphia: Saunders-Elsevier; 2013.
6. Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. J Bone Joint Surg Am. 2004;86-A(8):1629-35.
7. Sawyer JR, Kapoor M. The limping child: a systematic approach to diagnosis. Am Fam Physician. 2009;79(3):215-24.
8. Shah H. Perthes disease: evaluation and management. Orthop Clin North Am. 2014;45(1):87-97.
9. Sultan J, Hughes PJ. Septic arthritis or transient synovitis of the hip in children: the value of clinical prediction algorithms. J Bone Joint Surg Br. 2010;92(9):1289-93.
10. Weinstein SL, Mubarak SJ, Wenger DR. Developmental hip dysplasia and dislocation: Part II. Instr Course Lect. 2004;53:531-42.

CHAPTER 154

Pulled Elbow, Growing Pains, and Flatfoot

Premal Naik, Hitesh B Chauhan

PULLED ELBOW

Pulled elbow is a common injury in children under the age of 5 years. It is a minor soft-tissue injury of the radiohumeral joint caused by sudden traction on the hand, wrist, or forearm.

Incidence

Five percent of all upper limb injuries less than 10 years age:

- Boys more than girls
- Left more than right.

Mechanism of Injury

Forcible traction applied to the child's pronated hand or wrist with the elbow extended; common circumstances, which leads to such traction injury, are:

- Child's forearm or hand is held firmly by a parent as the child attempts to run away
- Child is lifted by an adult from the ground by his/her hands
- Child may be lifted by the hand from a lying or sitting position or may be swung around by the hands/wrist while playing.

Pathology

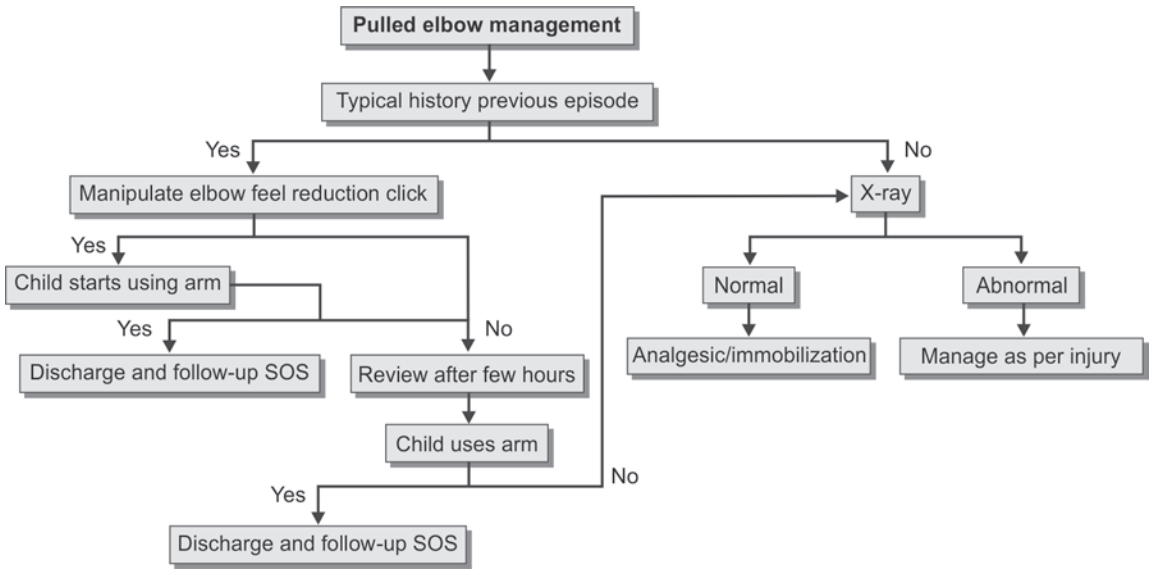
Traction on pronated forearm with extended elbow → partial escape of radial head from annular ligament → pulled elbow

Clinical Features (Algorithm 1)

Child presents with painful dangling arm (infant will present with pseudoparalysis), child does not use the affected limb for holding objects, keeps the elbow extended and forearm

ALGORITHM 1

Algorithm for pulled elbow patient



pronated, and resists supination of forearm. There is no obvious tenderness, edema, or deformity at elbow.

Investigations

Pulled elbow is a clinical diagnosis, but when the mode of trauma and history are not corroborative, X-ray is indicated.

Treatment

Reduction Maneuver

- Hold the child's wrist with one hand and with other hand support the elbow and palpate the radial head → supinate the forearm with upward push on the radial head → click is felt with radial head reduction
- Sometimes pronation and flexion of elbow is also required for reduction
- Click signals successful reduction, the child will be playful and will use the arm after sometime
- If the child is not using arm immediately, should be sent home with analgesics and should be called the next day.

Precautions

An important aspect in the management of pulled elbow is to advise the parents to avoid traction on the child's arm. They should not pull child from hands or wrists. Parents should be advised to discuss this with neighbors and relatives who are expected to handle the child any time.

Clinical Pearl

- Look for mode of trauma or mechanism of injury, age of the child, absence edema or deformity at elbow, pronation attitude of forearm, and presence of previous history of similar complaints → clinically pulled elbow → reduction maneuver → feel click → dramatic improvement in movements → no immobilization required.

GROWING PAINS (ALGORITHM 2)

These are idiopathic benign pains or discomfort in children.

Incidence

- Fifteen to thirty percent of all children
- More common in girls.

Etiology

Idiopathic in nature, no documented cause has been discovered.

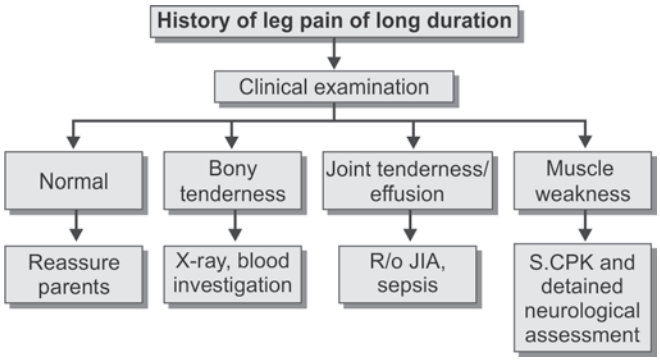
Clinical Features

Growing pain is a diagnosis of exclusion. All other causes of leg aches are to be excluded before stamping it as growing pain.

- History is typically vague and of long duration
- Not associated with any functional disability
- Usually occurs at night (just before going to sleep). Occasionally child may get up from sleep due to pain

ALGORITHM 2

Algorithm for growing pains



JIA, juvenile idiopathic arthritis; S. CPK, serum creatine phosphokinase.

- Pain is most commonly in calf and ankle region and sometimes is so severe that child cries with pain
- Few children demand massaging for relief of pain
- Primarily involves lower extremities and is mostly bilateral
- Typically child resumes normal activity next day.

On Examination

- Normal walking pattern without limp
- No local tenderness or swelling in joints and muscles
- No muscular spasticity or restriction of joints movements
- No wasting or neurological deficit. Gower test will be negative
- No limb length discrepancy or limb wasting.

Investigations

If history is not corroborative, any other condition should be ruled out with X-rays and blood investigations.

Differential Diagnosis

If there is history of trauma and excessive exertion with local bony tenderness, rule out stress fracture with X-ray. Tumor-like osteoid osteoma, osteogenic sarcomas, or Ewing's give rise to night pain, but are more aggressive and associated with localized swelling, tenderness and limb wasting.

Management

After ruling out any other cause of pain, diagnosis of growing pains is considered.

No specific treatment, hot fomentation, massage, and analgesic may help.

Most importantly, parents should be reassured and made to understand that growing pain are self-limiting and will subside in due course of time. One can be made to understand relation of pain with sudden increase in height of their child (growth spurt) in last few months.

Relapse may occur in next growth spurt. If any other symptoms like swelling, wasting, and fever develop on follow-up, child should be subjected to further investigation.

Clinical Pearl

Long and vague history, bilateral lower extremity, night pain, mainly calf and ankle, normal activities next day, no clinical findings → no radiological findings → diagnosis of exclusion → reassurance, diversion of mind, relapses may occur → look for warning signals.

FLATFOOT

Absence of medial longitudinal arch of foot is known as flatfoot (Algorithm 3).

Incidence

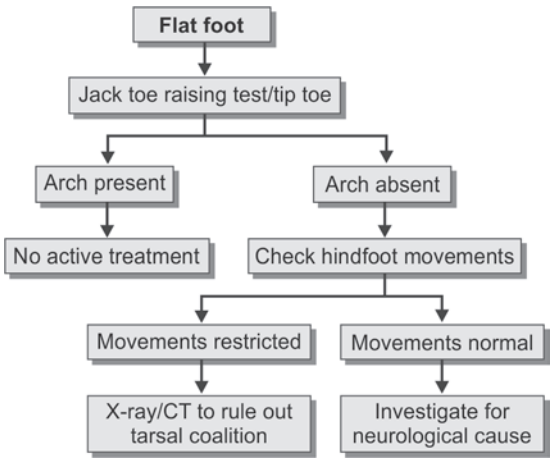
It occurs approximately 20–30% of general population.

Classification

- Flexible flatfoot: arch is absent when patient bears weight but appears off weight. It is be due to hyperlaxity of ligaments (Fig. 1)

ALGORITHM 3

Algorithm for flatfoot patient



CT, computed tomography.

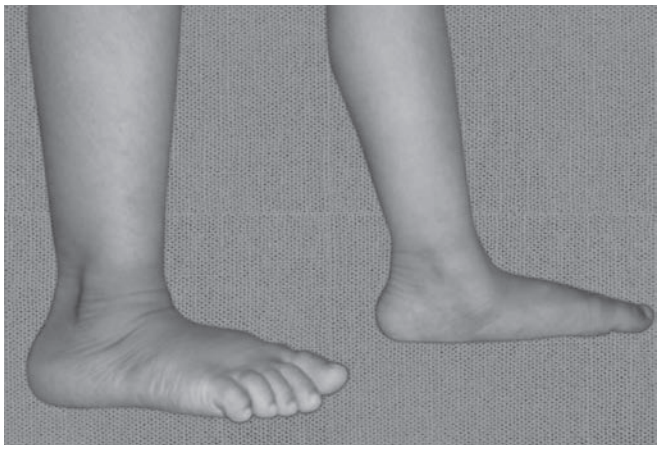


Fig. 1: Patient with flexible flatfoot

- Rigid flatfoot: arch is absent all the time, whether child is bearing weight or not. It may be due to:
  - Tarsal coalition
  - Juvenile chronic arthritis
- Neuromuscular flatfoot: flatfoot secondary to muscular imbalance, weakness or spasticity. Common causes are:
  - Cerebral palsy
  - Spina bifida.

Differential Diagnosis

Other conditions which give similar appearance as of flatfoot are:

- Congenital vertical talus
- Accessory navicular.

Clinical Features

- Primarily parents complaint of awkward appearance of foot, uneven shoe ware, or sometimes pain
- Family history may be positive: parents tend to have joint laxity and sometimes flatfeet as well. Tarsal coalitions can be autosomal dominant or recessive
- Many parents are bothered about future participation in sports and army recruitment.

Examination

- In flexible flatfeet: arch disappears on standing, and reappears on taking weight off. Arch also reappears when patient stands on toes (Fig. 2)
- Wind up test or Jack toe raising test: in flexible flatfoot, arch can be reproduced by extending great toe at metatarsophalangeal joint (Fig. 3)
- General assessment of signs of hyperlaxity should be looked for hyperextension of elbows, thumb touching to forearm, knee hyperextension
- In rigid flatfeet, arch is always absent, on or off weight. Extension of great toe or standing on toes does not form arch
- Movements of the hindfoot are restricted in rigid flatfeet and free in flexible flatfeet
- Heel is in valgus and corrects on tiptoeing in flexible feet

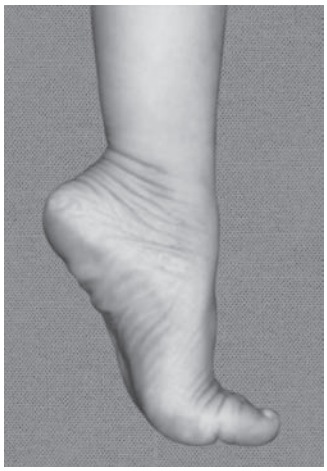


Fig. 2: Same patient showing good arch on tip toe

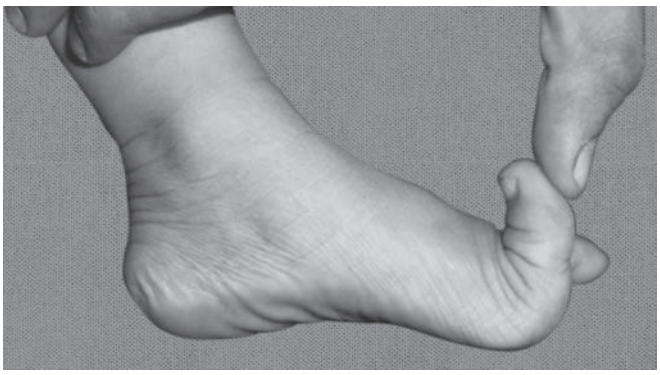


Fig. 3: Same patient showing good arch on extension of great toe

- Tendo achilles tightness should be looked for
- Detailed neurological examination if any suggestive findings are present.

Investigations

- In flexible flatfeet, no investigations are required, clinical diagnosis is adequate
- In rigid flatfeet, X-rays and computed tomography scan are helpful to rule out tarsal coalitions.

Management

- In flexible flatfeet:
  - Parents are reassured regarding benign nature of deformity
  - Promote bare feet walking in sand and garden
  - Special shoes have no role in management of flexible flatfeet (in fact early shoe wearing in city kids is found to have high incidence of flatfeet compared to rural children walking bare feet)
  - Arch support only if severe shoe wear and feet pain
  - Rarely surgery is advised for failed conservative treatment
- In tarsal coalitions: initially, conservative treatment in form of cast followed by splints and arch support is given. If it fails then bar excision surgery is required
- In neuromuscular flatfeet: Initial conservative treatment is orthosis. If it fails than surgery in form of muscle balancing or arthrodesis is required.

Clinical Pearl

- Absence of medial longitudinal arch, complaining of awkward feet and gait pattern, uneven shoe wear and tear, sometimes pain → Look for hyperlaxity, hindfoot movements, presence of arch off weight, jack toe raising test, neurological examination → Absence of radiological signs → Reassurance, barefoot walking, rigid arch support for pain

KEY POINTS

- ☞ Commonly loss of medial longitudinal arch
- ☞ Changes in the hindfoot movement
- ☞ Associated with hyperlaxity
- ☞ Differentiate from tarsal coalition and neurological flatfeet
- ☞ Forcible traction in pronation is the common mechanism
- ☞ Painful nonusage of arm results
- ☞ Reduce on outpatient department (OPD) basis two gentle attempts
- ☞ Reduction click gives dramatic relief
- ☞ Cause is idiopathic
- ☞ Commonly calf pain at night
- ☞ Stretching exercises and hydration maximum relief.

SUGGESTED READINGS

1. Evans AM. Growing pains: contemporary knowledge and recommended practice. J Foot Ankle Res. 2008;1(1):4.
2. Fabry G. Clinical practice. Static, axial, and rotational deformities of the lower extremities in children. Eur J Pediatr. 2010;169(5):529-34.
3. Harris EJ, Vanore JV, Thomas JL, Kravitz SR, Mendelson SA, Mendicino RW, et al. Diagnosis and treatment of pediatric flatfoot. J Foot Ankle Surg. 2004;43(6):341-73.
4. Irie T, Sono T, Hayama Y, Matsumoto T, Matsushita M. Investigation on 2331 cases of pulled elbow over the last 10 years. Pediatr Rep. 2014;6(2):5090.
5. Krul M, van der Wouden JC, van Suijlekom-Smit LW, Koes BW. Manipulative interventions for reducing pulled elbow in young children. Cochrane Database Syst Rev. 2009;(4):CD007759.
6. Mohanta MP. Growing pains: practitioners' dilemma. Indian Pediatr. 2014;51(5):379-83.
7. Mosca VS. Flexible flatfoot in children and adolescents. J Child Orthop. 2010;4(2):107-21.
8. Petersen H. Growing pains. Pediatr Clin North Am. 1986;33(6):1365-72.
9. Weiser P. Approach to the patient with noninflammatory musculoskeletal pain. Pediatr Clin North Am. 2012;59(2):471-92.

CHAPTER 155

Clubfoot Treatment: Current Concepts

Rujuta Mehta, Alaric J Aroojis

INTRODUCTION

Clubfoot is the one of the most frequent congenital deformity seen by a pediatrician and referred to a pediatric orthopedic surgeon. Recent estimates say over 50,000 children are born with clubfoot in India. Over 3,700 children are born with clubfoot in Maharashtra which means one in every 500 live birth is a clubfoot. Significant advances have been made over the last few decades regarding the treatment of clubfoot. This chapter will give the reader an overview of diagnosis and management in concurrence with the changing scenario and shift back to conservative treatment in view of recent successes *vis-a-vis* state of the art management.

DEFINITION

The term congenital talipes equino varus (CTEV) aptly describes the complex amalgamation of the following deformities of the entire foot: congenital, from birth; talipes, foot; equino, equinus posture of the foot complex (like a horse's heel) excessive plantar flexion; and varus, inversion and subluxation on talonavicular joint.

ETIOLOGY

Multifactorial inheritance system due to intrauterine environment factor leads to idiopathic CTEV (Box 1).

PATHOLOGY

Bony and soft-tissue pathology coexist in clubfeet (Fig. 1). It is a deformation occurring during the second trimester of pregnancy and not an embryonic malformation except in the teratologic variety. Congenital clubfoot is a complex three-dimensional deformity having four components: (i) equinus, (ii) varus, (iii) adductus, and (iv) cavus. The tarsal bones, which are mostly made up of cartilage, are in the most extreme positions of flexion, adduction and inversion at birth. The talus

Box 1: Multifactorial inheritance system

Most common etiology

- Idiopathic
- Neuromuscular etiology
- Syndromic/genetic etiology, e.g.:
  - Arthrogryposis multiplex congenita
  - Streeter's dysplasia (constriction band syndrome)
  - Secondary to decrease of size of the uterus resulting from early rupture of amnion with chorion remaining intact

Rarer syndromic etiology

- Autosomal dominant: whistling face/Freeman-Sheldon syndrome (craniocarpotarsal syndrome)
- Autosomal recessive:
  - Diastrophic dwarfism (micromelia)
  - Joint contracture, scoliosis, thumb deformities, congenital talipes equino varus
  - Larson syndrome
  - Down's syndrome
  - Mobius syndrome

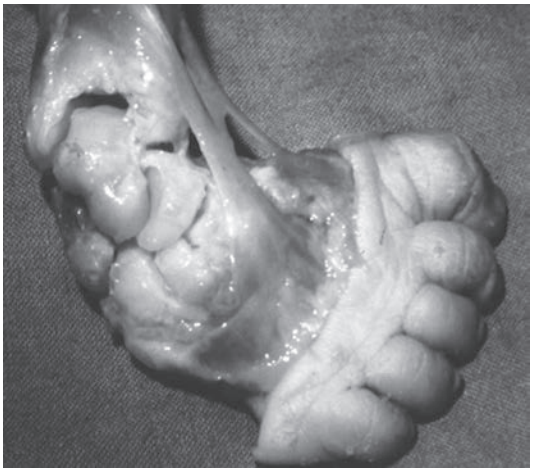


Fig. 1: Dissected fetal clubfoot showing typical bony and soft-tissue pathology

is in severe plantarflexion, its neck is deflected medially and plantarward, and its head is wedge-shaped. The navicular is severely medially displaced, in close apposition to the medial malleolus and articulates with the medial surface of the head of the talus. The calcaneus is adducted, plantarflexed and inverted under the talus. The forefoot is in some pronation, causing the plantar arch to be more concave (cavus). The calcaneocuboid joint is deviated posteromedially. The deltoid, tibionavicular ligament and the tibialis posterior tendon are thickened and merge with the short plantar calcaneonavicular ligament. The ligaments of the posterior and medial aspects of the ankle and tarsal joints are very thick and taut, thereby severely restraining the foot in equinus and the navicular and calcaneus in adduction and inversion. There is an excessive pull of the tibialis posterior abetted by the gastrocsoleus, the tibialis anterior and the long toe flexors.

HISTORY AND PHYSICAL EXAMINATION

The orthopedic officer must have a sensitive and kind approach to babies. After a general examination to rule out nonidiopathic clubfeet, parents must be reassured that their baby's deformity will be corrected in a few weeks. The baby will have a normal-looking and functional foot throughout life as long as they are faithful to all the details of the treatment program. Radiographs are not necessary.

MANAGEMENT

Treatment of clubfoot as a generic term cannot be clubbed together. It is therefore subdivided as follows:

- Treatment in the prewalking age
- Treatment after independent walking is achieved.

Treatment in the Prewalking Age

The most widely practiced current standard of care for treatment of clubfeet in the first 6 months of life is the Ponseti method of treatment (Fig. 2). This is a combination of weekly plastering and a semi-invasive procedure of tenotomy of the tendo-Achilles at the final step of correction. This technique of manipulation and casting is based on anatomical studies and a biomechanical understanding of the "kinematic coupling" of the subtalar joint. It corrects all elements of the deformity, resulting in a functional, pain free, looking plantigrade foot with good mobility, without calluses, and without the need for wearing special or modified shoes. Foot examination and corrective manipulations are best done with the baby resting on the mother's lap. When applying the plaster cast, the baby is placed at one end of the table to provide room for the mother and assistant on either side. It is best if the baby is breastfed through the treatment.

Results of the Ponseti Method of Clubfoot Treatment

The Ponseti method is a safe and effective treatment for congenital idiopathic clubfoot and radically decreases the need for extensive corrective surgery. it is the most effective method for children less than 1 or 2 years of age (Fig. 3).

Clinical Pearls

- Treatment can begin as early as first week of life
- Complex deformity yields better under influence of relaxin with serial casts
- Deformity is corrected within few weeks
- Adherence to protocol is a must.

Treatment after Independent Walking is Achieved

Various surgical modalities exist for addressing all grades of severity of clubfeet in the post-walking age group:

- Open surgery: soft-tissue releases and tendon transfer
- Bony surgery
- Fixators.

The axiom "No two clubfeet are exactly the same" is well accepted now and therefore the corollary that the surgical treatment has to be catered to the type and need of each case what is known as "A la carte" approach.

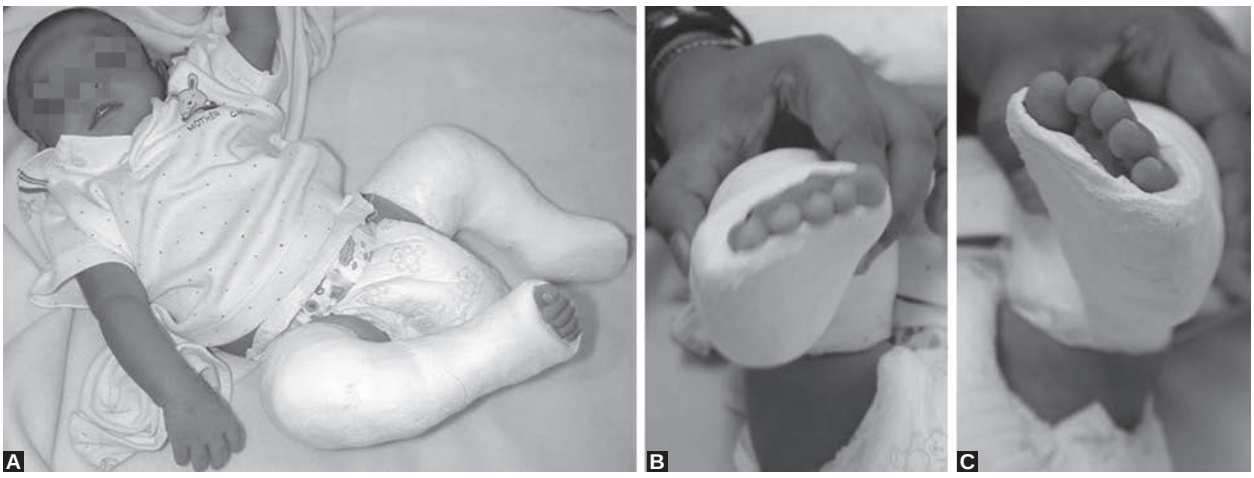


Fig. 2: Technique of Ponseti casting. Note the supination of the forefoot while it is being abducted

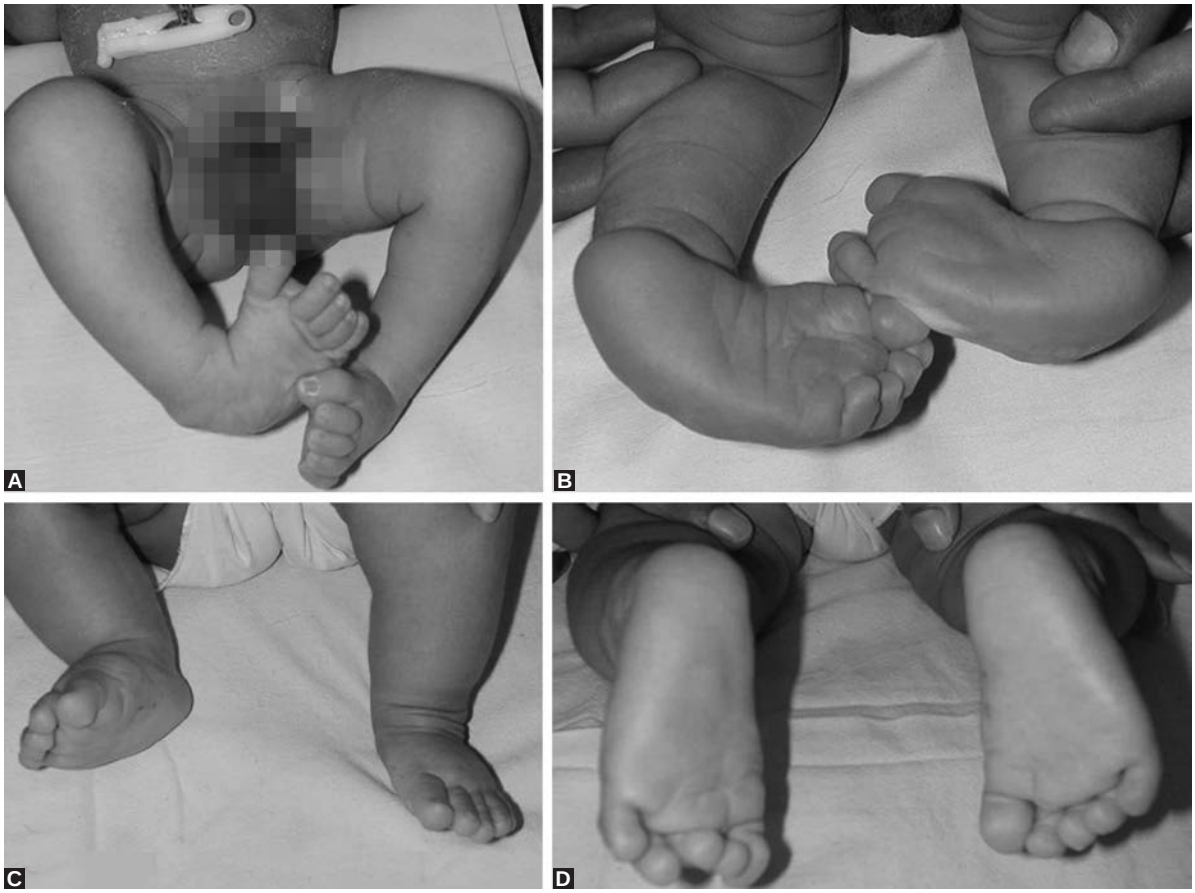


Fig. 3: Result of Ponseti method of treating clubfoot in a 1-week-old neonate. The deformity is fully corrected after five serial manipulations and casting followed by a percutaneous tendo-Achilles tenotomy

Open Surgery: Soft-tissue Releases

Failures of conservative treatment or late presentations after the age of 1 or 2 years usually mandate surgical release. Several operations have been described for this condition since early 1930s. The most widely followed surgery is a posteromedial release popularized by Vincent Turco in the 1960-70s after he published his original monograph with a 16-year follow-up. This surgery addresses almost all the deforming pathoanatomical structures on the anterior medial and posterior aspects of the foot and their abnormal interrelationships. The salient features of this surgery are as follows:

- Release of three joints:
  - Ankle
  - Subtalar
  - Talonavicular
- Release of three ligament groups:
  - Talocalcaneonavicular, spring ligament, and plantar fascia
  - Superficial deltoid or talocalcaneal
  - Calcaneofibular and talofibular.
- Lengthening of three tendons:
  - Tendo-Achilles
  - Tibialis posterior
  - Flexors digitorum and hallucis.

Results of this surgery are highly gratifying and long-lasting (Fig. 4), but not without their share of complications and morbidity.

Open Surgery: Tendon Transfer

Tendon transfers are indicated for age groups above 3–5 years mainly for residual uncorrected components of clubfoot deformities. Tibialis transfer to the medial cuneiform bone is indicated for dynamic supination and persistent metatarsus adductus deformity, which particularly occurs with relapses of the conservative or Ponseti method of plastering.

Bony Surgery

The incidence of bony surgeries has plummeted in recent years, particularly with the colossal success of conservative techniques; however, it deserves mention.

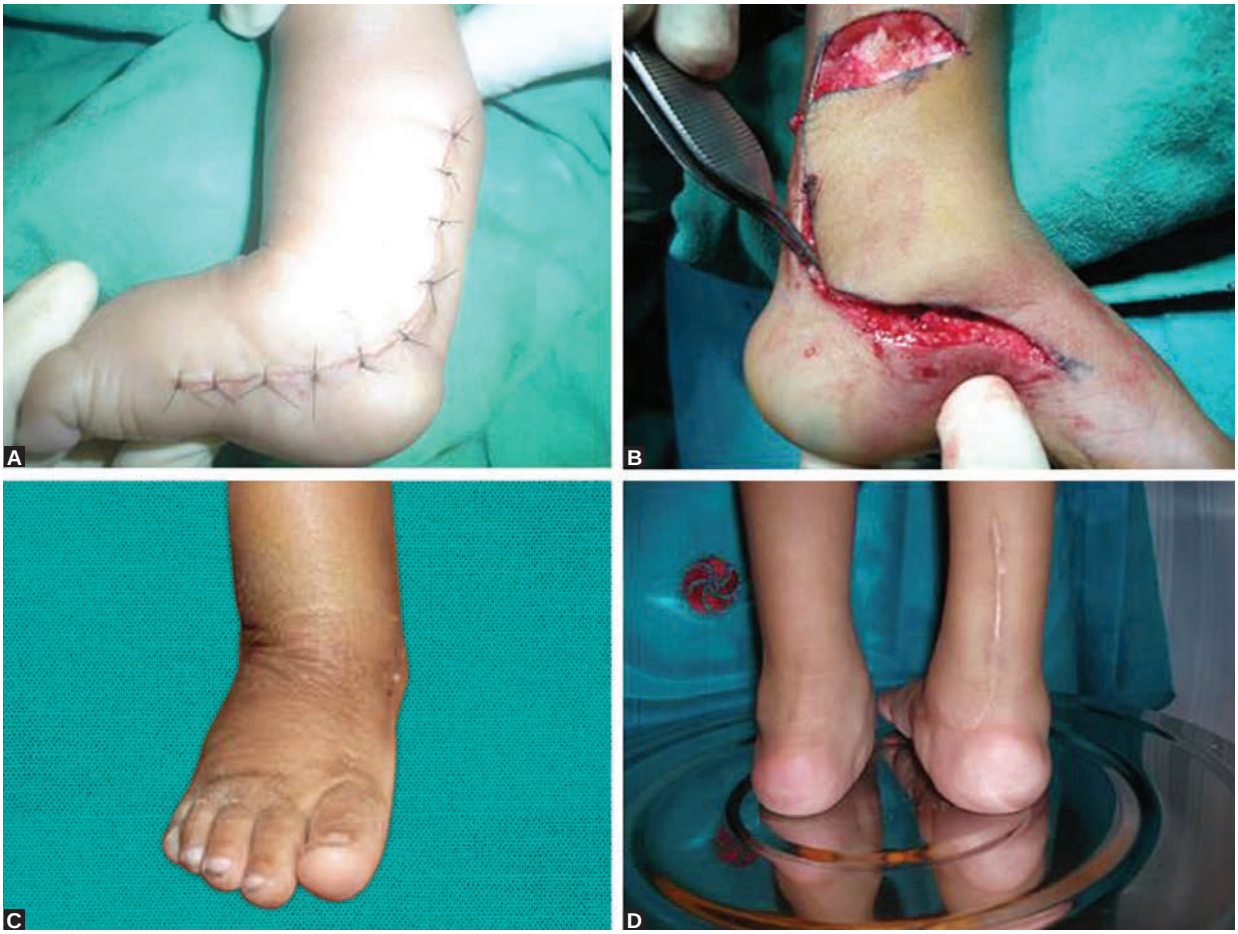


Fig. 4: Steps and result of posteromedial release surgical open release for a 17-month-old boy

- Osteotomies: particularly for hind- and midfoot correction above the age of 5 years, after majority of the tarsal bones have ossified
- Talectomy/naviculectomy: this is a surgery with a very select place for the treatment of severe arthrogrypotic feet where the deformity is so severe and no other operation can work so as to prevent plantigrade shoe wear
- Triple arthrodesis: this is a salvage procedure done at or around skeletal maturity for very severe or recalcitrant clubfeet, for the purpose of relieving pain or to facilitate normal shoe wear.

Fixators

In 1989, Dr BB Joshi from Mumbai, India, started using an indigenous external fixation system for gradual distraction of multiplanar deformities of clubfoot. The frame is essentially constructed on K-wires fixing three segments: (i) tibial, (ii) calcaneal, and (iii) metatarsal. These three segments are then interconnected using clamps, rods, and distraction assemblies are used at altering rhythms in a differential fashion, i.e., medial more than equinus more than lateral. The process has been analogous to an external version of Ponseti principles which gradually unlocks the talus and brings about a complete correction of all components of clubfoot, however, complex the deformity. Fixators are invaluable for neglected and relapsed and rigid clubfeet, particularly 3–14 years (Fig. 5).

Clubfoot is referred at any age and treatment can be instituted irrespective of age of referral. A simple flowchart on treatment of clubfoot treatment is depicted in algorithm 1.

ROLE OF EXERCISES AND SPLINTS

Any method of CTEV correction requires maintenance of correction and sustaining the same till skeletal maturity. This is achieved by using special footwear in the form of ankle-foot orthosis or stiff medial border shoes mounted on an abduction bar with external rotation correction. These are essentially static devices and need to be supplemented with active and assisted active exercises and stimulation of the muscles of the lateral aspect of the foot regularly several times a day over a number of years. The importance of a regular follow-up and prevention of relapse thus cannot be overemphasized.

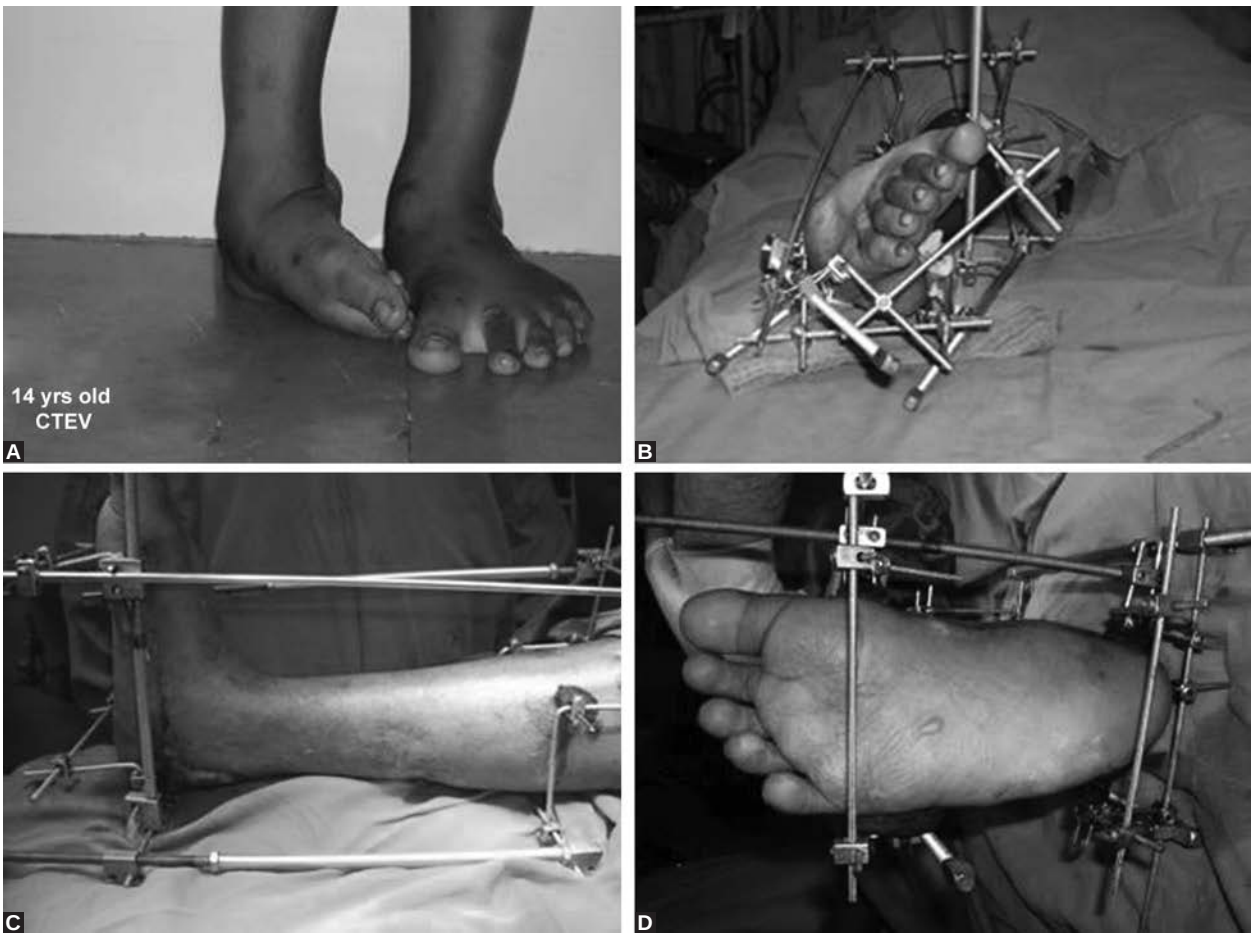
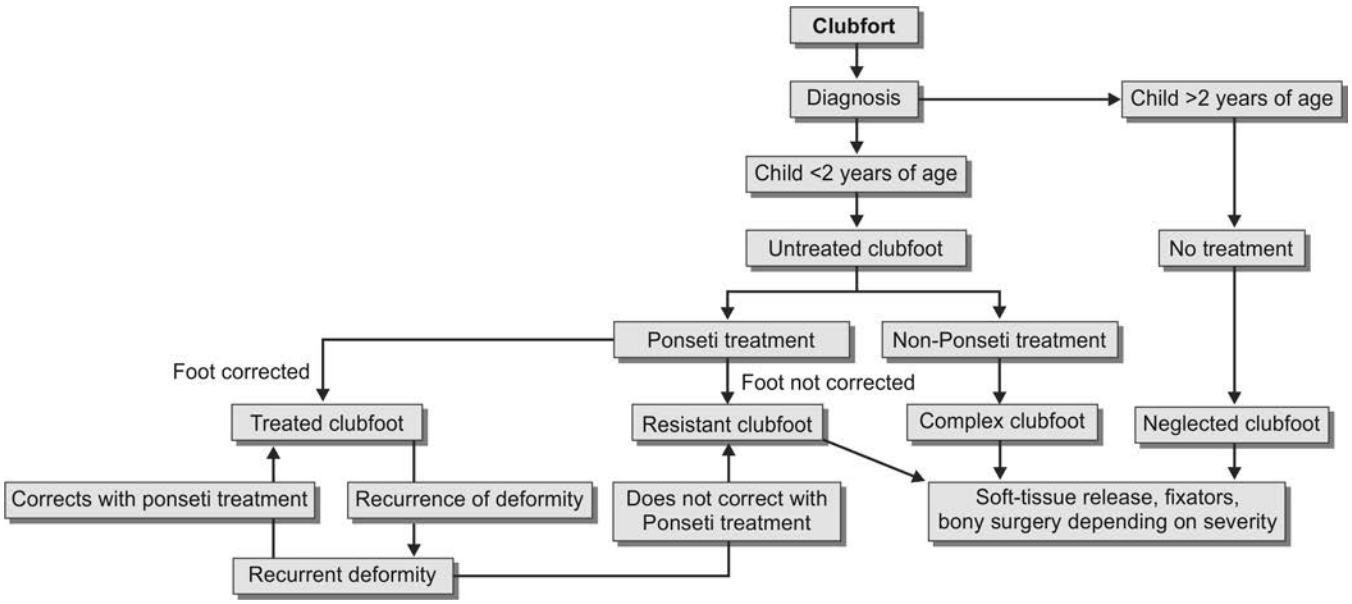


Fig. 5: Deformity, frame and result of external fixation system for neglected clubfoot

ALGORITHM 1

Clubfoot treatment



Clinical Pearls

What to tell the parents?

- Treat early
- Maintain serial casting and bracing protocol
- Correct treatment will ensure full correction of deformity and good function
- Surgery when indicated can give good results
- Postoperative bracing and rehabilitation has a vital role.

KEY POINTS

- ☞ Clubfeet vary in severity and presentation
- ☞ Early conservative treatment in the form of serial Ponseti casts is highly successful
- ☞ Recurrences are amenable to successful treatment too
- ☞ Neglected or resistant feet over the age of 1 or 2 years may be treated with surgery.

SUGGESTED READINGS

1. Cooper DM, Dietz FR. Treatment of idiopathic clubfoot. A thirty-year follow-up note. J Bone Joint Surg Am. 1995;77(10):1477-89.
2. Kite JH. The Clubfoot. New York, NY, USA: Grune & Stratton; 1964.
3. Laaveg SJ, Ponseti IV. Long-term results of treatment of congenital club foot. J Bone Joint Surg Am. 1980;62(1):23-31.
4. Morcuende JA, Weinstein SL, Dietz FR, Ponseti IV. Plaster cast treatment of clubfoot: the Ponseti method of manipulation and casting. J Pediatr Orthop B. 1994;B(3):161-7.
5. Ponseti IV. Congenital Clubfoot. Fundamentals of Treatment. Oxford, United Kingdom: Oxford University Press; 1996.
6. Turco VJ. Surgical correction of the resistant club foot. One-stage posteromedial release with internal fixation: a preliminary report. J Bone Joint Surg Am. 1971;53(3):477-97.
7. Warrier SS, Joshi BB. Use of external fixators for virgin and neglected club feet. Speaker Hand Out POSI. 2000. pp. 83-88.

CHAPTER 156

Developmental Dysplasia of the Hip

Jayanth S Sampath, Rujuta Mehta

SPECTRUM OF DEVELOPMENTAL DYSPLASIA OF THE HIP

Developmental dysplasia of the hip (DDH) is a term used to describe a spectrum of conditions where the hip joint fails to develop normally during childhood. In the past, descriptions such as congenital dislocation of the hip were used. The term hip dysplasia is also commonly used. All of the above terms refer to the same condition.

INCIDENCE OF DEVELOPMENTAL DYSPLASIA OF THE HIP

The widely quoted figure of 1–2 cases of dislocation per 1,000 live births is an approximation. The reported incidence of DDH in the literature is influenced by genetic and racial factors, cultural practices (tight swaddling of neonates amongst Native Americans), experience and training of the examiner, diagnostic criteria applied and age of the child at presentation. The incidence of neonatal hip instability may be as high as 1 in 100. Since the vast majority of unstable hips in neonates resolve spontaneously, this is termed physiological instability.

Clinical Pearl

A significant number of clinically unstable hips (Barlow positive) resolve spontaneously in the first few weeks of life. This is termed physiological instability. Hip ultrasound scan is mandatory in such cases.

CAUSES AND RISK FACTORS

Teratologic dislocations are caused by neuromuscular conditions such as arthrogryposis multiplex congenita, spina bifida, Larsen syndrome, and diastrophic dysplasia. A specific cause may not be readily identifiable in typical dislocations. A positive family history in first-degree relatives increases the risk of DDH. Wynne Davies reported a risk of 6% with 1 affected sibling, 12% risk with an affected parent, and 36% when a parent and a sibling are affected. Other risk factors for DDH, relative risk, and the presumed pathogenetic mechanisms are summarized in table 1.

TABLE 1: Risk factors for developmental dysplasia of the hip, relative risk, and the presumed pathogenetic mechanisms

Risk factor	Relative risk	Mechanism
Breech presentation*	5–6 times (greater risk if Frank breech with hip flexion and knee extension)	Intrauterine compression, though preterm breech babies also at risk
"Clicky" hips at birth	8 times compared to normal hip examination at birth	—
Birth order	>50% of developmental dysplasia of the hip in first born	Tight uterus
Girls	3–6 times greater than boys	Greater susceptibility in girl babies to the maternal hormone; relaxin causes ligamentous laxity
Side affected	Left:right ratio of 3:1	Left occipitoanterior position causes the left hip to rest against the mother's spinal column
Oligohydramnios	Higher risk if clinically significant, low risk if diagnosis made on sonography	Intrauterine compression
Postural foot deformity	Risk varies from 1 in 27 for postural talipes to 1 in 5 for calcaneovalgus feet	Extraneous compression of the hip on the affected side

*Successful external cephalic version for breech presentation reduces, but does not abolish developmental dysplasia of the hip risk. Ultrasound screening of the hips for babies in this category is recommended.

DIAGNOSING DEVELOPMENTAL DYSPLASIA OF THE HIP

Clinical Examination

There are no pathognomonic physical findings in DDH which will help the clinician make a reliable diagnosis at any age and in every child. Considerable skill, experience, and patience are therefore essential if an accurate diagnosis is to be made. The clinical features suggestive of DDH change as the child becomes older. An age-specific approach, therefore, needs to be adopted when examining the child with suspected DDH.

At or soon after birth (first few weeks of life), Barlow and Ortolani tests are provocative maneuvers with high specificity for DDH. They should be performed in every child at or soon after birth. Barlow test detects an enlocated hip which dislocates from the acetabulum, whereas the Ortolani is a "relocation" test which diagnoses a dislocated hip as it reduces back into the acetabulum. Other clinical signs which are associated with DDH include asymmetrical groin creases (Fig. 1), a positive Galeazzi test (Fig. 2) and limb length discrepancy. Reduced hip abduction (<60°) is a sensitive clinical indicator of DDH in children over the age of 3 months.

Developmental dysplasia of the hip should be borne in mind when examining a child with a limp or waddling gait. An important principle in the diagnosis of DDH is to detect asymmetry in the limbs (length, range of movement, etc.). However, it is worth remembering that bilateral DDH is frequently missed due to lack of asymmetry. Table 2 summarizes the clinical features of DDH at different ages.

Clinical Pearl

All newborns, irrespective of risk factors, should undergo a careful examination of the hip by a pediatrician at or soon after birth. Barlow and Ortolani tests should be performed and the results clearly documented.

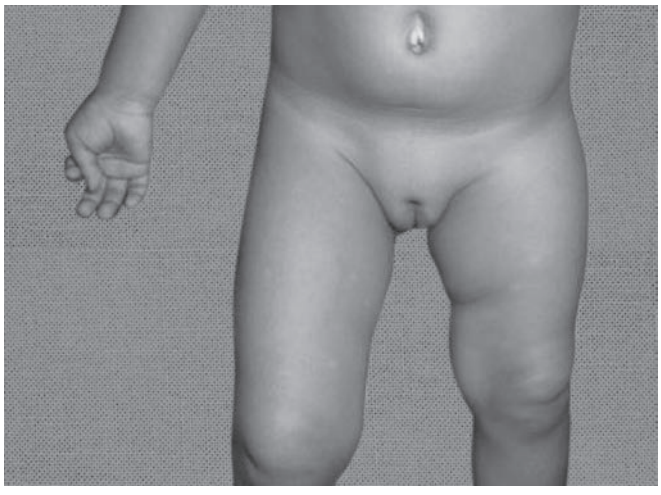


Fig. 1: Asymmetric groin creases

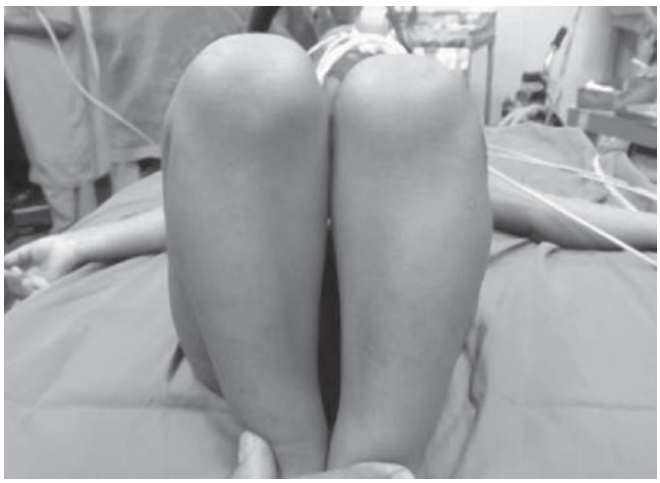


Fig. 2: A positive Galeazzi test

TABLE 2: Clinical features of developmental dysplasia of the hip at different ages

Age	Signs and symptoms of DDH
0–3 months	• Barlow and Ortolani test
3–12 months	• Reduced hip abduction • Leg-length discrepancy • Galeazzi test • Asymmetrical groin crease • Barlow/Ortolani tests may become negative by age 3 months
12 months and above	• Leg-length discrepancy • Painless limp • Waddling gait (bilateral DDH)

DDH, developmental dysplasia of the hip.

Investigations

Though clinical tests for DDH have high specificity (>90%), they lack sensitivity particularly in neonates and infants (around 60% only). By no means does a normal clinical examination rule out DDH. The clinician should, therefore, select an investigation which will conclusively confirm or rule out DDH. The choice of test again depends on the age of the child.

Children 0–4 months of age: ultrasound scanning of the hips using the Graf (static) and Harcke (dynamic) methods is recommended in children younger than 4 months.

In the Graf method, α and β angles are calculated and these angles guide treatment. The alpha angle is an indicator of the extent of development of the bony acetabulum (bony roof). The β angle is an indicator of development of the cartilaginous roof (Fig. 3).

The Graf method is precise and has been standardized to a high degree. Specific training in ultrasound scanning for hip dysplasia is necessary in order to obtain good quality ultrasound scans.

Ideally, all newborn babies should undergo a hip ultrasound scan. Though practiced in certain parts of Europe, Universal

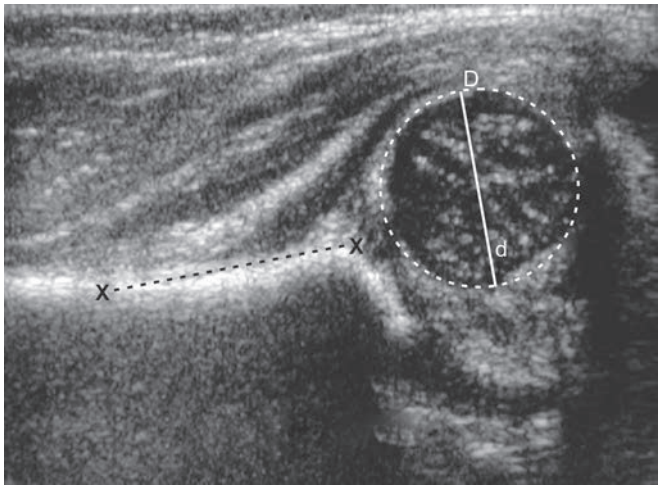


Fig. 3: Ultrasonography of subluxation of hip

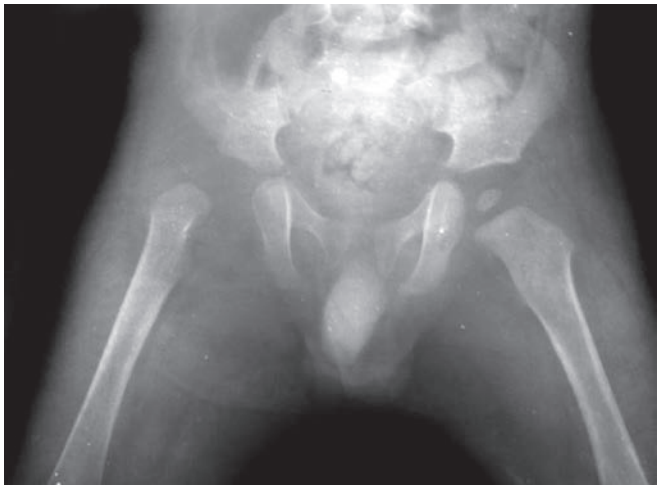


Fig. 4: An X-ray of developmental dysplasia of the hip

Neonatal Ultrasound Hip Screening cannot be justified due to cost, logistical hurdles and the relatively low incidence of abnormal hips requiring treatment. As mentioned earlier, many physiologically immature hips will resolve spontaneously by 6 weeks of age. Universal screening may result in overtreatment of immature hips and the possibility of iatrogenic complications such as avascular necrosis of the femoral head.

Selective ultrasound hip screening based on risk factors for DDH has been implemented more widely in the United Kingdom, United States, and other developed nations. Common indications and the timing of ultrasound screening are summarized in table 3.

Children older than 4 months: a good quality anteroposterior X-ray of the pelvis will clearly demonstrate the problem in the vast majority of cases. Various lines are drawn on the X-ray by orthopedic surgeons as illustrated but these are probably of little interest to pediatricians (Fig. 4).

Briefly, the Hilgenreiner's (horizontal) line and Perkin's (perpendicular) line result in four quadrants. The normal hip lies in the inner-lower quadrant.

TABLE 3: Common indications and the timing of ultrasound screening

Indication	Timing of ultrasound
• Positive Barlow-Ortolani tests • Clicky hip • Reduced hip abduction • Leg-length discrepancy	Immediate
• Breech • Oligohydramnios • Twins • Positive family history in first degree relatives • Postural foot deformity (e.g., calcaneovalgus foot) • Clubfoot (congenital talipes equino varus)	6–9 weeks postnatal (to avoid overtreatment of physiologically immature hips)

WHAT ARE THE TREATMENT OPTIONS?

Treatment of DDH is entirely dependent on the age of the child. The younger the child at diagnosis, the less the intervention required. It is, therefore, important that the diagnosis is made as soon after birth as possible.

Figure 5 summarizes the treatment options for DDH at different ages. Note that the treatment becomes progressively more invasive with increasing age at treatment.

Pavlik Harness

This is the least invasive method and, therefore, the most patient friendly. The harness can be used from birth to the age of approximately 4 months. The baby can kick both legs freely within the harness and it does not interfere with normal growth of the baby (Fig. 6).

Once the baby has been placed in a harness, ultrasound scans must be repeated every week until the hip is anatomically located back in the hip joint. This may take 2–4 weeks. Average time in the harness is likely to be between 10 weeks and

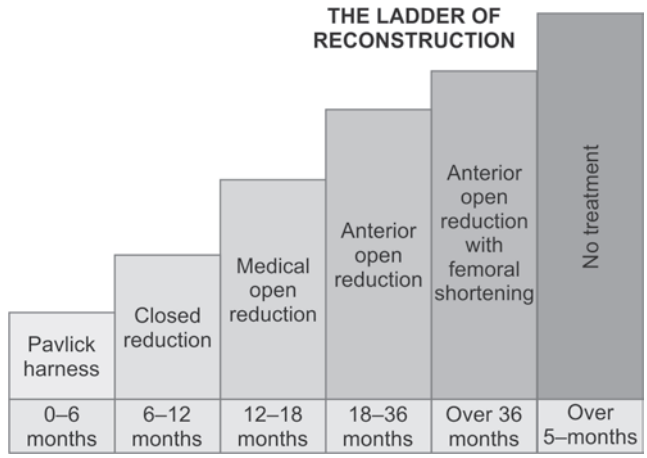


Fig. 5: Treatment options for developmental dysplasia of the hip at different ages

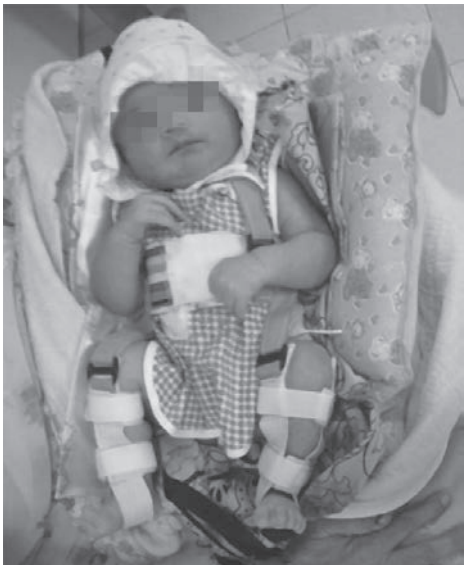


Fig. 6: Baby with Pavlik harness

12 weeks. In the vast majority of babies under 3 months (90% or more), treatment with the Pavlik harness is successful and results in radiographically normal hips when assessed at 5 years of age.

Clinical Pearl

In summary, early diagnosis (soon after birth) and Pavlik harness treatment should be considered as the gold standard in managing hip dysplasia.

Complications of Pavlik harness include avascular necrosis of the femoral head and transient femoral nerve palsy. These can be minimized through proper attention to technique during harness application.

Closed Reduction and Hip Spica Application

If the child is older than 6 months at diagnosis, Pavlik harness is not appropriate. In this group (6–12 months), an arthrogram will be necessary. A short general anesthetic is given. A radiopaque dye is also instilled into the hip joint to provide contrast. If the hip can be reduced without undue force, a hip spica is applied. The term closed reduction refers to reducing a dislocated joint without the need for an incision. This is in contrast to an open reduction where an incision is necessary. The total period in the spica ranges from 2 months to 6 months.

In a dislocated hip, concomitant acetabular dysplasia (shallow acetabulum) is almost always present. Children less than 18 months of age possess considerable remodeling capacity and early reduction of the hip typically results in spontaneous resolution of the acetabular dysplasia. In children older than 18 months at presentation, an additional procedure in the form of a pelvic osteotomy is usually required.

Medial Open Reduction

This is a minimally invasive procedure undertaken in children under 18 months of age. There are numerous advantages with this procedure compared to a traditional "anterior open reduction". The operation is performed through a small incision in the groin and, therefore, not visible to the outside. There is minimal blood loss and less postoperative pain.

The medial open reduction is also referred to as "assisted closed reduction" or "relaxed closed reduction". This term is used because a forcible closed reduction causes damage to the blood supply of the femoral head and poor long-term results.

Medial open reduction is followed by immobilization in a hip spica cast for 4–6 months. Long-term results of medial open reduction have proven that this is a minimally invasive procedure that is safe and effective.

Anterior Open Reduction with Femoral and Pelvic Osteotomy

This procedure is typically used in children older than 18 months who have been walking for a period of time on the dislocated hip. When a child walks on a dislocated hip, the capsule enlarges and becomes quite lax. This enlarged capsule needs to be tightened up in order to prevent the hip from re-dislocating after surgery. The anterior open reduction procedure is designed to address this particular problem of a capacious and redundant capsule. The anterior open reduction is performed through a "bikini" incision. There are several tight structures (muscles, tendons, and ligaments) that are divided or lengthened. The hip joint is relocated and the capsule repaired to keep the joint in place. Typically, the shallow socket (acetabulum) is also corrected by means of a pelvic osteotomy wherein the socket is divided and reset in the correct alignment. In addition to the pelvic osteotomy, a femoral osteotomy is also sometimes required.

Neglected Developmental Dysplasia of the Hip in the Older Child (Figure 7)

Unilateral neglected DDH can be treated safely up to the age of 8 years. The upper limit of age for treatment of bilateral

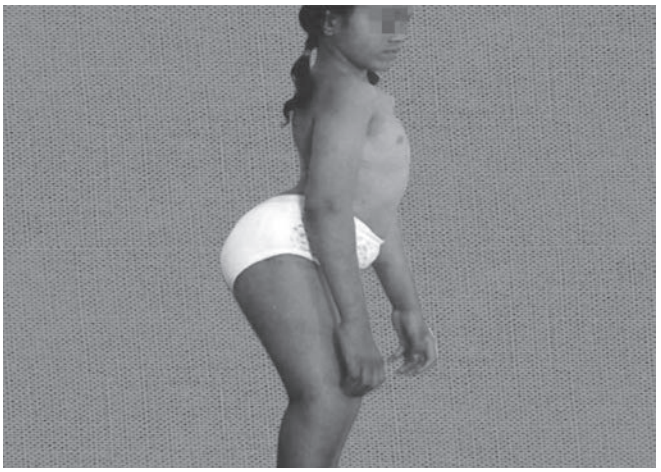
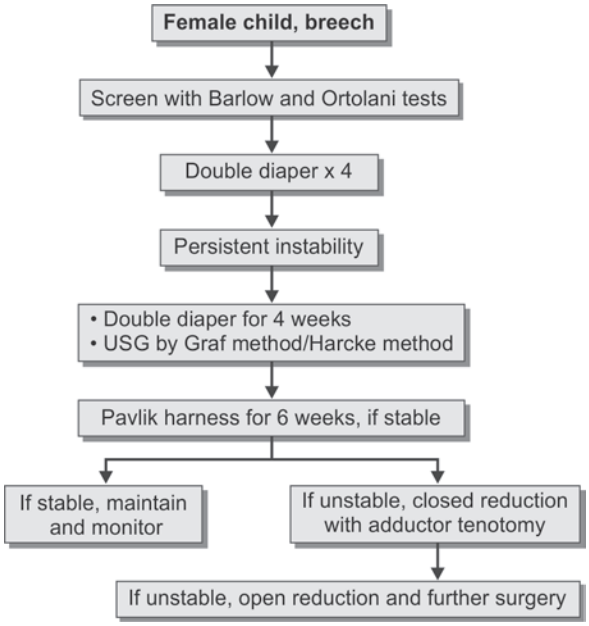


Fig. 7: Hyperlordosis

ALGORITHM 1

Management of developmental dysplasia of the hip



neglected DDH is approximately 5 years. In children older than these age thresholds, there is unacceptably high incidence of iatrogenic complications which compromises the eventual outcome.

Clinical Pearl

The key to successful management of developmental dysplasia of the hip is to identify risk factors for DDH in the newborn, confirm the diagnosis by hip ultrasound scan and institute early appropriate treatment.

KEY POINTS

- ☞ Prewalking dysplasia of the hip (DDH) treatment is more successful than postwalking. A painless unilateral limp or a bilateral waddle in a child must always be investigated for DDH
- ☞ Surgical treatment is indicated postwalking and can have a successful outcome
- ☞ Various options are available for the neglected DDH, surgically
- ☞ All varieties of DDH should be treated to eliminate the lurch and prevent secondary osteoarthritis, and problems with the lumbar spine which may occur if left untreated
- ☞ First screening for developmental DDH clinical in neonatal intensive care unit, Barlow's and Ortolani test
- ☞ Hips with persistent instability at 1 month need to be treated.

SUGGESTED READINGS

1. Barlow TG. Early diagnosis and treatment of congenital dislocation of the hip. J Bone Joint Surg. 1962;44-B(2):292-301.
2. Dunn PM. The anatomy and pathology of congenital dislocation of the hip. Clin Orthop Relat Res. 1976;(119):23-7.
3. Gage JR, Winter RB. Avascular necrosis of the capital femoral epiphysis as a complication of closed reduction of congenital dislocation of the hip. A critical review of twenty years' experience at Gillette Children's Hospital. J Bone Joint Surg Am. 1972;54(2):373-88.
4. Graf R. Classification of hip joint dysplasia by means of sonography. Arch Orthop Trauma Surg. 1984;102(4):248-55.
6. Harcke HT, Kumar SJ. The role of ultrasound in the diagnosis and management of congenital dislocation and dysplasia of the hip. J Bone Joint Surg Am. 1991;73(4):622-8.
7. Klisic PJ. Congenital dislocation of the hip--a misleading term: brief report. J Bone Joint Surg Br. 1989;71(1):136.
8. Laurenson R. The acetabular index: a critical review. J Bone Joint Surg. 19589;41-B:702.
9. Mubarak S, Garfin S, Vance R, McKinnon B, Sutherland D. Pitfalls in the use of the Pavlik harness for treatment of congenital dysplasia, subluxation, and dislocation of the hip. J Bone Joint Surg Am. 1981;63(8):1239-48.
10. Ortolani M. Congenital hip dysplasia in the light of early and very early diagnosis. Clin Orthop Relat Res. 1976;(119):6-10.
11. Severin E. Contribution to the knowledge of congenital dislocation of the hip joint: late results of closed reduction and arthrographic studies of recent cases. Acta Chir Scand. 1941;84(Suppl 63):1-142.
12. Strayer LM. Embryology of the human hip joint. Clin Orthop Relat Res. 1971;74:221-40.
13. Suzuki S, Yamamuro T. Correlation of fetal posture and congenital dislocation of the hip. Acta Orthop Scand. 1986;57(1):81-4.
14. Wenger DR. Congenital hip dislocation: techniques for primary open reduction including femoral shortening. Instr Course Lect. 1989;38:343-54.

Index

Page numbers followed by *f* refer to figure and *t* refer to table.

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z