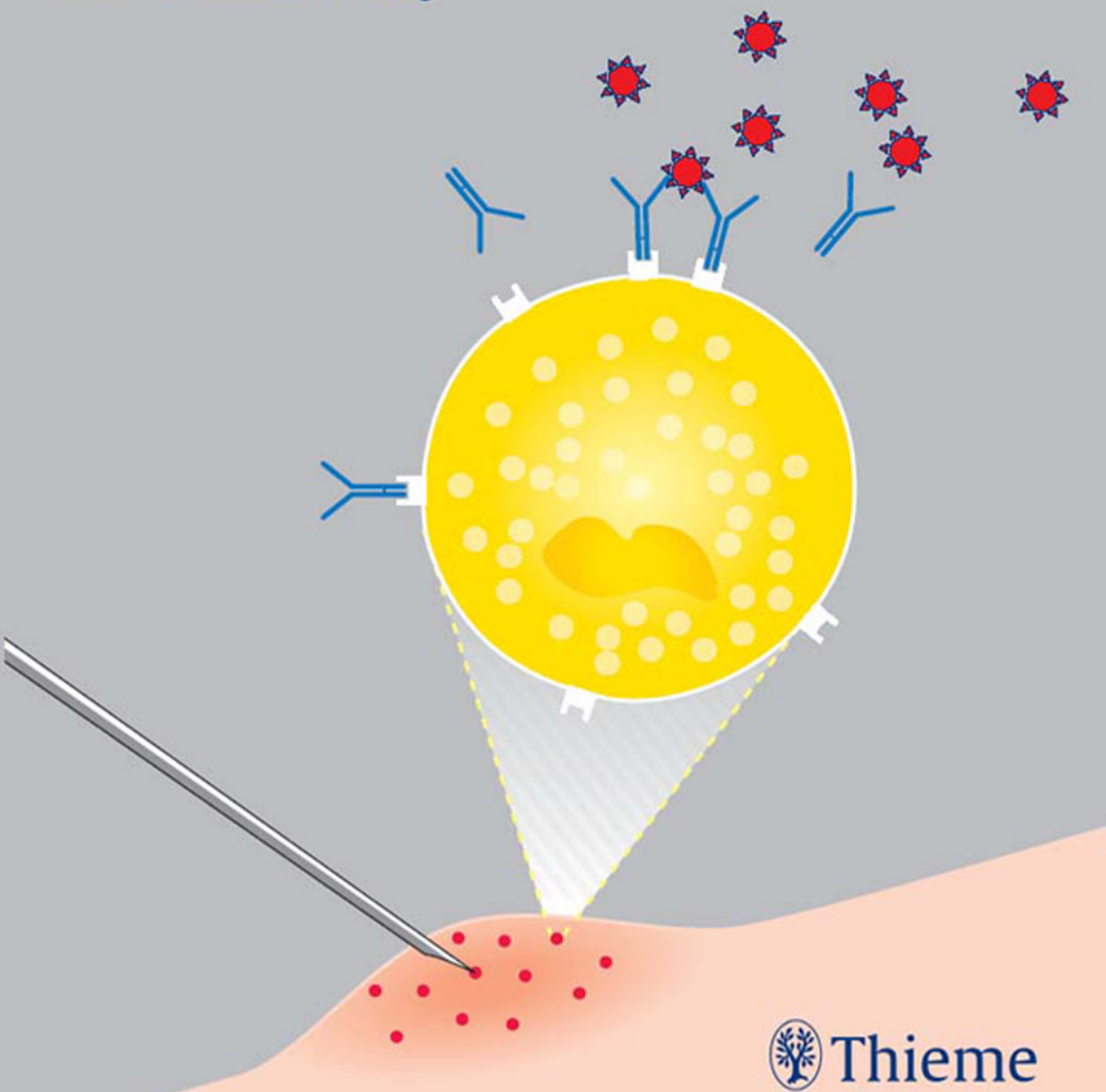
Quantitative Skin Testing for Allergy

IDT and MQT

Bradley F. Marple
Richard L. Mabry



Thieme

Quantitative Skin Testing for Allergy

IDT and MQT

Second Edition

Quantitative Skin Testing for Allergy

IDT and MQT

Second Edition

Bradley F. Marple, M.D.
Professor and Vice Chairman
Department of Otolaryngology–Head and Neck Surgery
T.C. Lupton Family Professorship in Patient Care
in honor of Dr. John Dowling McConnell and
Dr. David Andrew Pistenmaa
University of Texas Southwestern
Medical Center
Dallas, Texas

Richard L. Mabry, M.D., F.A.A.O.A., Sc.F.A.C.A.A.I.
Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
University of Texas Medical Branch
Galveston, Texas
University of Texas Health Science Center
San Antonio, Texas

Thieme Medical Publishers
New York • Stuttgart

Thieme Medical Publishers, Inc.
333 Seventh Ave.
New York, NY 10001

Consulting Editor: Esther Gumpert
Associate Editor: Owen Zurhellen
Vice President, Production and Electronic Publishing: Anne T. Vinnicombe
Production Editor: Becky Dille
Associate Marketing Manager: Verena Diem
Sales Director: Ross Lumpkin
Chief Financial Officer: Peter van Woerden
President: Brian D. Scanlan
Compositor: Techset Composition Ltd.
Printer: Maple-Vail Book Manufacturing Group

Library of Congress Cataloging-in-Publication Data

Quantitative skin testing for allergy: IDT and MQT/[edited by] Bradley
Franklin Marple, Richard L. Mabry.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-58890-430-0 (TMP : alk. paper)
ISBN-10: 1-58890-430-X (TMP : alk. paper)
ISBN-13: 978-3-13-142251-4 (GTV : alk. paper)
ISBN-10: 3-13-142251-3 (GTV : alk. paper)
1. Skin tests. 2. Allergy–Diagnosis. I. Marple, Bradley F. II. Mabry, Richard L.
[DNLM: 1. Skin Tests–methods. 2. Hypersensitivity. 3. Intradermal Tests–methods. QY 260 Q1 2006]
RC587.S6Q36 2006
616.97'075--dc22 2006010063

Important note: Medical knowledge is ever-changing. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may be required. The authors and editors of the material herein have consulted sources believed to be reliable in their efforts to provide information that is complete and in accord with the standards accepted at the time of publication. However, in view of the possibility of human error by the authors, editors, or publisher of the work herein or changes in medical knowledge, neither the authors, editors, nor publisher, nor any other party who has been involved in the preparation of this work, warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from use of such information. Readers are encouraged to confirm the information contained herein with other sources. For example, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this publication is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Some of the product names, patents, and registered designs referred to in this book are in fact registered trademarks or proprietary names even though specific reference to this fact is not always made in the text. Therefore, the appearance of a name without designation as proprietary is not to be construed as a representation by the publisher that it is in the public domain.

Printed in the United States of America

5 4 3 2 1

TMP ISBN 1-58890-430-X
TMP ISBN 978-1-58890-430-0
GTV ISBN 3 13 142251 3
GTV ISSN 978 3 13 142251 4

To my dear wife and family
B.F.M.

I dedicate this work to my late wife Cynthia, and to my
“second blessing,” my wife Kay
R.L.M.

Contents

Preface

Over a decade ago, the monograph *Skin Endpoint Titration* first appeared in print. It was meant to be a user-friendly tool that would enable physicians, nurses, and allergy assistants to incorporate quantitative allergy skin testing into their practice. The success of this monograph was attributable to its simple and straightforward explanation of a standardized approach to quantitative testing. As with any enduring document, however, its utility had become challenged by the evolution of our knowledge base and its impact on the practice of medicine.

Over the course of the past decade, several forces have come to bear on the role that allergy plays in the practice of otolaryngology. Demographic and practice analyses performed by the American Academy of Otolaryngology – Head and Neck Surgery support a long history of epidemiologic data strongly suggesting that allergy impacts virtually all aspects of otolaryngology (indeed any specialty that deals with diseases of the upper and lower respiratory tract). As such, the addition of allergy to one's practice appears to add value to patient care, enabling patients to receive more comprehensive care. The epidemiologic data have been the basis for recent national educational and practice certification changes mandating that allergy be included in the education of residents and fundamental to the practice of otolaryngology. This inclusion, in turn, has served to drive renewed interest in allergy in academia, which is necessary for increased research in the field. The end result is that the past ten years have set the stage for a renaissance in our understanding of skin testing methodology and have opened the door to the emergence of novel techniques.

This book, like its predecessor, is designed to be user-friendly and practical and is fundamentally based in the principles of evidence-based medicine. By the very nature of the project, it is our intent to introduce new approaches to skin testing while revisiting traditional techniques to enable contrast and comparison. The reader is encouraged to consult the references at the end of each chapter for further information and to augment the information contained herein by attendance at courses that provide more detailed information coupled with hands-on experience. The editors and contributors will be the first to say that this text will not

allow the untrained individual to practice quantitative skin testing for allergy. It is a tool, a practical resource for those who choose to employ quantitative skin testing for making the diagnosis of allergy. If you keep it handy, use it often, dog-ear the pages, and get them dirty, it will be serving the purpose for which it was created.

Acknowledgments

The two editors sincerely appreciate the work of each of the chapter contributors, who took time from exceptionally busy schedules to share their expertise and experience. Further, we want to express our gratitude to our teachers and mentors, a group too numerous to mention: you know who you are. And finally, we would like to acknowledge the profound influence of a very special person in the field of otolaryngic allergy. Cynthia Mabry, B.S., R.N., C.O.R.L.N., was not only a treasured friend to one of us and a devoted wife to the other, but also a dedicated teacher who taught allergy to countless residents, practitioners, nurses, and allergy assistants, making a complex subject more understandable and practical. She is, and will continue to be, sorely missed.

Contributors

Edwyn L. Boyd, M.D.
Hoover Ear, Nose, and Throat Associates
Hoover, Alabama

Stephen J. Chadwick, M.D., F.A.C.S.
Clinical Associate Professor
Department of Otolaryngology
Southern Illinois School of Medicine
ENTA Allergy, Head and Neck Institute
Decatur, Illinois

M. Jennifer Derebery, M.D., F.A.A.O.A.
House Ear Institute
Los Angeles, California

Bruce R. Gordon, M.D., F.A.C.S., F.A.A.O.A.
Clinical Instructor
Department of Otology and Laryngology
Harvard University
Cambridge, Massachusetts

Richard C. Haydon, III, M.D.
Professor of Surgery
University of Kentucky
Lexington, Kentucky

John H. Krouse, M.D., Ph.D.
Professor and Vice-Chair
Department of Otolaryngology–Head and Neck Surgery
Wayne State University
Detroit, Michigan

Bryan D. Leatherman, M.D., F.A.A.O.A.
Adjunct Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Coastal Ear, Nose and Throat
Gulfport, Mississippi

Richard L. Mabry, M.D., F.A.A.O.A., Sc.F.A.C.A.A.I.
Clinical Professor
Department of Otolaryngology–Head and Neck Surgery
University of Texas Southwestern Medical Center
Dallas, Texas
University of Texas Medical Branch
Galveston, Texas
University of Texas Health Science Center
San Antonio, Texas

Bradley F. Marple, M.D.
Professor and Vice Chairman
Department of Otolaryngology–
Head and Neck Surgery
T.C. Lupton Family Professorship
in Patient Care in honor of
Dr. John Dowling McConnell and
Dr. David Andrew Pistenmaa
University of Texas Southwestern
Medical Center
Dallas, Texas

1

The Evolution of Skin Testing in Otolaryngic Allergy

Richard L. Mabry

Until the 1930s, it was virtually unheard of for otolaryngologists to test and treat patients for allergy, and those who did do testing utilized the same types of tests employed by general allergists: scratch tests, prick tests, or single dilution intradermal tests. Early efforts at skin testing begin with Blackley,[1] who described a primitive form of scratch test in 1873. Intradermal skin tests were performed by Cooke[2] in 1915. Prick testing dates to the work of Lewis and Grant[3] in 1926. Scratch tests have since been abandoned as inaccurate and unsafe,[4] but prick testing and intradermal skin testing remain in use to the present time.

Almost from the inception of skin testing, some clinicians sought to increase the safety and accuracy of the tests by adding a degree of quantitation to them. In 1911 Leonard Noon[5] attempted to roughly quantitate the responses to both scratch testing and conjunctival challenge tests. Intradermal and prick testing were semiquantitatively scored by grading systems based on the size of the wheal and flare they produced.

In 1963 Rinkel,[6] influenced by the earlier work of Hansel,[7] introduced a concept that was to become the hallmark of skin testing by otolaryngic allergists for decades to come. Using fivefold dilutions of antigens, and starting with an anticipated nonreacting concentration, Rinkel raised intradermal wheals with progressively higher antigen strengths until he found the concentration that first caused a positive wheal. He called this concentration the "endpoint of titration," and postulated that it

represented the strongest concentration of antigen at which immunotherapy could be safely begun. He proved the efficacy of this method in his own clinical experience, and with few modifications, this concept of skin endpoint titration (SET) has remained the benchmark methodology of allergy testing by otolaryngologists since Rinkel introduced it.

Allergists, on the other hand, have traditionally utilized prick testing as their major skin test methodology. Since prick testing introduces much less antigen than single dilution intradermal testing, it is the safer of those two methodologies. However, the argument can be made that if prick testing alone is used, patients with low degrees of sensitivity will be missed.[8] Although some allergists perform single dilution intradermal testing to follow up negative prick tests, many do not. It is this philosophical difference that separates the general allergist from the otolaryngic allergist.

Because of confusion about some of the low-dose immunotherapy espoused by Hansel and immunotherapy beginning at the endpoint concentration as recommended by Rinkel, the term *skin endpoint titration* came to have a pejorative connotation.[9] In January 2003 the board of directors of the American Academy of Otolaryngic Allergy endorsed the terminology change introduced with the 2003 American Medical Association (AMA) manual *Current Procedural Terminology 2003*,[10] wherein the broad practice of sequential intradermal testing is known as intradermal dilutional testing (IDT). The term IDT encompasses not only the basic methodology of SET, but also the more recent refinements designed to make testing more efficient and cost-effective.

Under pressure by third-party payers who required that screening prick testing must precede intradermal testing (i.e., the methodology employed by most general allergists), many otolaryngic allergists began to employ a blend of prick testing and intradermal dilutional testing. These methods will be discussed in detail in this book, and have also been described elsewhere.[11]

No matter whether the otolaryngic allergist chooses to depend entirely on IDT (in either its most complete form or an optimized version) or combine it with prick testing, it is important that the clinician performing allergy testing have a full understanding of all the methods available, their limitations and advantages, and the potential dangers involved in administering allergy skin tests and/or injections. With appropriate training and attention to detail, it is possible to safely and effectively treat the vast majority of allergic patients who present to the otolaryngologist.

References

1. Blackley CH. Experimental Researches on the Causes and Nature of Catarrhus aestivus (hay fever of asthma) London: Balliere, Tindale & Cox, 1873
2. Cooke RA. The treatment of hay fever by active immunization. Laryngoscope 1915;25:108–112
3. Lewis T, Grant RT. Vascular reactions of the skin to injury. Heart 1926;13: 219–225
4. Council on Scientific Affairs (AMA). In vivo diagnostic testing and immunotherapy for allergy. JAMA 1987; 258:1363–1367
5. Noon L. Prophylactic inoculation for hay fever. Lancet 1911;1:1572
6. Rinkel HJ. The management of clinical allergy: part II: etiologic factors and skin titration. Arch Otolaryngol 1963; 77:42–75
7. Hansel FK. Coseasonal intracutanous treatment of hay fever. J Allergy 1941;12:457
8. Gordon BR. Allergy skin tests for inhalants and foods. Comparison of methods in common use. Otolaryngol Clin North Am 1998;31:35–53
9. Van Metre TE, Adkinson NF, Lichtenstein LM, et al. A controlled study of the effectiveness of the Rinkel method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;65:288–297
10. American Medical Association. Current Procedural Terminology 2003. Chicago: American Medical Association, 2003
11. Krouse JH, Mabry RL. Skin testing for inhalant allergy 2003: current strategies. Otolaryngol Head Neck Surg 2003;129:S33–S49

2

Preparing the Office for Skin Testing

Bryan D. Leatherman

Preparing an office to perform skin testing utilizing the intradermal dilutional testing (IDT) and modified quantitative testing (MQT) techniques requires time, training, personnel, space, equipment, and supplies. For most physicians, skin testing is added to an existing practice and office space. Because offices and practices vary, there are no hard-and-fast rules that apply to this preparation. Some basic information can help make the setup process more efficient and successful. If a current staff member is going to be designated as the allergy assistant, getting his or her input into preparing the allergy area and designing the layout may facilitate smoother and more efficient daily procedures. This is especially true if the staff member has previous allergy practice experience. In general, preparing an office for the incorporation of allergy requires the proper personnel, space, and equipment. This chapter provides practical information and advice to help the physician with this process.[1]

◆ Physician Education

Like most other endeavors in medical practice, proper education is the first step in achieving optimal results. A physician needs a good understanding of the day-to-day processes involved in providing allergy services. Many resources are available to the physician to obtain the proper training.

Many nationally accredited organizations, such as the American Academy of Otolaryngic Allergy (AAOA), offer allergy courses. The AAOA provides basic and advanced allergy courses each year. The basic allergy course provides a fundamental curriculum that includes in-depth and hands-on training in the processes involved in allergy skin testing and immunotherapy administration. The knowledge provided should give practical insight into the space and equipment needs. Attendance at other AAOA venues, such as the advanced course and annual meeting instructional courses, can provide further insight into some of the more intricate nuances of optimal allergy care. A variety of allergy supply companies are willing to offer advice on the physical space and equipment needed to start the allergy practice. Visiting an office with an existing, vibrant allergy practice can also be very useful. Utilizing these educational resources can be quite valuable in the initial setup and ultimate long-term success of the allergy practice.

◆ Space

Establishing an allergy section in an existing office does not require a tremendous amount of extra space. Ideally, the space should be separate from the general office space. A separate waiting area for allergy patients is preferred. This separation allows for a more efficient flow of allergy patients who come often for allergy treatment. Of equal or greater importance, such separation can help protect the physician handling routine patient flow from frequent interruptions by allergy patients wishing to ask questions or just talk **(Fig. 2–1)**.

An average examination room should provide adequate space for testing and treatment needs. Additional space can be allocated as the allergy practice grows. The room should provide sufficient counter space to hold the supplies used during testing and treatment. Cabinet space is necessary to hold extra supplies, some of which are purchased in bulk. Most offices require a refrigerator, which may be conveniently placed in the allergy area **(Fig. 2–2)**. The allergy room should contain a place where a patient can lie down in the event of a vagal or true anaphylactic reaction. This can be accomplished with a reclining chair, an exam table, or a folding cot. The allergy assistant should be able to close off the room to provide a quiet environment, completely free from interruption during testing and treatment vial preparation. This is an important measure to help prevent potentially harmful errors during vial mixing. It is helpful to have a “Do Not Disturb” sign that can be hung on the door during vial mixing time.

Fig. 2–1 If space allows, a separate waiting area for allergy patients improves patient flow and allows easier monitoring after injections.

Fig. 2–2 Not much space is needed for an allergy workroom. This vial mixing room is also sufficient for testing one patient at a time if necessary.

Testing of multiple patients can be accomplished in an open room, possibly with curtains or dividers. This allows the allergy assistant to test and monitor several patients at once. With the new HIPPA privacy concerns, some physicians prefer either testing one patient at a time, or using individual rooms for each patient being tested.

◆ Personnel

Selection of an allergy assistant is probably the most important decision when preparing an office for allergy practice. This person will have the most interaction with the allergy patients and is in a key position to collect information about the ongoing progress, new areas of concern, and potential weaknesses in the treatment plan. A good assistant will be able to obtain this valuable insight and provide the physician with the information necessary to effectively direct the treatment program for each patient.

The allergy assistant may sometimes be recruited from existing office staff. This can be beneficial because the person's personality and abilities will already be known. More often, the allergy assistant will be newly hired. The assistant does not necessarily need a nursing background. Some physicians prefer to employ those with other educational backgrounds, such as medical assistants or technicians, for this task. Whatever the educational background, several personality traits are important for the assistant to optimally fulfill the important role of this position. The allergy assistant (1) should enjoy frequent patient interaction; (2) should be inquisitive by nature, as gathering ongoing information from the patient is an important part of the job; (3) should like working with some autonomy, yet understand the role of the physician in directing the overall treatment plan; and (4) should be enthusiastic about the challenge of learning, developing, and maintaining the skills needed for this position.

Once an assistant is selected, the physician must be committed to the time and expense of giving this person proper training. A lot of the training will be provided on the job from the physician, but formal training is valuable to provide the greater depth of knowledge required for the daily performance and autonomy expected of the assistant. Many opportunities exist for formal training. The AAOA basic course is an excellent resource for providing education for the new allergy assistant. It is particularly beneficial for the physician and assistant to attend the course together. This helps ensure that both the physician and the assistant are familiar with the same information and techniques. Then

they can more effectively work together to apply this information to their practice. Continuing education can also be obtained through reading books, monographs, and articles in peer-reviewed allergy literature. Strong consideration should be given to training a second person in the office to perform at least the essential functions of the allergy assistant. This will help avoid disruption of the allergy practice when the primary assistant is absent.

Visiting an office with a busy, established allergy practice is a worthwhile final step in the training process. The physician and the assistant can gain practical insight into how the vast amount of material presented in the courses can be incorporated into a successful allergy program.

◆ Furniture Requirements

Very little extra furniture is required for the new allergy section. If a separate waiting area is available, only basic furnishings will be needed, including reading materials for entertainment. Allow a few extra chairs for family members. In the testing and treatment room, a chair is required for the patient. A standard exam chair can be used, but a smaller chair is usually preferable. It is also helpful if the patient chair is a little higher than that of the person performing the test. Some practices have found it helpful to use a comfortable bar stool as a patient chair. A standard secretary's chair, without arms, is a good choice for the person doing the testing and treatment. The testing room may also need to contain extra chairs for family members. Sufficient counter space is necessary to accommodate supplies used during the testing and treatment, as well as during vial mixing **(Fig. 2–3)**. If sufficient counter space is not available, a standard secretary's desk will provide adequate space. A file cabinet for storing forms and educational materials is also helpful. A refrigerator will be needed to store the allergen stock vials, testing and treatment vials **(Fig. 2–4)**. The largest size refrigerator your space will accommodate is recommended. Consider purchasing a unit with a freezer compartment to store serum for in vitro allergy testing, but avoid a self-defrosting freezer, which may result in thawing of samples during the defrost cycle.

◆ Supplies

Some specialized supplies are needed. It is usually more economical to purchase them in bulk, but don't buy too much in the beginning. The volume can be increased as the practice grows.

Fig. 2–3 Adequate counter space for vial mixing allows for better organization and helps prevent errors.

Fig. 2–4 A large refrigerator is a necessary component of the allergy workroom. Vial racks can be organized neatly for easy access.

Fig. 2–5 Vial labels should clearly identify the contents of the vial and date prepared. Using a typewriter takes a little more time, but makes the labels easier to read.

Glass vials with aluminum-protected rubber stoppers are necessary for testing set and treatment vial preparation. For IDT testing, 5-mL vials containing 4 mL of buffered saline diluent can be purchased to save time on measuring. Empty 5-mL vials will also be needed for treatment vial preparation. Some physicians use single-dose 1-mL bottles for treatment vials prepared for home injections. Each vial needs a label for proper identification of its contents **(Fig. 2–5)**.

Racks for holding the allergen vials are a necessity from the start. Multiple sizes are available. Enough rows should be available to accommodate all the allergens to be tested. This can be accomplished with one or multiple racks. For IDT testing, the racks should be at least six rows deep.

Disposable syringes used in the allergy practice come with the needle attached and are hubless to eliminate the dead space. This provides for a more accurate and reliable dose. The most practical size is a 1-mL syringe with a 26- or 27-gauge needle and a $\frac{3}{8}$- to $\frac{1}{2}$-inch needle length. For testing, needles with a shorter, intradermal bevel should be used for easier wheal formation. A regular beveled needle can be used for vial mixing and immunotherapy injections. Safety needles have become available in the last few years to help reduce accidental needle sticks. Many allergy

assistants have found these needles to be cumbersome and prefer not to use them. It is unclear to what extent the Occupational Safety and Health Administration (OSHA) requires the use of the safety needles. If your assistant prefers to use regular needles, it is prudent to at least have some safety needles available. The assistant should also sign a document acknowledging that the safety needles are available for use if desired. This document can be kept in the assistant's employment file as proof that the assistant has been given the option of using safety needles.

Many prick-testing devices are manufactured by various companies. Some are designed for a single antigen test, whereas others are capable of delivering multiple allergens to the skin at once. Use of the multiple-antigen devices is the most practical for ease of use and saving time during testing. It is advisable also to have single-prick devices available for repeat testing of an antigen or for adding an antigen that is not included in the typical testing panel.

Antigens need to be purchased for testing and treatment. Some antigens are available in standardized allergy units, whereas others are sold in variable concentrations. For each individual antigen, it is important to consistently purchase the same concentration, or make proper adjustments during mixing and testing vials if the stock concentration changes. Initially, order enough antigen to last a year. For most start-up practices, one stock vial for each antigen should be sufficient initially. The specific antigens ordered will depend on the practice's geographic location. Lists of common local allergens can be obtained from antigen supply companies, reference books, local universities, and from fellow allergists. A good reference source for the distribution of pollens in the United States and portions of Canada is the text by Lewis et al.[2] A practical guide to allergen selection can be found in the book *Allergy and Immunology: An Otolaryngic Approach*.[3]

Phenolated, buffered saline is the most common diluent used in vial preparation. It is bactericidal and virucidal. Normal saline and human serum albumin are also potential diluents, but are seldom used by otolaryngologists. Glycerine can be purchased in a 50% solution and functions as an antigen preservative. It is commonly added during preparation of the more dilute treatment vials.

Table 2–1 lists some additional supplies necessary to perform IDT, skin prick testing, and allergy injections. In addition to these supplies, appropriate emergency supplies must be readily available in case a severe systemic or anaphylactic reaction occurs in the office during testing or treatment. Each office staff member must also have adequate training in how to respond during an emergency. Treatment of emergencies is covered in more detail in Chapter 10.

Table 2–1 Supplies Necessary for Intradermal Dilutional Testing and Skin Prick Testing

Sterile bottles/vials
Syringes and needles for mixing and injections
Racks or trays for vial storage
Vial labels
Diluent
Antigens
Glycerin preservative
Skin markers
Measuring device
Cotton balls
Alcohol swabs
Timers
Sharps containers
Prick devices
Multiple- and/or single-prick devices
Multi-well trays for multiple-prick devices

Some patients, such as those with dermatographism, require in vitro allergy testing **(Fig. 2–6)**. When an office is just starting to provide allergy services, it is usually not practical to perform these in vitro tests in the office. It is more practical initially to outsource these tests to a testing company. Supplies will be needed for the collection and preparation of the blood specimen. Testing companies can supply information on how the blood sample should be processed in the office prior to submitting it for testing.

◆ Forms

A substantial amount of paperwork is necessary for administrative purposes, medical record keeping, and patient education. Pamphlets describing your approach to allergy evaluation and treatment are helpful for patients to read in the waiting room to begin the educational process that is important for optimal allergy care. It is also a good marketing tool to promote the availability of allergy services in your clinic. Also, a detailed allergy questionnaire can be filled out by the patient in advance, which saves a lot of time in history taking. Some allergy supply companies offer sample questionnaires, or you can develop your own **(Fig. 2–7)**. For those patients undergoing allergy testing and immunotherapy, it is helpful to provide a handout detailing your fees and what portion the

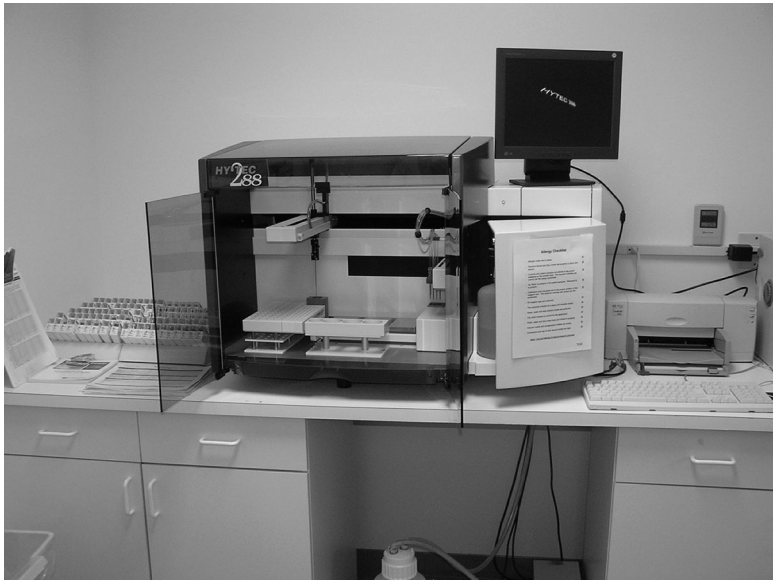


Fig. 2–6 In vitro testing can be performed in the allergy office. The equipment is compact but requires a large volume to justify the associated time and expense.

Fig. 2–7 An allergy questionnaire is provided to the patient to fill out prior to the initial allergy evaluation.

patient will have to pay out of pocket. A form should be provided (by mail or at a prior visit) describing medications to avoid prior to testing, and what type of clothing to wear during testing. The patient should also sign authorization forms that explain the benefits and potential risks of allergy testing and immunotherapy. Also, you will likely need to add several treatment codes to your charge sheet. There are multiple Current Procedural Terminology (CPT) codes related to allergy testing, vial mixing, and immunotherapy administration. These codes can be found in the CPT reference book.[4] The proper diagnostic codes must also be linked to the charges. Third-party payers have different policies regarding allergy. You must become familiar with these to receive proper reimbursement.

Patient education forms are an important part of successful allergy management. They can provide valuable information for the patients and save a lot of time for the physician and assistant. Forms should explain environmental controls, the general concept of allergy and its treatment, foods that cross-react with inhalants, and other topics appropriate to your patient population. Many educational forms are available commercially, and others can be created. Lists of stores that sell allergy-related materials (such as dust mite covers for bedding) are helpful. The more education in writing you can provide to a patient, the more likely the patient will comply with the treatment plan.

Several forms are needed for the medical record, such as allergy testing, vial mixing, and shot administration forms. Visiting a functioning allergy clinic can prove useful in helping develop these forms, and you can ask the clinic for sample forms to guide the creation of your own forms. If the same chart is used for general office visits and allergy records, it is helpful to have a separate section of the chart to keep allergy records. Because allergy patients usually have frequent office visits, some physicians store the charts of patients who are receiving allergy treatment in a separate area from other charts to allow easy access.

If allergy shots are going to be administered outside of your office, such as at home or another health care facility, detailed instructions must be provided to the patient in writing. The instructions should include information on when to give and not give shots, exact dosing instructions, and instructions on what to do in case of a reaction. Also include instructions on what to do if a shot has to be skipped or is missed. You should also provide forms for recording the shots and any reactions. Do not assume that another health care facility understands how to give injections. Always send very detailed instructions and encourage the facility to call your office with any questions.

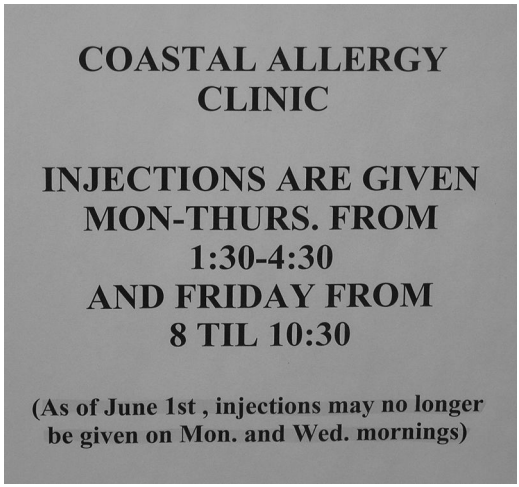


Fig. 2–8 Having the "shot hours" clearly posted in the office helps prevent the inconvenience of patients showing up for injections when the doctor is not present.

◆ Time

It is very important that the physician allocate enough time to manage an allergy practice, including time to review test results, direct the treatment plans, and answer patient and staff questions. As the allergy assistant becomes more experienced, he or she can answer more patient questions. The allergy assistant must allocate time to perform the important task of vial mixing. Before every injection, the assistant must take the time to ask about recent illnesses or problems with past injections.

Having scheduled times for testing and injections is important for properly managing the allergy office. Allergy testing and immunotherapy injections should only be given when the physician is in the office. "Shot hours" should be clearly posted in the waiting area to avoid confusion **(Fig. 2–8)**. Changes in the shot times should be made far enough in advance to allow patients to adjust their schedules.

◆ Conclusion

Preparing an office for providing allergy skin testing and immunotherapy requires some advanced planning. It is well worth taking time to carefully decide how to incorporate allergy patients into the physical flow of your office, to obtain the proper equipment and supplies, and to purchase or create good administrative and patient education forms. The time spent

on these aspects of office preparation will pay off richly as you begin to expand your allergy practice. Probably the most important aspect of preparing for an allergy practice is good education for the physician and assistants, both initially and on an ongoing basis. Keep in mind that as your practice grows, you will inevitably discover things that work and do not work well for your practice, so be willing to make changes as necessary. Patients will receive better allergy care and appreciate the efficiency with which it is provided.

References

1. King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2005
2. Lewis W, Vinay P, Zenger V. Airborne and Allergenic Pollen of North America. Baltimore: Johns Hopkins University Press, 1983
3. Krouse JH, Gordon BG, Parker MJ. Inhalant allergy. In: Krouse et al, eds. Allergy and Immunology: An Otolaryngic Approach. Philadelphia: Lippincott Williams & Wilkins, 2002:35–49
4. Current Procedural Terminology, standard edition. Chicago: American Medical Association Press, 2005:547

3

Antigen Choice for Skin Testing

Edwyn L. Boyd

The patient's history is the most useful diagnostic tool available for identifying suspected allergenic offenders. Antigen selection for both screening and completion of testing may be in part empiric, but it is also based on portions of the history that suggest specific triggers, both seasonal and perennial. Prior to selecting the type and number of antigens to be tested, it is important to consider the patient's age, occupation, living accommodations (including prior fire or water damage to the dwelling), pets, hobbies, and frequent travel to different geographic areas. Consequently, even though such a situation would be ideal, neither the screening panel nor a complete testing battery can be developed as a "one size fits all" tool because each patient has a different lifestyle with different allergen exposures.

Proper selection of antigens for allergy testing is critical to achieving a positive clinical outcome in patients receiving immunotherapy. Generally this process begins after the patient fails environmental avoidance and the proper use of pharmacotherapy. Avoidance of allergens, both known and suspected, is the basic tenet of allergy management, representing the treatment of choice. Unless the patient has only a few obvious specific triggers, however, avoidance may be difficult, if not impossible, to accomplish.

When the decision is made to perform allergy testing, the first step is the selection of an appropriate antigen panel for initial screening.

Screening batteries are very important and should be routinely employed because they provide the patient and practitioner with an economical, rapid, same-day "yes/no" answer about the presence or absence of immunoglobulin E (IgE)-mediated disease. In 1982 King[1] found a diagnostic sensitivity of 99.2% using an in vitro screen of only six antigens. This initial screen included one representative pollen for trees (mountain cedar), grasses (Bermuda), and weeds (ragweed), plus two molds (*Alternaria* and *Mucor*) and one dust mite. A subsequent study by Lehr et al[2] showed an efficiency of nearly 100% using a "midiscreen" of nine antigens, and even better success with 13 antigens. It is currently accepted that the patient with negative results using a screening battery of up to 14 antigens will probably not benefit from further testing.

There is a significant financial difference between the use of a screen versus initial testing with 30 to 50 antigens. If positive results are obtained using the screening battery, however, then further testing with an expanded panel, including a realistic number of antigens, is performed to complete the testing process. Details of the process may be found in the references cited.

Prior to selecting allergens for use in the testing battery, practitioners must be familiar with relevant antigens in their own geographic region. This implies knowledge of not only prevalence, but also clinical correlation with the likelihood of producing symptoms. Furthermore, in the overall management of the allergic patient, "sins of omission" can be equally as detrimental as "sins of commission." That is to say, not only may relevant allergens be omitted from the patient's treatment set, causing a suboptimal outcome, but ignorance of the phenomenon of cross-reactivity, resulting in the inclusion of multiple similar allergens in the prescription, could provide effective overdosing, causing a serious systemic reaction.

Cross-reactivity, the sharing of like epitopes (antigenic combining sites), is likely to be a problem when more than one allergen from the same plant family is selected for testing and treatment, and is especially important among the grasses. The grasses exist within a single family with four subfamilies, two of which have the most clinical significance. Testing (and treatment) should include only one representative from the major subfamilies. For the Pooideae, either timothy or perennial rye grass is generally chosen. Bermuda grass is the usual representative of the Chloridoideae.[3]

Trees, on the other hand, are distributed among many unrelated families, making the likelihood of cross-reactivity producing overdosage less problematic. However, it is noteworthy that juniper, cedar, and cypress (members of the cypress family) cross-react strongly. In areas

where oak is predominant, selection of a single oak should suffice for adequate coverage of the entire family.

Like trees, the weeds are also distributed among unrelated families, but short, giant, false, and western ragweed are similar enough that selection of one of these is adequate for testing and treatment. Short ragweed is the representative most often chosen for this family.

According to Ramanarayanan,[4] cross-reactivity between grasses in the same genus is >95%, within the same tribe and subfamily >90%, within related tribes and same subfamily >75%, within distant tribes and same subfamily >50%, and within distant tribes and different subfamilies >20%. Weeds and trees within the same genus have a cross-reactivity of >95%, within the same family >75%, within related families >50%, and within unrelated families >20%.

Dust mites are not as significant as a cause of allergy in arid, higher elevations as they are in other climes. Significant antigenic similarity exists between *Dermatophagoides farinae* and *D. pteronyssinus*, but they are different enough that many practitioners choose to test and treat for each individually.

Molds are encountered indoors and outdoors in every geographic area of the United States. They thrive in warm, humid, climates, and thus are much more significant to allergic patients in the Gulf Coast states than to those living in the cooler Rocky Mountain and arid southwestern regions. Furthermore, there is little, if any, snow and ice on the ground in the South during the winter months, thus exposing the inhabitants to year-round, high concentrations of mold. This is in contrast to residents of northern and Rocky Mountain states, where such ground cover during the winter months reduces outdoor mold exposure significantly.

Alternaria is probably the most important outdoor mold. Other molds of clinical significance throughout the United States include, but are not limited to, *Hormodendrum, Cephalosporium, Pullularia*, and *Helminthosporium.* There are many other molds that are more clinically significant regionally than nationally.

Pollens are ubiquitous offenders across North America, and there are hundreds of different species of pollen-producing, seed-bearing trees and plants with the potential to induce allergic symptoms in genetically predisposed individuals. Selection of relevant seasonal pollens to include in a screening panel or complete testing battery must be based on the patient's history and exposure to those allergens. One or two representative pollens from each of the weeds, trees, and grasses should be chosen based on the patient's geographic region and the knowledge that that allergen is a known offender in that locale. Generally, weed pollen is responsible for symptoms in the fall, grass pollen in the summer, and tree pollen in the

spring. Exceptions include regions where mountain cedar is prevalent, causing symptoms from early December through January, and in southern California, where grasses can be considered almost perennial offenders.

To stimulate the immune system and ultimately cause symptoms, pollens from plants must fulfill Thommen's postulates. That is, their pollen must be small, produced in abundance in close proximity to human populations, be wind-borne, and possess a protein allergen capable of stimulating the immune system to induce a symptom producing reaction. Some plants have more potential for causing symptoms than others. This potential is related to the amount of pollen they produce and its potency, the extent of the area of their distribution, and the dispersion of their pollen based on its weight. In the southeastern part of the United States, for example, pine trees are found in abundance and they produce a tremendous amount of pollen, but they are not highly relevant offenders in the production of allergic symptoms. Another example would be crabgrass. Although it is found throughout North America, it does not produce a great amount of pollen, thereby limiting its concentration in the air and subsequent exposure to humans.

The choice of a screening battery must take into account the patient history, with attention to exposure and symptom production linked to season and circumstance, the prevalence of antigens in the region in question, and the clinician's experience. A reasonable screening battery for relevant allergens in the southeastern United States would include 11 antigens: short ragweed, Bermuda grass, Timothy grass, hickory, oak, *D. farinae*, *D. pteronyssinus*, *Alternaria, Hormodendrum*, cat, and dog. Other examples of regional screening test batteries and antigens to be considered for additional testing may be found in Appendix 2 at the end of this book.

Standardized allergenic extracts are commercially available, and should be used for testing and treatment when available. Standardization allows for an increased reproducibility of testing, as the variability in biologic activity of the extract between lot numbers within the same manufacturer and between manufacturers is lessened (but not totally eliminated). Prior to the availability of standardized extracts, broad variability in potency existed between lot numbers within the same manufacturer, as well as among the products of different manufacturers. Some standardized extracts are available in different concentrations. One example is dust mite, which is offered in strengths of 3000, 5000, and 10,000 allergy units (AUs).

Unfortunately, not all extracts are available in standardized form. In fact, of the hundreds of allergens available for purchase, only extracts for cat hair and pelt, *D. farinae, D. pteronyssinus*, short ragweed, Bermuda grass, Timothy grass, Kentucky bluegrass, perennial rye grass, meadow

fescue, orchard grass, red top, sweet vernal, and Hymenoptera venom are available as standardized products.

The concentration of nonstandardized extracts is generally expressed as weight per volume (w/v), representing the weight of antigen in grams extracted in 100 mL of solution. The w/v concentration in most common use is a 1 : 20 strength, although other strengths are also available.

A third class of extracts has recently been introduced. These are "well-characterized extracts," which have not met the Food and Drug Administration criteria for standardization but about which much more data are available than for the common w/v extracts. This manufacturer-driven initiative for better quality control and reproducibility among extract lots is in its infancy, but it holds great promise for the future.

Because there are literally hundreds of allergens from which to choose, the selection of antigens for testing and treatment can be a daunting task. Commercial manufacturers generally know which allergens are more likely offenders in each geographic region, and they can be immensely helpful in assisting the clinician with choices. The local county extension agent can also be very helpful, as can a local university botany department.

In conclusion, once the decision to perform allergy testing is made, the next task facing the clinician is selection of the allergens that are most appropriate for testing and treatment of a particular patient. Using the principles detailed here, a reasonable number of allergens can be chosen, and the process of screening, subsequent additional testing, and treatment can begin.

References

1. King WP. Efficacy of a screening radioallergosorbent test. Arch Otolaryngol 1982;108:781–786
2. Lehr AJ, Mabry RL, Mabry CS. The screening RAST: is it still a valid concept. Otolaryngol Head Neck Surg 1997;117:54–55
3. King HC, Mabry RL, Mabry CS, et al. Allergy in ENT Practice: The Practical Guide, 2nd ed. New York: Thieme, 2004:53–56
4. Ramanarayanan MP. Allergenic Cross-Reactivity Among Pollen Bearing Plants: A Monograph. Teaneck, NJ: Windsor Park Laboratories, 1988

4

Whealing Responses to Intradermal Testing: The Basis for Intradermal Dilutional Testing (IDT)

Richard L. Mabry

Intradermal testing using varying dilutions of antigens has been the cornerstone of skin testing in otolaryngic allergy for over a half century. Reliance on the methodology of intradermal dilutional testing (IDT) demands an understanding of the normal and abnormal responses to intradermal skin testing in allergic and nonallergic individuals. In this era of evidence-based medicine, it is unfortunate that much of our information is still based on the reported anecdotal experience of Herbert Rinkel. Fortunately, he proved to be a very astute observer, and most of his recommendations have stood the test of time thus far.

◆ Historical Background

Cooke,[1] who was a pioneer in the area of intradermal testing, thought that a proper intradermal injection of 0.01 cc should produce a wheal of 2 to 3 mm in diameter. This belief was echoed by Rinkel's mentor, Dr. French Hansel.[2] However, Rinkel observed that the injection of 0.01 cc, when "truly intracutaneous," formed a wheal 4 mm in diameter, a papule that was pale and sharply demarcated with abrupt edges. Furthermore, when there was no antigenic response, this 4-mm wheal usually enlarged to a diameter of 5 mm at the end of 10 minutes, although it would sometimes reach 6 mm in size.[3] An increase of the wheal to 7 mm or greater in

diameter (i.e., 2 mm larger than the typical negative 5-mm wheal) was thought by Rinkel to indicate an allergic reaction, and was interpreted as a positive response.

Furthermore, Rinkel found that if he applied an intradermal test with antigen that was yet five times stronger, the resulting wheal was 2 mm or more larger than the preceding positive wheal. Although allergists had for decades used 10-fold dilutions in treatment, Rinkel thought that fivefold dilutions offered distinct advantages. First, he noted the increment in the whealing response to be constant through three or four consecutive dilutions in almost three quarters of patients tested. In addition, he found that treating using fivefold dilutions carried less risk of overdosing in going to the next stronger treatment vial.[3]

Rinkel called the antigen strength producing the first positive response the "endpoint of titration," signaling the concentration at which immunotherapy could safely be initiated. The next stronger concentration, producing yet a larger positive wheal, he termed the "confirming wheal." The importance of testing to obtain a confirming wheal lies in conclusively demonstrating that the endpoint concentration has initiated progressive positive whealing, establishing that one is dealing with a true endpoint.

◆ Antigen Dilutions

Antigens are prepared in fivefold dilutions, beginning with a concentrate. For years, almost all antigens were designated in weight per volume (w/v) strengths, and most otolaryngic allergists employed a 1 : 20 w/v strength as concentrate. By convention, dilution No. 1 was a 1 : 100 solution, No. 2 was 1 : 500, and so forth to No. 6, or 1 : 312,500. Now many antigens are available as standardized solutions, but the convention of naming test concentrations by how many times they have been diluted is still followed.

Although Rinkel often began testing with extremely dilute antigen concentrations, based on studies using direct immunoglobulin E (IgE) assay by radioallergosorbent test (RAST) methods, it has been determined that it is rarely, if ever, necessary to begin testing and treatment with concentrations weaker than a 1 : 312,500 weight/volume solution (i.e., a No. 6 dilution).

◆ Normal Whealing Responses

In allergy testing, enlargement of a 4-mm-diameter intradermal wheal beyond normal physical spreading to 5 mm is due to a reaction between

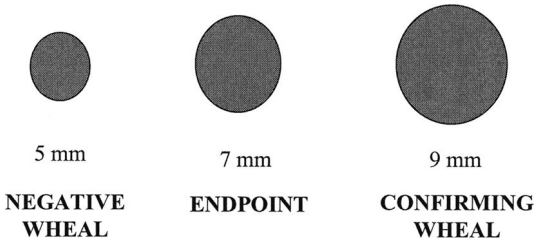


Fig. 4–1 Normal whealing response.

the injected antigen and mast cells in the skin with specific IgE for that antigen fixed to them. The antigen reacts by bridging two adjacent IgE molecules, resulting in mast cell dissolution and the release of preformed and newly formed mediators of inflammation. After ~5 minutes, swelling of the skin begins due to increased vascular permeability, producing the "wheal" response. The size of the wheal is proportionate to the amount of mast cell activation, and it is considered to be an indicator of the amount of IgE-mediated release of mediators from mast cells. Other mediators, including substance P and platelet-activating factor, cause local erythema, the "flare" seen around some skin tests. The wheal reaches its maximum at 10 to 15 minutes, although the wheal and flare may persist to some degree for some time thereafter.[4]

A late-phase reaction may cause further enlargement of a wheal after 20 to 30 minutes. Should this occur, it is noted but not necessarily taken into account when initially determining the endpoint of titration. Rinkel and most clinicians after him thought that the presence and size of the erythema (flare) around an intradermal test had little if any clinical value in determining endpoints.

When testing with antigen concentrations that increase in strength in fivefold increments, and reading test results at 10 to 15 minutes, a typical pattern would be one or more negative (i.e., 5 mm) wheals, then a positive wheal (7 mm or larger), followed by a larger positive wheal (9 mm or larger). This is a normal whealing progression, and holds true in almost 80% of patients tested **(Fig. 4–1)**.

◆ Unusual Whealing Responses

In the early days of skin endpoint titration, most practitioners, including Rinkel, began testing with extremely weak antigen concentrations, often as weak as ~1: 40,000,000 (No. 9 dilution).[3] In some instances, he found positive responses to the weakest concentration applied, diminishing in

size until negative wheals occurred, followed by progressive positive whealing as more concentrated antigens were injected. He termed this phenomenon an *hourglass reaction with a clear central zone*. Because modern technique involves testing beginning with concentrations of 1 : 312,500 (No. 6) or stronger, this phenomenon is rarely seen. However, production of a large wheal by the first test applied must always be followed by applying a stronger concentration, to show progressive positive whealing, rather than the smaller wheal that would typify an hourglass response.

Although the increment by which positive wheals enlarge as more concentrated antigens are applied is typically 2 mm, in a *variant increment response* progressive wheals may differ by 3 or 4 mm in diameter from the preceding ones. So long as one obtains a sequence of negative wheal, positive wheal, and larger positive wheal, it is possible to accurately designate the wheal that initiates progressive positive whealing as the endpoint of titration. An example would be wheals of 5 mm, 8 mm, and 11 mm, with the 8-mm wheal representing the endpoint.

There may be instances in which the first positive wheal is followed by another positive wheal of the same size when a stronger concentration is applied. This signals a *plateau reaction*. If a confirming wheal is obtained with the next stronger concentration, technically the second of the two initial positive wheals is considered the endpoint. For example, if dilution No. 6 yielded a 5-mm wheal, dilutions No. 5 and No. 4 produced a 7-mm wheal, and dilution No. 3 yielded a 9-mm wheal, the endpoint would be considered to be at No. 4—the concentration that initiated progressive positive whealing **(Fig. 4–2)**.

Rinkel described patients in whom, when testing reached the No. 2 or No. 3 antigen concentrations, very large wheals (i.e., 13 mm) resulted. When retested the next day, these patients were found to have endpoints

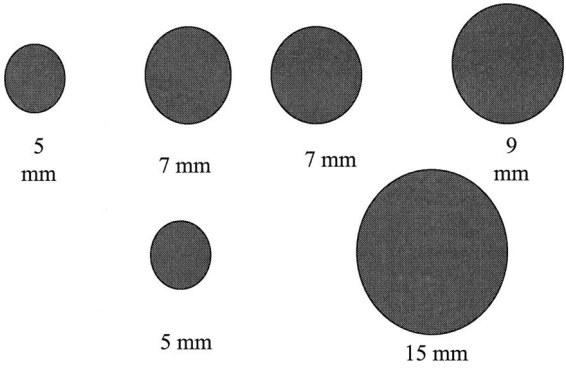


Fig. 4–2 Abnormal whealing response.

at much lower concentrations. He termed this a *flash response*.[3] This term is now applied to any circumstance in which a series of negative wheals is followed by a very large positive wheal, for example, 5-mm wheals from No. 6 and No. 5 dilutions, followed by a 13-mm wheal from the No. 4 dilution **(Fig. 4–2)**. The flash response is generally thought to be due to ingestion of a concomitant (i.e., cross-reacting) food, and the recommended procedure in such cases is to discontinue testing at that point, and to return the patient in 4 to 7 days, at which time one usually obtains a much more normal response to testing.

◆ Factors Affecting Whealing

Several factors affect whealing responses. Some of these are self-evident: the volume and potency of the substance injected, the depth to which it is injected, the degree of sensitization of skin mast cells, and the reactivity of the skin to mediators released as part of the allergic reaction. Other factors exert interesting but clinically irrelevant influences on reactivity: time of testing (more reactive at night than morning), part of the body tested (decreasing sensitivity from the back to the arm), and patient age (decline in skin reactivity after age 50).[5]

The skin of some patients responds to the physical trauma of a skin test with a wheal and flare reaction, a condition called *dermatographia*. To rule out this condition, skin testing is always preceded by a negative control of an intradermal test using sterile diluent.

Antigen concentrates contain 50% glycerin as a preservative, so a No. 1 dilution contains 10% glycerin, and a No. 2 dilution contains 2% glycerin. Although not all patients show skin reactivity to glycerine alone, in some patients it has been noted at levels as low as 0.5%.[6] If testing involves antigen dilutions No. 2 or No. 1, a glycerin control (2% or 10%) is also applied, to assess the amount of skin reactivity to those substances.

Some *medications*, especially antihistamines, suppress the wheal and flare response. This is true of antihistamines administered orally or intranasally, all of which should be omitted for 48 to 72 hours before skin testing. The newer antihistamines, loratadine and its metabolite desloratadine, can inhibit wheal and flare responses for up to 7 days, and must be omitted for this period.[7] Tricyclic antidepressants should also be omitted for 3 to 4 days before testing. Skin test responses are not suppressed by decongestants (topical or systemic), bronchodilators, corticosteroids (topical or systemic), H2 blockers, or leukotriene modifiers.[8] To ensure that the skin reactivity is not artificially suppressed, a positive skin test of histamine is applied prior to allergy skin testing.

◆ Importance of Understanding Whealing Responses

The modern otolaryngic allergist may choose from among several testing methodologies. Current in vitro tests owe a great deal to the work of Nalebuff and Fadal,[9] whose modification of the original Phadebas RAST improved its sensitivity and specificity. It is important to note that, because these in vitro results correlate with those obtained through IDT using fivefold antigen dilutions,[10] it is possible to move back and forth between in vitro and IDT results in preparing antigen sets. Skin prick tests are now used frequently by otolaryngic allergists, but they are most often blended with some form of IDT to obtain quantification of positive results. With a thorough knowledge of normal and abnormal whealing responses, it is possible to perform an optimized form of IDT, saving patients time, discomfort, and expense. Whatever method or methods are chosen, the principles of intradermal titration testing must be well known to the otolaryngic allergist. Although skin endpoint titration (SET) has given way to IDT, the advice of Dr. William King (personal communication, 1987) remains valid today: "If you're in doubt, SET will bail you out."

References

1. Cooke RA. The treatment of hay fever by active immunization. Laryngoscope 1915;25:108
2. Hansel FK. Allergy of the Nose and Paranasal Sinuses. St. Louis: CV Mosby, 1936:290–296
3. Rinkel HJ. The management of clinical allergy: part II: etiologic factors and skin titration. Arch Otolaryngol 1963; 77:42–75
4. Kaliner MD. What actually happens in an allergy skin test. Immunol Allergy Practice 1987;9:74–79
5. King HC, Mabry RL, Mabry CS, et al. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2004:109–110
6. Hurst DS, Gordon BR, Krouse JH. The importance of glycerin-containing negative control tests in allergy research studies that use intradermal skin tests. Otolaryngol Head Neck Surg 2002;127:177–181
7. Simons FE, Silver NA, Gu X, et al. Clinical pharmacology of H1-antihistamines in the skin. J Allergy Clin Immunol 2002;110:777–783
8. Krouse JH, Mabry RL. Skin testing for inhalant allergy 2003: current strategies. Otolaryngol Head Neck Surg 2003;129:S33–S49
9. Nalebuff DJ, Fadal RG. RAST-based immunotherapy. Rhinology 1984;22:11–19
10. Tandy JR, Mabry RL, Mabry CS. Correlation of modified rasioallergosorbent test scores and skin test results. Otolaryngol Head Neck Surg 1996; 115:42–45

5

The Mechanics and Interpretation of IDT

Bradley F. Marple and Richard L. Mabry

Ideally, skin testing should provide two key pieces of information important to the evaluation and treatment of allergic disease. At one level it should identify and confirm the presence of antigen-specific allergic sensitivity. At another level, if performed in a quantitative or semiquantitative manner, it should provide information that will allow determination of the relative sensitivity to a specific allergen (known as an "endpoint"). Although the specific methodology may vary among practitioners, the resulting information should ideally be the same. Intradermal dilutional testing (IDT) constitutes one standardized technique of allergy evaluation, and it appears to be as much or more effective than other types of skin testing in achieving these desired goals.

The current methodology of IDT varies little from the technique Rinkel[1] originally described for skin endpoint titration (SET). The changes that have occurred over the years have been based on observation, experience, and anecdotal material.[2] Although the technique described here is recommended as useful, there is no question that scientific validation and investigation of the benefits and drawbacks of IDT are desirable.

◆ Preparation for Testing

Other chapters have detailed the required equipment and personnel necessary for performing IDT, as well as the method by which antigens

may be chosen. As with any medical procedure, some preparation and planning is required before initiation of testing. First, the value of appropriate education and training cannot be overemphasized. Everyone involved in allergy skin testing must be appropriately trained to prevent, recognize, and treat any of the adverse consequences that may result from that testing, including anaphylaxis. Further, prior to initiation of IDT, an explanation of the procedure, its risks, and its benefits should be provided for the patient and documented with a consent form.

The tester can wear nonsterile gloves, or may choose not to do so, but the option should be made available. As a practical matter, most allergy assistants seem to feel some clumsiness when wearing gloves, whereas others appreciate the perception of safety.

◆ Application of Controls

Although patients should be counseled to avoid drugs that might interfere with skin whealing (as discussed in Chapter 4), the application of controls should precede full skin testing.

Positive Control

To ensure that the potential for a whealing reaction exists, the application of a histamine control is necessary. If this positive control wheal fails to grow as expected, further skin testing should be aborted at that sitting. A common reason for such an occurrence is the recent ingestion of an antihistamine or other substance that suppresses whealing. Further skin testing will not be valid until that suppression has worn off.[3]

The positive control most often used is histamine, at a concentration of ~0.004 mg/mL. This dilution is made by making three fivefold dilutions of a stock solution of histamine, 2.75 mg/5 mL. An intradermal wheal of 4-mm diameter is raised using this histamine control, and the diameter of the wheal is measured after 10 to 15 minutes. A positive response is represented by enlargement of the wheal to a diameter of 7 mm or more. There is no particular significance to a histamine control that enlarges to a greater diameter, but failure to produce a “positive” wheal indicates the need to further investigate the integrity of the whealing response.

Negative Control

The skin of some individuals will react to physical trauma alone, raising the potential for a false-positive response during the process of allergy testing.

It is therefore necessary to screen for these individuals, called *dermatographs*, by applying a 4-mm wheal of diluent, which is referred to as a *negative control*. In most cases the diluent consists of phenolated saline. The wheal resulting from the application of a negative control should not enlarge beyond a 5-mm diameter at 10 to 15 minutes. If the wheal enlarges further, it is likely that false-positive skin tests will result from further testing, rendering the patient a poor candidate for this method of testing. In this situation, in vitro allergy testing will be helpful.

Glycerin Control

At sufficiently concentrated levels glycerin can cause local cutaneous reactions that can also be falsely interpreted as a positive result.[4] The concentrations that hold the most potential to give rise to this reaction are contained within antigens at the No. 1 (10% glycerin) and No. 2 (2% glycerin) concentrations. This must be kept in mind if testing is to be done with antigens at these concentrations. Antigenic concentrates contain 50% glycerin as a preservative. The No. 1 dilution (1 : 100 weight per volume w/v) is made up of a fivefold dilution of this antigenic concentrate and will therefore contain 10% glycerin. The No. 2 dilution (1 : 500 w/v) is diluted another fivefold and will contain 2% glycerin. It is often necessary to test an otherwise negative patient using the No. 2 dilution of antigen, and if this is the case, it is wise to apply a 2% glycerin control (made by making two fivefold dilutions of a stock solution of 50% glycerin). A positive antigenic response is indicated by enlargement of the antigen test wheal *beyond* the size of the wheal produced by the glycerin control. Although it is uncommon to test a patient with a No. 1 concentration antigen, the same procedure can be followed in such a case.

◆ Application of Antigens

The intradermal tests are generally applied on the upper arm, in areas identified using marking pens. A corresponding key drawn on a sheet of paper may be especially helpful for the novice. Antigens are applied beginning with an anticipated nonreacting concentration. In most cases, this is the No. 6 dilution of the antigen. Approximately 0.05 mL of the test solution should be drawn into a testing syringe. Note that the amount drawn up is immaterial and simply represents a convenient amount that is both sufficient in volume and provides for ease of use. Testing syringes designed specifically for the purposes of intradermal testing are available. These

units typically consist of a needle with a short bevel attached directly to the syringe as a single unit, and are intended for increased accuracy of measurement and ease of use while performing skin tests.

Prepare the skin with alcohol, then grasp the upper arm with the non-dominant hand and draw the skin taut. Brace the heel of the dominant hand on the patient's arm. Hold the syringe with the thumb and second finger, very much like a dart. The index finger rests lightly on the plunger. Introduce the needle, with the bevel down, just beneath the skin. Some experienced testers then elevate the tip of the needle slightly, resulting in a mild "tenting" of the patient's skin to aid in delivery of the injection. Once the needle is in position, aspiration for possible blood vessel penetration is unnecessary, but may be done if desired. Gently depress the plunger to form a wheal of 4-mm diameter. Of note, the volume of antigen containing solution that is usually required to raise a 4-mm wheel is about 0.01 to 0.02 mL, but it is important to remember that it is the size of the wheal that is more important than the precise volume that is delivered. Following formation of the appropriate sized wheal, withdraw the needle and set the timer for 10 minutes.

Measure the wheal after it is made. If a wheal is too large or too small, it may be crossed out with a marking pen, and another wheal raised nearby. With practice, it is possible to raise 4-mm wheals without difficulty.

Every antigen to be tested is initially placed at the No. 6 dilution, using a new syringe for each antigen and discarding it after use. In theory, the controls should be placed and read, then all No. 6 tests applied and subsequently read, and so forth. As a practical matter, the controls and the No. 6 tests are all placed one after the other. The timer is set after the controls have been applied, and by the time all wheals have been made, only a short wait is necessary before these tests can be read. If the controls confirm the presence of whealing capabilities and a normal response to diluent and glycerin, the test wheals are read and the results charted.

If a positive wheal (i.e., one with a diameter exceeding that of the original wheal by at least 2 mm) results from the No. 6 application, it is only necessary to apply a No. 5 dilution to produce a confirming wheal, and titration would be completed. If this concept is not clear, the reader should review Chapter 4 before proceeding.

If a negative wheal results from the No. 6 dilution, progressively more concentrated solutions are applied until a positive wheal is obtained. The first positive wheal is then followed by yet one more wheal at the next stronger concentration to produce a confirming wheal. This establishes the endpoint, and titration for that particular antigen is completed.

Most clinicians feel that if a positive wheal has not been obtained by the time testing has proceeded to the No. 2 dilution, the test should be

considered negative. Their reasoning is that even if a positive wheal results from a test with the No. 1 dilution, it would be impossible to obtain a confirming wheal (because testing *never* is performed with concentrate material). In addition, there is a school of thought that holds that tests using a very concentrated antigen (such as the 1 : 100 w/v No. 1 extract dilution) may yield a significant number of false-positives. Unfortunately, there is no definitive information to resolve this controversy,[4] and it is likely that the clinical significance of testing at this concentration will remain controversial.

◆ Completing the Titration

To complete a formal titration, each antigen is tested with progressively stronger concentrations up to the No. 2 dilution, or until an endpoint wheal, followed by a confirming wheal with the next stronger concentration, is obtained **(Table 5–1)**. The endpoint wheal will be 2 mm or more greater in diameter than a negative wheal. The confirming wheal will be at least 2 mm larger than the endpoint wheal. Recall that a 4-mm wheal will enlarge to 5 mm by physical spreading, so a positive wheal will be 7 mm or greater in diameter. Chapter 4 discusses the normal and abnormal progression of wheals that may be seen.

Table 5–1 Full Intradermal Dilutional Testing

Antigen	**6**	**5**	**4**	**3**	**2**
Bermuda	5	5	(7)	9	
Timothy	5	5	6	(8)	11
Ragweed	5	(7)	9		
Pigweed	5	5	(8)	10	
Marsh elder	5	5	5	(7)	9
Oak	(7)	9			
Elm	5	(8)	11		
Mountain cedar	5	5	(7)	9	
Alternaria	5	5	6	(8)	10
Cladosporium	5	5	(7)	9	
Helminthosporium	5	5	(8)	10	
D. farinae	5	5	5	(7)	10
Cat	5	(7)	9		
Controls					
Diluent	5				
Glycerine No. 2	5				
Histamine No. 3	7				

Note: Titration begins at the No. 6 dilution. This is the safest and most complete form of intradermal titration, and it should be employed when the patient is "brittle" or "labile," as explained in the text. It is also recommended for beginners. This example requires 54 needle sticks (including controls). Endpoints are represented by "()."

A few considerations will shorten the time required for complete IDT testing. For example, if testing at a No. 6 dilution is negative, it is self-evident that both the No. 5 and No. 4 dilutions of that antigen must be applied. If the No. 5 is positive, a test with No. 4 will be required to provide a confirming wheal. If No. 5 and No. 4 test results are negative, both a No. 3 and No. 2 test may be applied at the same time, based on the same logic. If a positive response is obtained at any point in titration, testing with the next stronger concentration will be necessary to provide a confirming wheal.

Placing tests with two dilutions of an antigen at the same time (without waiting to read the results of the test using the weaker strength) will cut the time required for a full titration, but there are other measures that can further increase the efficiency of IDT.

◆ Increasing the Efficiency of Titration

Doing a full titration from No. 6 through No. 2 requires five needle sticks per antigen. If a 14-antigen panel is utilized, up to 70 sticks could be required. There is no question that performing complete intradermal dilutional testing is a safe and accurate test methodology. In today's medical practices, however, measures to make testing more time- and labor-efficient must generally be adopted.

Patients likely to experience a significant reaction to skin testing should always have testing begun at a No. 6 dilution. This group, often called "brittle" or "labile" patients, includes asthmatics (especially steroid-dependent asthmatics), patients on beta-blocking agents, and those with a history of prior severe reactions to testing or immunotherapy. It is also wise to begin testing at the No. 6 dilution of any antigen that is currently in season. All other patients can usually have testing begun at the No. 4 dilution **(Table 5–2)**. This is a time- and labor-saving maneuver.

A thorough knowledge of normal and abnormal whealing responses enables the clinician to more accurately predict a specific response within the spectrum of possible response patterns. If we accept that testing with progressively fivefold or stronger concentrations of antigen results in positive wheals, each of which is 2 to 3 mm larger in diameter than the test preceding it, it becomes fairly intuitive to "fill in the blanks" of a titration by extrapolation. For example, if an isolated test with the No. 4 dilution produces a 9-mm wheal, it is most likely that the No. 5 dilution would give a wheal of $\sim$7 mm, and would represent the endpoint of titration.

Table 5–2 IDT performed in September in Texas, on a Nonlabile Patient

Antigen	**6**	**5**	**4**	**3**	**2**
Bermuda			(7)	9	
Timothy			6	(8)	11
Ragweed	5	(7)	9		
Pigweed	5	5	(8)	10	
Marsh elder	5	5	5	(7)	9
Oak					
Elm	(*)		11		
Mountain cedar			(7)	9	
Alternaria			6	(8)	10
Cladosporium			(7)	9	
Helminthosporium			(8)	10	
D. farinae			5	(7)	10
Cat		(*)	9		
Controls					
Diluent	5				
Glycerine No. 2	5				
Histamine No. 3	7				

Note: Weeds are in season and testing begins with a No. 6 dilution, but titration is begun on all other antigens at a No. 4 dilution. In two instances, the endpoint is estimated, extrapolating backward from a large positive, assuming a 2-mm increment in growth with each dilution. This example requires 34 needle sticks (including controls). Endpoints are represented by "()" and extrapolated endpoints by "(*)."

Thus, in a nonlabile patient, testing could be initiated for all out-of-season antigens at a No. 4 dilution **(Table 5–3)**. If those tests are nonreactive, then No. 2 dilutions would be applied. Negative responses would signal a negative titration. Positive responses would be interpreted by extrapolation. For example, a 9-mm wheal at No. 4 would suggest an endpoint at No. 5. A 10-mm wheal at No. 2 suggests that the endpoint is at No. 3. Any of these extrapolations may be confirmed by testing at the presumed endpoint.

◆ Benefits of Intradermal Dilutional Testing

As distinguished from prick testing or single-dilution intradermal testing, IDT provides the benefit of determining not only to what antigens the patient is sensitive, but also the degree of that sensitivity. This identifies antigens likely to cause more severe reactions as immunotherapy proceeds, and it allows immunotherapy to commence with antigens at a concentration likely to begin producing beneficial immunologic effects.

There are other methods of testing for allergy,[5] and these are detailed in the chapters that follow. Whatever method is chosen, the clinician must

Table 5–3 Maximally Optimized IDT performed in February in Texas, on a Nonlabile Patient

Antigen	**6**	**5**	**4**	**3**	**2**
Bermuda			(7)		
Timothy			6	(*)	11
Ragweed		(*)	9		
Pigweed			(8)		
Marsh elder			5	(*)	9
Oak					
Elm	(*)		11		
Mountain cedar			(7)		
Alternaria			6	(*)	10
Cladosporium			(7)		
Helminthosporium		(8)			
D. farinae			5	(*)	10
Cat		(*)	9		
Controls					
Diluent	5				
Glycerine No. 2	5				
Histamine No. 3	7				

Note: No pollens are in season, and only the No. 4 and No. 2 dilutions are tested. Other endpoints are estimated by extrapolation, although they may be confirmed by testing with the assumed endpoint dilution. This method is only recommended for experienced testers, on nonlabile patients. This example requires 19 needle sticks (including controls), and confirming endpoints would add 7 more. Endpoints are represented by "()" and extrapolated endpoints by "(*)."

remember that any test is just that: a laboratory test. The results must be interpreted and a treatment plan formulated in the context of patient symptomatology, physical findings, and environmental factors.

References

1. Rinkel HJ. The management of clinical allergy. Arch Otolaryngol 1963;77:42–75
2. King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2005:105–145
3. Galant SP, Bullock J, Wong D, Maibach HI. The inhibitory effect of antiallergy drugs on allergen and histamine-induced wheal and flare response. J Allergy Clin Immunol 1973;51:11–21
4. Fornadley JA, Corey JP, Osguthorpe JD, et al. Allergic rhinitis: clinical practice guidelines. Otolaryngol Head Neck Surg 1996;115:115–122
5. Krouse JH, Mabry RL. Skin testing for inhalant allergies 2003: current strategies. Otolaryngol Head Neck Surg 2003;129:S33–S49

6

The Mechanics and Interpretation of Multiple-Prick Testing

John H. Krouse

Prick testing, also known as epicutaneous testing, is among the earliest forms of skin testing employed for the diagnosis of inhalant allergy. Prick testing has been used for over 100 years, and has been the primary testing methodology, both in the United States and internationally, for the diagnosis of allergic sensitivity. In prick testing, a small amount of antigen is introduced into the superficial skin through a small puncture. The reactivity of the skin is then noted, and the response is judged to be positive or negative. There are several approaches to prick testing, and a variety of devices have been developed to aid in the placement of tests.

Devices for skin testing can be broadly divided into two categories: single-prick devices and multiple-prick devices. With single-prick devices, antigen is placed onto a small puncture wound created in the skin with a needle or lancet, or it is delivered with a multiple-tined device that introduces the antigen into the skin at the same time the puncture is made. Common devices used for single-prick testing include the Morrow-Brown needle (Antigen Laboratories, Liberty, Missouri) and the DuoTip device (Lincoln Diagnostics, Inc., Decatur, Illinois).

Multiple-prick devices utilize the same basic principle, introducing a small amount of antigen directly into the superficial skin, but these devices contain a set of testing arms linked together into a single unit. Through the use of these multiple-prick devices, several tests can be placed into the skin simultaneously. In addition, research suggests that

these multiple-prick devices provide more reliable, accurate, and replicable testing results, even when used by less experienced examiners.[1,2] Multiple-prick devices available for testing include the Multi-Test II (Lincoln Diagnostics, Inc.) and the Quintest (Hollister-Stier, LLC, Spokane, Washington). Because these multiple-prick devices appear to be superior in their testing properties to single-prick methods, only multiple-prick testing are discussed in this chapter.

◆ The Mechanics of Multiple-Prick Testing

With all forms of skin testing, patient safety is a primary concern. The patient is first questioned about relevant medical history, including prior testing for allergy, asthma, and history of anaphylaxis. In addition, the patient is asked about medications that may interfere with skin testing (e.g., antihistamines, tricyclic antidepressants) and medications that may increase the risk of testing (e.g., beta-blockers). Once the complete history is obtained, and the testing is described to the patient, the testing procedure may begin. Testing is usually done on the volar forearms, so the forearms are cleaned with alcohol or another acceptable antimicrobial agent. If testing is done on the back or anterior thighs, these areas are cleaned in a similar manner.

In the practice of skin testing, regardless of the type of testing performed, it is essential to assess the ability of the skin to react to an allergen challenge. A positive response to an antigen depends on the release of histamine from activated mast cells and the interaction of that histamine with receptors in the skin that stimulate edema and induration. Medications such as antihistamines can interfere with receptor binding and can therefore prevent response even though the patient is truly allergic to the antigen. Skin testing, therefore, requires the placement of a histamine challenge to act as a positive control, assuring that the skin will develop whealing in response to the presence of histamine. Some patients may be dermatographic, responding with histamine release to minor skin trauma or even light pressure, so that the placement of the skin testing device alone could create nonspecific whealing. To assess for this effect, it is important to utilize a negative, saline control in testing. The introduction of normal saline should not create any whealing with a prick test.

In using multiple-prick test devices, antigens are often preloaded into a tray that may contain up to 24 different antigens in individual wells, and

may accommodate up to three individual testing devices. As already noted, it is important to use two of the wells for control solutions of histamine and saline, delivering these controls simultaneously with delivery of the specific antigens. Although consideration can be given to using one of the wells for a glycerin control, glycerin reactivity in prick testing is very rare.

Prick tests may be placed on various skin surfaces, although the volar forearms provide an accessible and reliable location for testing. It is important to realize that not all skin sites are equal in reactivity. The middle and upper back are the most responsive to skin testing, although the forearm does provide a useful and less sensitive location. It is practical to place up to 16 individual tests on each forearm, so that by using both arms, up to 32 prick tests may be placed in one individual testing session. In the rare case in which more antigens will be tested, the anterior thighs or back also provide excellent areas for placement of prick tests. In addition, the anterior thigh is often a preferred site in young children, because the amount of skin surface at the volar forearm is limited in these small patients.

The skin is first marked with a washable pen to indicate the location of each of the testing panels. Each device is then individually applied to the skin at the outlined location with moderate pressure, rocking it from side to side and from back to front to provide adequate delivery of the test substances. Small droplets will remain at the testing sites once the device is removed, and should not be wiped away for at least 5 minutes. In addition, patients should be advised to avoid moving their arms for at least 5 minutes, to avoid cross-contamination of puncture sites. The puncture sites will begin to develop whealing with positive antigens within a few minutes. Complete development of whealing and erythema occurs by 20 minutes, at which time the tests are measured.

Although various methods for evaluating test results are utilized, the most accurate method for assessing positivity involves the measurement of wheal sizes. While noting that the erythema surrounding the wheal is useful (the so-called flare), it is the whealing response that is specific for histamine release. The wheal size for each individual antigen test site is measured and recorded. Most guidelines suggest that a positive wheal is defined as a wheal that is at least 3 mm in diameter and at least 3 mm greater in diameter than a saline (negative) control wheal. The size of the wheal is recorded rather than simply recording the response as positive versus negative because the size of whealing can be used to roughly estimate the strength of response.

◆ Interpretation of Results with Multiple-Prick Testing

Prick testing can provide a useful measurement of reactivity to antigens. It is a qualitative test, meaning that results primarily reflect whether or not an individual is allergic to a specific antigen. Although wheal sizes can be used to estimate the degree of sensitivity within very broad parameters, in this case they must be viewed as semiquantitative at best. Using the information gained from multiple-prick testing, immunotherapy can be prepared and safely delivered, but approaches to immunotherapy must be different from those based on intradermal dilutional testing (IDT).

The first priority in the delivery of immunotherapy is patient safety. Because the administration of antigen to sensitized patients can have life-threatening consequences, it is vital to treat the patient with concentrations of antigens to which they will have a very low risk of an adverse reaction. In nonquantitative testing, in contrast to quantitative testing such as IDT and modified quantitative testing (MQT), no attempt is made to quantify the degree of responsiveness. For that reason, the only safe manner in which to initiate immunotherapy is to prepare initial treatment vials with very dilute concentrations of antigens. If therapy is based on prick testing alone, many allergists choose the safest approach, which is to prepare treatment vials in which all antigens to be treated are initiated at 1 : 1,000,000 weight per volume (w/v) concentrations to significantly decrease the likelihood of a significant systemic reaction. In quantitative testing, in contrast, endpoints have been derived that have been assayed through testing to be safe on the skin. For that reason, with quantitative testing, starting concentrations of antigen can be much higher, even as high as 1 : 500 w/v.

In another method of utilizing multiple-prick testing results to guide immunotherapy, prick test responses can be divided into two or more categories on the basis of wheal size, for example, high responders and low responders.[3] One such method that can be used is to dichotomize prick testing results in a semiquantitative fashion into two discrete categories: low level and high level. This classification assumes that the strength of the reaction on the skin is an accurate representation of the underlying allergic sensitivity. By utilizing this two-level classification system, vial preparation can include two distinct levels of antigen concentration. For practical purposes, discrimination of sensitivity based on wheal diameters alone is inaccurate, and it is therefore not recommended that the physician divide treatment vials into more than two antigen strengths based on prick testing alone.

One specific two-level system that can be used easily and appears to have good effectiveness employs two ranges of wheal diameters to define two-allergen sensitivity; these ranges are then assigned specific intradermal dilutional titration endpoint values for vial preparation. Testing results can be categorized by placing wheal diameters of 3 to 8 mm in the low-level sensitivity group, and wheal sizes of 9 mm or greater in the high-level sensitivity group. The low-level group would be arbitrarily assigned an intradermal dilutional titration endpoint 4, because it has a lesser degree of skin reactivity, and the high-level group would be assigned an intradermal dilutional titration endpoint 6, based on its greater degree of skin response. Again, it must be stressed that this approach is only semiquantitative because estimates of skin sensitivity are made only on the basis of response to a single prick test. Without the precision and refinement of either IDT or blended techniques such as MQT, semiquantitative approaches such as the one described here should be used carefully, and only by experienced physicians.

In those cases in which semiquantitative approaches are used to prepare immunotherapy vials, the use of an intradermal vial test from each new vial is essential in confirming the safety of that vial.[4] For the vial test, a 4-mm intradermal wheal is placed in the upper arm using the mixture from the prepared vial to be tested. A period of 10 minutes is allowed to elapse, and the size of the wheal is measured. If the wheal that is generated by this vial test is greater than 13 mm in diameter, the vial is considered to be overly potent, and injections are not given from that vial. It is diluted fivefold and a vial test from this diluted vial is applied. If the wheal diameter is less than 13 mm, immunotherapy injections may proceed at that time. If the wheal is precisely 13 mm in diameter, the vial is acceptable, although the initiation of therapy is delayed until the next visit, at least 72 hours from the time of the vial test.

◆ Implications of Multiple-Prick Testing

When used appropriately, multiple-prick testing can be an effective way of establishing qualitatively whether an individual is allergic to a specific antigen or antigens. It can also be used as a basis for the preparation of treatment vials for immunotherapy. It is clear that the ability to prepare precise treatment vials quantitatively is limited by utilizing this method alone. In cases in which patients have difficulty tolerating injections based on prick testing, or if it becomes difficult to advance patients beyond the level that they would be expected to achieve, it may be necessary to retest the patient using a quantitative technique such as IDT or MQT.

These approaches would be expected to more accurately define the precise antigen sensitivities and allow preparation of a more specific treatment set for the patient.

◆ Conclusion

Multiple-prick testing techniques can be a significant addition to the testing options available to the practicing allergist. When used properly, in conjunction with a careful history and general evaluation, they can accurately assess the presence or absence of allergic sensitivity in patients. They can also be used to guide the preparation of treatment vials, on either a qualitative or a semiquantitative basis. When employed with care, they are safe and effective methods for assisting in diagnosing and treating allergy.

References

1. Nelson HS, Lahr J, Buchmeier A, et al. Evaluation of devices for skin prick testing. J Allergy Clin Immunol 1998; 101:153–156
2. Mahan C, Spector S, Siegel S, et al. Validity and reproducibility of multi-test skin device. Ann Allergy 1993;71:25–28
3. Krouse JH, Mabry RL. Skin testing for inhalant allergy 2003: current strategies. Otolaryngol Head Neck Surg 2003;129:S33–S49
4. Haydon RC III, Gordon BR. Aeroallergen immunotherapy. In: Krouse JH, Chadwick SJ, Gordon BR, et al, eds. Allergy and Immunology: An Otolaryngic Approach. Philadelphia: Lippincott Williams & Wilkins, 2002:151–182

7

Blending Methods: Modified Quantitative Testing (MQT)

John H. Krouse

As previously discussed, intradermal dilutional testing (IDT) can be an effective and sensitive method for the diagnosis of inhalant allergy. It is a safe technique, in that it systematically assesses allergic sensitivity beginning with very dilute levels of antigen, and it sequentially progresses to stronger concentrations to quantify the degree of sensitivity. It has been employed successfully for the diagnosis and treatment of inhalant allergy for over a half century.

Although IDT demonstrates good clinical efficacy, there are circumstances in which the use of complete dilutional testing might not be indicated. Time constraints, personnel availability, and economic factors often require compromises in testing. Because quantitation in testing provides advantages in safety and in accurately determining starting doses for immunotherapy, it is useful for any testing technique to provide results indicating the degree of antigen sensitivity, within the constraints of practical issues in staffing, time, and cost. One method that has been designed to provide this effective compromise is modified quantitative testing (MQT).

The MQT method was first described in 2003, where it was presented as a blended method of prick and intradermal techniques that was developed to yield "an estimate of the strength of the allergic response that can be interpreted using standard [IDT] nomenclature and used in vial preparation."[1] MQT was described in greater detail in a monograph

published later that year.[2] Since being introduced in the early 2000s, MQT has become increasingly used as a method for testing for inhalant allergy, and it has proven to be both sensitive and specific in clinical practice.

◆ The Technique of MQT

MQT is a blended method for the assessment of inhalant allergy. It initially uses prick testing to estimate an approximate range of skin reactivity to individual antigens, and then it employs one specific intradermal test for each antigen at a predetermined dilution to further refine and quantify the degree of allergic sensitivity. Prick testing devices and methods vary in their clinical measurement properties. MQT generally employs more current, multipronged testing devices such as the Multi-Test II device (Lincoln Diagnostics, Inc., Decatur, Illinois) or the Quintest device (Hollister-Stier Laboratories, LLC, Spokane, Washington) because they produce testing results that are more accurate and reproducible than the single-stick devices.[3,4]

As with all forms of skin testing, safety is essential. The patient is questioned about his or her medical history, including prior testing, asthma, and history of anaphylaxis. In addition, the patient is asked about medications that may interfere with skin testing (e.g., antihistamines, tricyclic antidepressants) and medications that may increase the risk of testing (e.g., beta-blockers). Once the history is complete, the testing is described to the patient and his or her agreement to proceed is obtained. At this point the upper and lower arms are exposed and are cleansed with alcohol or another acceptable agent for sterilization.

In performing an MQT battery, it is important first to ensure that the skin is able to respond to antigen placement, as with all forms of skin testing. A histamine control is used to check responsiveness, and it can be placed in one testing well of a multipronged tray. An alternate approach that can be used to assess skin responsiveness is the placement of a No. 3 dilution histamine intradermal wheal, as would be used for IDT. Because a No. 2 glycerin wheal must also be placed to allow interpretation of the intradermal tests, both intradermal wheals can be raised at the same time prior to prick testing. It is also important to include a saline control in one well of the prick-testing tray, as a small number of patients have a dermatographic response to the prick test and demonstrate whealing as a result of the mild trauma of prick test placement.

If skin responsiveness has been demonstrated through a positive histamine control, prick tests are placed on the volar forearms using the

multipronged testing devices as described in the preceding chapter. After placement, 20 minutes are allowed to elapse for development of positive whealing. The placement of a subsequent intradermal test is based on the size of the wheal produced by prick testing. The degree of sensitivity is estimated from the blended responses of both the prick and intradermal test results, and a quantification of this sensitivity is made using the same endpoint (EP) system defined in IDT.

In MQT testing, a wheal size of 3 mm in diameter defines a positive skin response. The patient is assumed to be sensitive to that antigen, and further testing will be necessary to refine the estimate of the degree of sensitivity. If the patient has a very vigorous response to prick testing, which is defined as a wheal of 9 mm or greater in diameter, the patient is considered to have a maximal response, and additional intradermal testing of that specific antigen is not conducted. In the circumstance of a 9 mm or larger wheal, the patient is assigned an IDT EP of No. 6 for that antigen, and testing for that antigen is complete.

In testing antigens that demonstrate wheals of less than 9 mm by prick testing, responses are categorized as those less than 3 mm in diameter and those 3 mm to 8 mm in diameter. Patients in the first category are classified as negative to that antigen on the basis of prick testing alone. To further assess whether the patient is able to respond to a less concentrated antigen, and is therefore truly positive to that antigen, a No. 2 IDT dilution [1 : 500 weight per volume (w/v)] of that antigen is then placed intradermally in the lateral aspect of the upper arm. A period of 10 minutes is allowed to elapse, and the diameter of that intradermal wheal is measured. A wheal of 7 mm or greater in diameter is interpreted as positive, and the patient is therefore considered to be reactive to that antigen. To be conservative and safe, the endpoint value assigned to that positive test is IDT EP 3. If the wheal size is less than 7 mm, the patient is judged to be negative to that antigen.

In the second category, where the prick test demonstrates a wheal size of between 3 and 8 mm in diameter, testing has already classified the patient as positive to that antigen. A single intradermal test of IDT No. 5 (1 : 62,500 w/v) is then used to further refine the degree of positivity to that antigen. The purpose of this intradermal test is to assess whether the prick test reflects a maximal antigen challenge, or whether placement of a less concentrated challenge would also produce an effect. Once the No. 5 wheal is placed, 10 minutes is allowed to elapse and the size of the wheal is measured. Three results may be encountered after placement and measurement of this wheal: a wheal of less than 7 mm in diameter is interpreted as a negative response, and a value of IDT EP 4 is assigned; a wheal of 7 or 8 mm in diameter is interpreted as a positive test, and a

value of IDT EP 5 is assigned; a wheal of 9 mm or greater in diameter is a maximal response to the prick test, and a value of IDT EP 6 is assigned.

◆ Interpretation of MQT Results

The purpose of the blended MQT approach to testing is to provide a quantitative value for antigen sensitivity that can be used for preparation of immunotherapy. To allow ready communication of testing results, and to employ a system that has acceptance and familiarity, MQT testing defines degree of sensitization on the basis of IDT endpoints. Through using IDT methodology in this manner, the preparation of vials for immunotherapy can proceed in a standard fashion.

The blend of skin responses to the prick test and the subsequent single intradermal test allows the assignment of discrete IDT endpoints, as noted in **Fig. 7–1.** Once again, the initial prick test allows a determination of prick-negative (<3 mm), prick-positive (3 mm or greater), and maximum positivity (9 mm or greater). A negative prick test is refined with a No. 2 dilution intradermal test, and it is either intradermal-negative (<7 mm) or intradermal positive (7 mm or greater). A No. 2 intradermal-negative test is interpreted as negative, and a No. 2 intradermal-positive test is assigned a value of IDT EP 3. A positive prick test is refined with a No. 5 dilution intradermal test, and it is either intradermal-negative (<7 mm), intradermal-positive (7 mm or 8 mm), or maximally positive (9 mm or greater). A No. 5 intradermal-negative test is assigned a value of IDT EP 4, a No. 5 intradermal-positive test is assigned a value of IDT EP 5, and a maximally positive No. 5 intradermal test is assigned a value of IDT EP 6. In the case of a maximally positive prick test, again this test is assigned a value of IDT EP 6. The endpoints determined through MQT are interpreted in the same way as they would be for full IDT testing, and vial preparation proceeds in the same manner.

In using blended techniques, it is useful to employ vial testing to confirm the safety of each treatment vial prior to proceeding with injections. The method of vial testing and its interpretation is described in Chapter 8.

◆ Conclusion

The principles of quantitative testing have been employed in skin testing for inhalant allergy for many years. They have provided a sound foundation

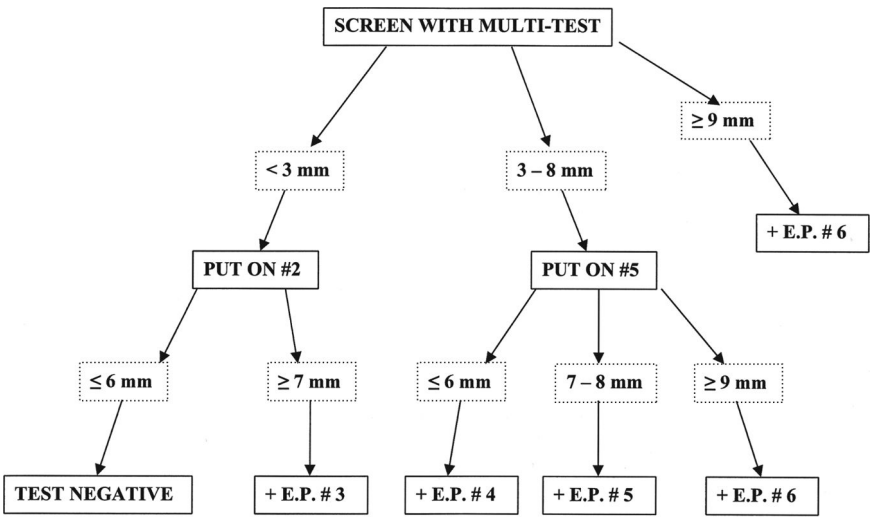


Fig. 7 – 1 Algorithm for determining endpoint sensitivities using modified quantitative testing (MQT). Measurements in millimeters reflect the size of the testing wheals. EP, endpoint dilutions from intradermal dilutional testing (IDT). Dilution numbers refer to standard IDT fivefold dilutions.

for the detection of clinical allergy, and they have assisted in determining the degree of reactivity to specific antigens. These principles have a long record of safety and have been used effectively by thousands of physicians to manage immunotherapy. MQT provides an efficient method for evaluating allergic responsiveness and allows accurate assessments of quantitative sensitivity in an efficient and cost-effective manner. It offers the practicing allergist an additional tool that may be employed for testing and treatment. The effective allergist must have a variety of tools and techniques available for practice, and the flexible application of these methods permits successful diagnosis and management of the allergic patient.

References

1. Krouse JH, Stachler RJ, Shah A. Current in vivo and in vitro screens for inhalant allergy. Otolaryngol Clin North Am 2003;36:855–868
2. Krouse JH, Mabry RL. Skin testing for inhalant allergy 2003: current strategies. Otolaryngol Head Neck Surg 2003;129:S33–S49
3. Nelson HS, Lahr J, Buchmeier A, et al. Evaluation of devices for skin prick testing. J Allergy Clin Immunol 1998;101:153–156
4. Mahan C, Spector S, Siegel S, et al. Validity and reproducibility of multitest skin device. Ann Allergy 1993;71: 25–28

8

Vial Preparation Based on Quantitative Testing

Richard C. Haydon III

The objective of immunotherapy is to alter the level of tolerance to allergenic stimulation. This is achieved through the systemic administration of antigens that have been proven to cause immunoglobulin E (IgE)-mediated hypersensitivity. Two polarized goals in this effort are to achieve symptom relief quickly and at the same time avoid anaphylaxis. Paramount to these goals is the proper administration and interpretation of quantitative testing and the proper preparation of treatment vials based on these results.

Regardless of which test methods are chosen to prove IgE-mediated allergy, in the end the clinician must find a dosing schedule that is safe and efficient. In the ideal world the actual dose at which to begin immunotherapy depends on the results of precise intradermal dilutional testing (IDT) as described previously in this text. IDT defines the endpoint for each positive antigen tested. The endpoint represents the antigen dose at which the patient first exhibits *local* mast cell degranulation. The endpoint represents the amount of antigen that begins to stimulate the immune system through local anaphylaxis without causing systemic anaphylaxis. An immunotherapy dosing schedule that begins in this endpoint dilution range is safe and will theoretically lead to quicker immunotolerance and symptom relief than will be achieved with weaker starting dose schedules. In the real world, less precise forms of quantitative tests are often used to predict the IDT endpoint; however, in theory, the clinician

should always use these other test results to ascertain what the endpoint would have been had IDT been used. The clinician should ask the question: "If I had performed IDT instead of radioallergosorbent testing (RAST) or modified quantitative testing (MQT), what would have been the endpoint?"

◆ IDT-Based Subcutaneous Immunotherapy Starting Doses

Experience and history have shown that a subcutaneously administered starting dose of 0.05 mL of the endpoint dilution is safe and builds the path for immunotherapy efficiency. However, it should also be safe *in theory* because historically these patients were nearly all IDT-tested, and during this testing, antigen amounts totaling more than 0.05 mL of the endpoint dilution antigen were already administered. This is because 0.01 mL of the dilution that was one dilution stronger than the endpoint dilution was safely administered as a confirmatory wheal during IDT. The antigen amount in this confirmatory wheal was equivalent to 0.05 mL of the endpoint dilution. Adding to that the 0.01 mL of endpoint dilution already given leads to the conclusion that more than 0.05 mL of endpoint antigen units have already been given to the patient during testing.[1,2]

◆ IDT-Based Preparation of Multidose, Multi-Antigen Treatment Vials

In the early days, there were not many antigen extracts available, and thus the clinician had a comparatively easy task of injecting starting doses of 0.05 mL of one or two antigens by drawing up in a syringe their corresponding endpoint dilutions from the IDT board **(Table 8–1)**. However, as time went on and numbers of available antigens increased, and the practice of drawing up of solutions of antigens from the test board for each patient each week waned **(Table 8–2)**, because therapy with multiple antigens required either several injections of small volumes or single injections of large volumes, neither of which was acceptable to patients. How can this problem be solved? The discussion that follows describes a simple and well-accepted method of administering injections from a treatment vial prepared specifically for each patient. Such a vial (1) requires beforehand preparation only once for many injections; (2) contains

Table 8–1 Traditional Escalation with One Antigen, 1:5 Dilutions, and Endpoint No. 4 Dilution

No. 4 vial from the test/treatment board
Week 1: 0.05 mL
Week 2: 0.10 mL
Week 3: 0.15 mL
Week 4: 0.20 mL
Week 5: 0.25 mL
Week 6: 0.30 mL
Week 7: 0.35 mL
Week 8: 0.40 mL
Week 9: 0.45 mL
Week 10: 0.50 mL
No. 3 vial from the test/treatment board
Week 11: 0.05 mL
Week 12: 0.10 mL
Week 13: 0.15 mL
Week 14: 0.20 mL
Week 15: 0.25 mL
Week 16: 0.30 mL
Week 17: 0.35 mL
Week 18: 0.40 mL
Week 19: 0.45 mL
Week 20: 0.50 mL
No. 2 vial from the test/treatment board
Week 21: 0.05 mL
Week 22: 0.10 mL
Week 23: 0.15 mL
Week 24: 0.20 mL
Week 25: 0.25 mL
Week 26: 0.30 mL
Week 27: 0.35 mL
Week 28: 0.40 mL
Week 29: 0.45 mL
Week 30: 0.50 mL

Table 8–2 Adding Just Two More Antigens Increases Injection Volume Above 0.5 mL by Week 4

Week	Antigen 1	Antigen 2	Antigen 3	Total Volume
1	0.05	0.05	0.05	0.15 mL
2	0.10	0.10	0.10	0.30 mL
3	0.15	0.15	0.15	0.45 mL
4	0.20	0.20	0.20	0.60 mL
5	0.25	0.25	0.25	0.75 mL
6	0.30	0.30	0.30	0.90 mL
7	0.35	0.35	0.35	1.05 mL
8	0.40	0.40	0.40	1.20 mL
9	0.45	0.45	0.45	1.35 mL
10	0.50	0.50	0.50	1.50 mL

multiple antigens; (3) delivers these multiple antigens in a single injection; (4) maintains the volume of injections in a range of 0.05 to 0.50 mL; (5) allows each antigen strength to be individualized according to its assigned endpoint; and (6) allows for the equivalent of 0.05 mL of the endpoint dilution of each individual antigen to be administered as the starting dose.

Testing and Treatment Boards

For smaller allergy practices, and for those just starting, time and expense can be saved by using the same set of antigens for intradermal testing and for preparation of treatment vials. But because the intradermal testing antigens are diluted with phenolated normal saline (PNS) or human serum albumin (HAS), dilutions Nos. 2 to 6 in the test board contain less than a 10% concentration of glycerine. Thus, the potency may diminish after 6 to 8 weeks (and even sooner if not properly refrigerated!). Therefore, when one board is used for both intradermal testing and treatment vial preparation, it is important that the board be kept refrigerated as much as possible, and that it be replaced with newly prepared dilutions every 6 to 8 weeks.[2–4]

The creation of a completely separate treatment board for the sole purpose of preparing treatment vials is an option for the very busy allergy practice. This may be especially advantageous when mixing treatment vials becomes a nearly full-time job. A separate mixing board minimizes cross-traffic, needle entries, and premature depletion of certain dilutions. And because the treatment board is not used for testing, one can prolong the potency of even the weakest dilutions to 12 months or more by adding enough glycerine to create a 25 or 50% concentration.[1,4] (Glycerine should *not* be added to dilutions to be used in *intradermal testing*, due to the irritative, painful, and whealing enhancement properties known to be associated with glycerine.)

It is important to note that the vial mixing examples that follow assume that the one-board concept, using the same antigens in both intradermal testing and treatment vial preparation, is being utilized. Therefore, these examples assume that no extra glycerine has been added to the dilutions created for use on this combination test and treatment board.

Directions for IDT-Based Preparation of Immunotherapy Treatment Vial (Table 8–3)

1. Select the antigens to be included for immunotherapy, based upon history, physical examination, and IDT.

Table 8–3 Sample Multi-Antigen, Multidose Treatment Vial

Antigen	Endpoint	Multidose Vial
Ragweed	5	0.2 mL No. 3
Pigweed	4	0.2 mL No. 2
Timothy	6	0.2 mL No. 4
Maple	6	0.2 mL No. 4
Total antigen		Volume 0.8 mL
Add 50%		Glycerine 1.0 mL
Add		Diluent 3.2 mL
Total:		5.0 mL

2. From the test board, in separate syringes, draw up 0.2 mL of each antigen, from the dilution that is positioned two dilutions to the right (two dilutions stronger) of the endpoint dilution for each antigen selected.
3. Put these antigens in a sterile 5-mL glass treatment vial.
4. Add enough diluent (usually PNS) and 50% glycerine (usually 1.0 mL for potency preservation; see below) to increase the total volume of antigens + diluent + glycerine in the treatment vial to 5.0 mL.

After performing the safety vial test and obtaining the proper results, one can then administer a 0.05-mL injection from this treatment vial, which is equivalent to 0.05 mL of the endpoint dilution for each individual antigen.

For those who wish to prove the concept just described, consider the following **(Tables 8–4** and **8–5)**:

1. During IDT a patient's endpoints are on a No. 4 dilution.
2. You could give the patient a starting dose consisting of 0.05 mL of the No. 4 dilution.
3. But . . . to accomplish the goal of small-volume injections containing multiple antigens, a better alternative follows:
4. Multiply the starting dose amount (0.05 mL of the No. 4) by 100, now giving a volume of 5.0 mL of No. 4. This amount now contains 100 starting doses.
5. Due to the fivefold dilution concept used in preparing test dilutions, recall that the number of antigen particles in 5.0 mL of a No. 4 dilution is the same as is contained in 1.0 mL of a No. 3 dilution or 0.2 mL of a No. 2 dilution (one-fifth the volume in each case).

Table 8–4 Example of Mixing a 5-mL Multidose Multi-Antigen Vial

Draw up 0.2 mL of each antigen dilution that is positioned two dilutions to the right (i.e., two dilutions stronger) of the endpoint dilution for each antigen (each in a separate syringe) (two antigens, A and B, in this example).

Dilutions	No. 6	No. 5	No. 4	No. 3	No. 2	No. 1	Concentrate
IDT wheal growth results, antigen A	5 mm	5 mm	8 mm	10 mm			
Antigen equivalents			5.0 mL	1.0 mL	0.2 mL		
IDT wheal growth results, antigen B			5 mm	5 mm	8 mm	10 mm	
Antigen equivalents					5.0 mL	1.0 mL	0.2 mL

6. In other words the amount of antigen in 5.0 mL of a No. 4 dilution is the same as that contained in a volume 1/25th as great of a dilution that is 25 times stronger (0.2 mL of the No. 2 dilution).
7. See item 4 above. If the 0.2 mL of a No. 2 dilution were injected into the patient, it would result in a dose that was 100× the starting dose.
8. Therefore, if we choose to use the No. 2 dilution to start immunotherapy, we must figure out a way to decrease the antigen amount to be given to the patient by a factor of 100.

Table 8–5 Mathematical Explanation of Vial Preparation and Starting Doses Using Higher Concentrations of Endpoint Dilution Antigens in Smaller Volumes (EP = No. 4 dilution)

Concentrations:	1:312,500	1:62,500	1:12,500	1:2500	1:500	1:100
Dilutions:	No. 6	No. 5	No. 4	No. 3	No. 2	No. 1
Example titration:	5 mm	6 mm	7 mm	9 mm		
Starting dose in mL			0.05	0.01	0.002	
Multiply starting dose by 100			5	1	0.2	
Divide by a factor of 25 by diluting the 0.2 mL of No. 2 by 4.8 mL diluent					0.008	
Divide by a factor of 4 by injecting only 0.05 mL instead of 0.2 mL					0.002	

9. To solve this problem, begin by putting the 0.2 mL in a 5-mL sterile glass treatment vial. Then decrease the antigen concentration by a factor of 25 by adding 4.8 mL of diluent. (This is one part antigen and 24 parts diluent, which is 1: 25.) Now the total volume in the treatment vial is 5.0 mL.
10. If 0.2 mL from this treatment vial were *now* injected into the patient, it would result in a dose that is 4× the starting dose.
11. Therefore, we must figure out a way to decrease the antigen amount to be given to the patient by a factor of 4.
12. This is accomplished by, instead of injecting 0.2 mL, administering 0.05 mL from the treatment vial. This decreases the antigen amount by a factor of 4.
13. Now, 0.05 mL of volume drawn from the treatment vial mixed accordingly will deliver a dose that is antigenically equivalent to 0.05 mL of the endpoint dilution.

To summarize, we ascertain the endpoint dilutions of those antigens that test positive and are chosen for therapy. And for each chosen antigen we place 0.2 mL of the antigen strength that is two dilutions stronger than the endpoint dilution of each antigen into a 5-mL treatment vial. We top off the volume already created by the antigens with enough diluent (and glycerine as needed) to reach a volume of 5 mL. The first dose from this vial (after an appropriate safety vial test) is an injection of 0.05 mL subcutaneously, which is antigenically equivalent to 0.05 mL of the endpoint dilution for each and every antigen.

Immunotherapy dosage escalation continues by increasing the volume in each subsequent injection usually by 0.05- to 1.0-mL increments until an injection volume of ∼0.5 mL is reached (this is discussed in more detail in Chapter 9). At this point a new vial is usually created that is mixed with the same antigens, but each at one dilution stronger than the previous vial. With this new vial, dosage escalation can continue, but it can do so using smaller volumes (again) because a 0.1-mL injection from the new vial should be antigenically equivalent to 5.0 mL from the previous vial. Escalation can continue in a similar fashion until a maintenance dose range is reached.

Although this is not necessarily recommended, **Table 8–6** illustrates that as many as 25 antigens can physically be put into one treatment vial. Under these circumstances no diluent would be added, but there would also be no room for any glycerine needed to preserve potency. In practice, keeping the number of antigens in one vial in the 10 to 12 range or less is generally recommended. Some authorities have discouraged

Table 8–6 Using 5-mL Treatment Vials and 0.2-mL Antigens Theoretically Allows for the Inclusion of 25 Antigens in One Treatment Vial

Antigen No.	Endpoint	Dilution to Put in Treatment Vial	Volume
1	6	4	0.2 mL
2	4	2	0.2 mL
3	2	C	0.2 mL
4	3	1	0.2 mL
5	4	2	0.2 mL
6	5	3	0.2 mL
7	5	3	0.2 mL
8	4	2	0.2 mL
9	6	4	0.2 mL
10	3	1	0.2 mL
11	4	2	0.2 mL
12	5	3	0.2 mL
13	2	C	0.2 mL
14	4	2	0.2 mL
15	3	1	0.2 mL
16	4	2	0.2 mL
17	3	1	0.2 mL
18	4	2	0.2 mL
19	3	1	0.2 mL
20	5	3	0.2 mL
21	4	2	0.2 mL
22	6	4	0.2 mL
23	6	4	0.2 mL
24	3	1	0.2 mL
25	2	C	0.2 mL
		Antigen volume	5 mL
		Diluent to add	0 mL
		Total volume	5 mL

combining certain antigen groups within the same treatment vial due to enzymes that might lead to premature degradation and loss of potency; however, from a practical standpoint, this has not proven to be a problem. It is recommended that, when necessary, two different treatment vials be prepared, separating those antigens with strong endpoints (dilutions 2 and 3) from those antigens with weak endpoints (dilutions 4, 5, and 6). This is done because, in the beginning, reactions to the antigens to which the patient is most sensitive may cause local reactions, slowing the progress of dosage advancement. Later in the course of escalation, as these antigen dilutions approach one another, they can then be combined into the same vial.

There are other ways to mix vials and administer injections. One is limited only by the math and the technology to mix the solutions

accurately and efficiently. For example, some clinicians create 2.5-mL treatment vials by dividing by two each of the volume amounts described in the recipe above. However, the method just described using 5-mL vials is most commonly used in otolaryngic allergy and seems to work well for most practices.

The Use of Glycerine as a Part of the Diluent Formula in Treatment Vials

The following discussion assumes that the testing and the treatment boards are one and the same, and thus no glycerine has been added when the dilutions were created. Under these circumstances, the potency of extracts in a 5-mL treatment vial is maintained for about 6 to 8 weeks when diluted with phenolated saline *only* (unless the vial contains at least five concentrates; see below). But how long does a 5-mL treatment vial usually last before there is not enough left to give another injection? That depends on the immunotherapy schedules employed, which usually is in the range of 6 to 12 weeks; most schedules are in the 10- to 12-week range. Therefore, diluting treatment vials with PNS *only* brings the potency during the last few weeks into question. However, potency is maintained for at least 3 months if the vial contains a 10% glycerine concentration. And immunotherapy injections containing 10% glycerine are usually well tolerated. Therefore, in most cases—certainly those where the life of a treatment vial is predicted to be in the 10- to 12-week range—the clinician should substitute enough *glycerine in place of the phenolated saline diluent* to create a 10% glycerine concentration. Examples of how to accomplish this are illustrated in **Tables 8–7** through **8–12**.

To summarize, **Table 8–13** gives guidelines for achieving at least a 10% glycerine concentration in 5-mL treatment vials. It is also important to note that the irritation level, and thus pain and confusion over injection reactions, can continue to rise with glycerine concentrations above 10%.

Table 8–7 How Much Glycerine Is Present When Extracts Manufactured in 50% are Titrated into Dilutions 1 to 6?

Dilution	No. 6	No. 5	No. 4	No. 3	No. 2	No. 1	C
Glycerine %	0.0032	0.016	0.08	0.40	2	10	50

Table 8–8 Glycerine Concentration of 10% in Treatment Vial

The glycerine concentration present in the treatment vial in this example is 10%. This is because the five concentrate antigens each contain 50% glycerine, and they total 1.0 mL of 50% glycerinated antigen. The 1.0 mL of antigen is then diluted by the 4.0 mL of diluent giving an overall concentration of 10% glycerine in this treatment vial.

Antigen No.	Dilutions	% Glycerine	Amount to Put in 5-mL Treatment Vial
1	CONC	50%	0.2 mL
2	CONC	50%	0.2 mL
3	CONC	50%	0.2 mL
4	CONC	50%	0.2 mL
5	CONC	50%	0.2 mL
		Antigen volume	1.0 mL
		Diluent to add	4.0 mL
		Total volume	5.0 mL

Therefore, when more than five concentrates (each containing 50% glycerine) are placed into a 5-mL treatment vial, it may be wise to consider dividing them into two treatment vials so as to keep the glycerine concentration as close to 10% as is feasible.[2]

Table 8–9 Glycerine Concentration of 20% in Treatment Vial

The glycerine concentration present in the treatment vial in this example is 20%. This is because the ten concentrate antigens each contain 50% glycerine and they total 2.0 mL of 50% glycerinated antigen. The 2.0 mL of antigen is then diluted by the 3.0 mL of diluent, giving an overall concentration of 20% in this treatment vial.

Antigen No.	Dilutions	% Glycerine	Amount to Put in 5 mL Treatment Vial
1	CONC	50%	0.2 mL
2	CONC	50%	0.2 mL
3	CONC	50%	0.2 mL
4	CONC	50%	0.2 mL
5	CONC	50%	0.2 mL
6	CONC	50%	0.2 mL
7	CONC	50%	0.2 mL
8	CONC	50%	0.2 mL
9	CONC	50%	0.2 mL
10	CONC	50%	0.2 mL
		Antigen volume	2.0 mL
		Diluent to add	3.0 mL
		Total volume	5.0 mL

Table 8–10 Glycerine Concentration of <10% in Treatment Vial

The glycerine concentration present in the treatment vial in this example is <10%. This is because the 2.0 mL of diluent dilutes the overall concentration of 10% and 2% glycerine contained in the No. 1 and No. 2 dilutions. [In fact it would take 25 antigens containing 10% glycerine (all No. 1) to give an overall concentration of 10% glycerine.] To achieve a slightly greater than 10% glycerine concentration in this example, one should decrease the diluent to 1.0 mL and add 1.0 mL of 50% glycerine.

Antigen No.	Dilutions	% Glycerine	Amount to Put in 5-mL Treatment Vial
1	No. 1	10%	0.2 mL
2	No. 1	10%	0.2 mL
3	No. 1	10%	0.2 mL
4	No. 1	10%	0.2 mL
5	No. 1	10%	0.2 mL
6	No. 1	10%	0.2 mL
7	No. 1	10%	0.2 mL
8	No. 1	10%	0.2 mL
9	No. 1	10%	0.2 mL
10	No. 1	10%	0.2 mL
11	No. 2	2%	0.2 mL
12	No. 2	2%	0.2 mL
13	No. 2	2%	0.2 mL
14	No. 2	2%	0.2 mL
15	No. 2	2%	0.2 mL
		Antigen volume	3.0 mL
		Diluent to add	2.0 mL
		Total volume	5.0 mL

◆ Semiquantitative Test-Based Vial Preparation

The mixing of immunotherapy treatment vials based on combination prick and single-dilution intradermal tests (MQT), prick tests alone, or in vitro RAST tests is no different from that used for IDT. The endpoint for each antigen tested should be estimated with all of these techniques so that treatment vials may be mixed according to these estimates. As long as immunotherapy treatment vials are safety tested on the patient (see Vial Safety Testing, later in chapter) prior to administering the first injection, then such estimates should be safe.

◆ MQT-Based Vial Preparation

The mixing of immunotherapy treatment vials that are based on MQT testing is virtually identical to that employed in IDT-based therapy.

Table 8–11 Glycerine Concentration of >10% in Treatment Vial

The glycerine percentage present in the treatment vial in this example is >10%. This is because the five concentrates each containing 50% glycerine give a 10% concentration by themselves. Any additional glycerine increases the amount to greater than 10%.

Antigen No.	Dilutions	% Glycerine	Amount to Put in 5-mL Treatment Vial
1	CONC	50%	0.2 mL
2	CONC	50%	0.2 mL
3	CONC	50%	0.2 mL
4	CONC	50%	0.2 mL
5	CONC	50%	0.2 mL
6	No. 1	10%	0.2 mL
7	No. 1	10%	0.2 mL
8	No. 1	10%	0.2 mL
9	No. 1	10%	0.2 mL
10	No. 1	10%	0.2 mL
11	No. 2	2%	0.2 mL
12	No. 2	2%	0.2 mL
13	No. 2	2%	0.2 mL
14	No. 2	2%	0.2 mL
15	No. 2	2%	0.2 mL
		Antigen volume	3.0 mL
		Diluent to add	2.0 mL
		Total volume	5.0 mL

One simply applies the endpoint derived from the combining of prick and single-dilution IDT as described in the MQT section and uses this derived endpoint to calculate appropriate dilutions for vial mixing.[5]

◆ Prick-Based Vial Preparation

Vial preparation and immunotherapy that is based on prick tests alone is commonly practiced by allergists. As long as care is given to the details and a safety vial test is used, such a strategy can be safe and effective for the treatment of inhalant allergy. It is important to prepare starting-dose treatment vials with relatively dilute concentrations. This may cause immunotherapy escalation to take longer than when endpoints are more precisely determined as with IDT.

A suggested strategy for prick-based dosing, referred here as “two-tiered” prick-based dosing, requires prick test results to be categorized

Table 8–12 Example of an Immunotherapy Escalation Sequence that Gradually Increases the Antigen Strengths through the Preparation of Subsequent Treatment Vials*

Antigen	Original Endpoint	Dilutions to Mix in Initial Treatment Vial	Dilutions to Mix in Next Treatment Vial	Dilutions to Mix in Next Treatment Vial	Dilutions to Mix in Next Treatment Vial	Dilutions to Mix in Next Treatment Vial
A	5	3	2	1	C	C
B	4	2	1	C	C	C
C	3	1	C	C	C	C
D	3	1	C	C	C	C
E	5	3	2	1	0	C
F	6	4	3	2	1	C
G	6	4	3	2	1	C
H	3	1	C	C	C	C
I	3	1	C	C	C	C
J	5	3	2	1	C	C
Antigen volume		2.0 mL	2.0 mL	2.0 mL	2.0 mL	2.0 mL
Diluent volume		3.0 mL	3.0 mL	3.0 mL	3.0 mL	3.0 mL
Rx vial volume		5.0 mL	5.0 mL	5.0 mL	5.0 mL	5.0 mL
Glycerine concentration		<10%	~8%	~10%	~14%	20%
50% glycerine to add		1.0 mL	0.2 mL	0	0	0
Adjusted diluent		2.0 mL	2.8 mL	3.0 mL	3.0 mL	3.0 mL
Total volume for treatment vial		5.0 mL	5.0 mL	5.0 mL	5.0 mL	5.0 mL

*Notice that as the number of concentrates in the later vials increases, the amount of additional glycerine needed to achieve at least 10% concentration decreases.

Table 8–13 Guidelines for Achieving an at Least 10% Glycerine Concentration in 5-mL Treatment Vials

No. of Concentrates Contained in the 5-mL Treatment Vial	Amount of 50% Glycerine to Add to the Treatment Vial IN PLACE of an EQUAL VOLUME of PNS	Approximate Final Glycerine Content in the 5-mL Treatment Vial
0 (none)	1.0 mL	10%
1	0.8 mL	10%
2	0.6 mL	10%
3	0.4 mL	10%
4	0.2 mL	10%
5	0 (add nothing)	10%
6	0 (add nothing)	12%
7	0 (add nothing)	14%
8	0 (add nothing)	16%
9	0 (add nothing)	18%
10	0 (add nothing)	20%

into either high-sensitivity or low-sensitivity responses based on the size of the positive wheal response. Then two different dilutions of antigen can be used in preparation of immunotherapy vials. Low-level responses, with wheal sizes of 3 to 8 mm, can be assigned an IDT endpoint of No. 4. High-level responses, with wheal sizes of 9 mm or greater, can be assigned an IDT endpoint of No. 6.

◆ In Vitro–Based Vial Preparation

Similar to in vivo skin tests, in vitro blood tests that measure allergen-specific IgE antibody can also be used to identify and quantitate the degree of sensitivity to inhalant allergens and preparation of immunotherapy treatment vials. Vial preparation and immunotherapy is based on fivefold dilutions, in the same fashion as with IDT. And because the patient has not been skin tested with the antigens about to be received for immunotherapy, a safety vial skin test should *always be performed* prior to starting in vitro–based immunotherapy.

Generally speaking, there is an acceptable correlation between IDT and in vitro test results. For instance, a patient who has a class 4 RAST IgE score for ragweed should theoretically have an endpoint on a No. 4 dilution if tested for ragweed with IDT. However, due to sensitivity differences, comparisons of the RAST and IDT are *not* always linear.

Table 8–14 Preparation of RAST-Based Treatment Vial Using RAST Minus 1 Method*

RAST score	6	5	4	(3)	2	1
Corresponding endpoint titration	5 mm	5 mm	5 mm	(7 mm)	9 mm	
Corresponding IDT endpoint dilutions				(No. 3)		
RAST minus 1 adjustment			(No. 4)			
Dilution to put in the 5 mL treatment vial					(0.2 mL)	

*To the left is "minus"; therefore, a RAST score of 3 is assigned to an endpoint of 4 ("to the left of 3"), which will require the mixing of 0.2 mL of a No. 2 dilution (two dilutions to the right) for the 5-mL treatment vial.

Furthermore, legitimate safety concerns can be raised about injecting patients with antigens that have not been used to test them in an in vivo fashion. Therefore, a safe and conservative approach has been advocated for in vitro–based initial dosing called the "RAST minus 1" rule for preparation of in vitro–based immunotherapy treatment vials. The RAST minus 1 rule dictates that initial dosing is started at a strength that is one dilution *weaker* than the in vitro class score. As an example, if a patient has a RAST class 3 score for ragweed, then a No. 4 IDT endpoint is assigned for purposes of treatment vial mixing **(Tables 8–14, 8–15**, and **8–16)**.[1,2]

Table 8–15 "RAST Minus 1" Means Assigning an IDT Endpoint One Dilution Weaker than the RAST Score

Counts	RAST Class	Corresponding IDT EP in Theory	Corresponding IDT EP (R − 1) in Practice	Dilution to put in the Treatment Vial
250–500	0			
501–750	0/1			
751–1600	1	1	2	C
1601–3600	2	2	3	No. 1
3601–8000	3	3	4	No. 2
8001–18,000	4	4	5	No. 3
18,001–40,000	5	5	6	No. 4

Table 8–16 In Vitro Vial Preparation Using RAST Minus 1 Method

Allergen	In Vitro Class	RAST Minus 1 Adjustment	How to Mix the Treatment Vial
Antigen A	4	No. 5	0.2 mL No. 3
Antigen B	5	No. 6	0.2 mL No. 4
Antigen C	2	No. 3	0.2 mL No. 1

◆ Vial Safety Testing

Initial or starting immunotherapy doses can cause anaphylaxis for several reasons. First, it is possible to improperly calculate or mix the treatment vial. Second, during this initiation period, IgE antibodies increase unopposed prior to the increase in protective IgG blocking antibodies. And third, if such dosing has been derived from quantitative testing, then the clinician will in all likelihood begin therapy at stronger levels due to the confidence afforded in such testing. And when dosing is based on in vitro tests, it is important to remember that the patient has never been skin tested to the actual antigens that will be used in therapy. For these reasons and others, an intradermal safety vial test is recommended prior to the beginning of immunotherapy. This allows the clinician to assess the reaction locally prior to subjecting the patient to higher systemic exposure as occurs with a subcutaneous injection. Indications for the safety vial test include (1) any patient who is receiving immunotherapy for the first time; (2) in vitro–based first dose; (3) prick-based first dose; (4) MQT–based first dose; (5) when antigen contents have been changed in comparison to previous treatment vial; and (6) for any new treatment vial.

The safety vial test begins with appropriately placed and interpreted intradermal positive and negative controls. Then, using the treatment vial contents, raise a 4- to 5-mm intradermal wheal, identical to the test wheals utilized in intradermal testing **(Table 8–17)**. If the wheal resulting

Table 8–17 The Safety Immunotherapy Treatment Vial Test Technique

1. Produce a 4-mm wheal with the treatment vial solution and read after 10 minutes.
2. If wheal growth is $\leq$11 mm, give first dose (0.05 mL).
3. If wheal growth is 12–13 mm, wait at least 72 hours and then give first dose (0.05 mL).
4. If the resulting wheal is $>$13 mm, dilute the vial with 1 mL from the vial and 4 mL of diluent and either retest or give first dose from this new vial.
5. If multiple vial dilutions are required, it may be necessary to recheck the skin endpoints by partially retesting the patient.

from the vial test is too large, dilutions may be performed until a vial test resulting in an acceptable wheal size is found. If multiple vial dilutions are required, it may be wise to recheck the skin endpoints by partially retesting that patient.[1]

References

1. Haydon RC, Gordon B. Aerollergen injection immunotherapy. In: Gordon B, Krouse J, Derebery J, Chadwick S, eds. Allergy and Immunology: An Otolaryngic Approach. Philadelphia: Lippincott Williams & Wilkins, 2001
2. King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF. Vial Preparation and Immunotherapy. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2005:205 – 268
3. Mabry RL. Technique of skin endpoint titration. In: Mabry RL, ed. Skin Endpoint Titration, 2nd ed. New York: Thieme, 1994:32 – 36
4. King HC. Immunotherapy. An Otolaryngologist's Guide to Allergy. New York: Thieme, 1994:132 – 152
5. Krouse JH, Mabry RL. Skin testing for inhalant allergy: current strategies. Otolaryngol Head Neck Surg 2003; 129:S33 – S49

9

Immunotherapy Based on Quantitative Testing

Stephen J. Chadwick

Having identified the patient with allergy whose disease merits immunotherapy, it is time to commence that treatment. It is assumed that objective, quantitative testing via in vitro [modified radioallergosorbent test (RAST), etc.], or in vivo [intradermal dilutional testing (IDT), modified quantitative testing (MQT)] methods has been completed. Indications for the institution of immunotherapy have been established and met.

Antigen treatment vials have been prepared. This chapter gives a map for the initiation, escalation, maintenance, and discontinuance of immunotherapy. The approach is basic and very conservative, with safety in mind. Modifications from this protocol, expanded commentary on the subject matter presented, and complementary information on other forms of immunotherapy are beyond the scope of this chapter, yet may be found elsewhere.[2,3] Repetition and redundancy have been incorporated at times to reinforce important information. Treatment begins with the vial test.

◆ The Vial Test

The initiation of immunotherapy, administration of a starting dose and a subsequent dose escalation sequence should not take place without the successful completion of a vial test for each vial in the treatment set.

This is a safety and quality control measure. The vial test is a bioassay, an intradermal skin test performed on the patient using the mixture of antigens in the treatment vials of that specific patient, the content of which is based on the patient's responses to quantitative testing of those antigens. The vial test result must fall within a range previously observed to correlate with the likelihood of a safe response to the initial treatment dose. In the case of in vitro–based immunotherapy, the vial test is the *only* bioassay that is performed in the process of testing and initiation of treatment. *An appropriate response to a vial test is mandatory before initiating in vitro–based immunotherapy.* Although IDT and MQT have evolved from methodologies that infer safety in the initiation of subsequent immunotherapy, the added bioassay of the vial test as a safety measure is still advocated in these situations.

Even with the predictable safety of mRAST/ImmunoCap®-, IDT-, and MQT-based immunotherapy, unforeseen circumstances or possible errors during the act of testing and the transition to the initiation of immunotherapy raise potential safety concerns. First, the antigen used in the in vitro test is not exactly the same in potency or character as the same-named antigen used in the treatment vial, due to differences in manufacturing, state of the antigen, etc. Second, there may be a potential for synergistic, clinically adverse effects among some of the antigens when mixed in a treatment vial, an effect that would not be detectable or necessarily predictable at the time of individual antigen testing. Changes in the season, and therefore changes in patient sensitivity, between the time of testing and the initiation of treatment may occur. Technician or equipment error in testing is always possible, as are errors in the storing and mixing of antigens. Unrecognized concomitant food or drug sensitivity may make a patient less tolerant of a dose of immunotherapy. Some individuals may develop a nonspecific hyperreactive state due to environmental or other disease processes/conditions, adversely impacting immunotherapy. These are the patients who just seem to react to everything: odors, multiple foods, and drugs, etc. Considering all the above, it is evident that the vial test represents a useful tool to ensure safety in immunotherapy.

Conventional subcutaneous injection immunotherapy typically involves periodic injections from one or more patient-specific treatment vials of antigen(s). A vial test should be performed for each treatment vial before treatment dosing is initiated and subsequently escalated. *The ability to perform IDT, even if the clinician is an in vitro allergist, is a prerequisite for performing the vial test because the performance of the test and subsequent resolution of an abnormal result requires IDT skills.*

The vial test is performed as follows. A 4-mm intradermal wheal is raised using a small volume of antigen (usually 0.01 mL) from the treatment vial being tested. Remember to apply both positive (histamine) and negative (diluent) controls at the same time. The technique is described elsewhere.[2–4,7] After 10 minutes, the size of the vial test wheal is measured. A wheal diameter of 13 mm or less is a passing (acceptable) response. A first immunotherapeutic injection from this vial is now predictably safe. That being said, any time a treatment injection is given, the materials, equipment, and expertise for treating adverse reactions, including anaphylaxis, should be in place, and the patient should be observed for an appropriate amount of time as described elsewhere.[5,6] Most authorities consider the antigen quantity applied during an acceptable vial test (producing a wheal of 12 or 13 mm) to constitute the first dose in the treatment escalation scheme. Others would allow an additional 0.05 mL of antigen to be given subcutaneously (SC) on the vial testing day if the vial test result is 11 mm or less.[2,3] I prefer the more conservative approach, especially for novice clinicians, of simply commencing treatment with 0.05 mL of the treatment vial 5 to 7 days after the vial test is administered.

What if the result of the vial test is unacceptable? If the resultant wheal is greater than 13 mm in diameter, a satisfactory margin of safety cannot be predicted based on the antigen vial as it has been prepared. When the initial vial test result is greater than 13 mm, one may simply repeat the test 48 to 72 hours later. If the initial unacceptable test is due to a time-limited, concomitant, or synergistic effect of inhalant allergen, food sensitivity, chemical sensitivity, technical error in doing the vial test, or associated physical or disease-related condition(s), the repeat test *may be* acceptable and commencement of immunotherapy is predictably safe. This situation has been compared with the "flash response" in abnormal IDT whealing patterns described elsewhere.[7,8] If the wheal resulting from the repeat test is still greater than 13 mm in diameter, the patient should be tested with a fivefold weaker dilution, and successive fivefold weaker dilutions of the treatment vial if necessary, until an acceptable result (13 mm or less) is found. This IDT-like approach has been called *titrating the vial*. I believe the subsequent weaker test(s) should be done up to 96 hours after each preceding test(s) to minimize possible adverse effects due to antigen loading. If the problem with the initial vial test is one of antigen potentiation due to an additive effect on potency in the antigen mix (synergy), an acceptable fivefold dilutional mix of the initial vial should be found and therapy can then commence with a predictable safety. If this does not produce an acceptable result, or if at any time

there is a question of the accuracy in the mixing of the initial treatment vial, the in vitro or in vivo diagnostic testing results should be reviewed. The vial should be mixed again, and, for the sake of safety, the vial test performed at a fivefold weaker dilution.

If the above algorithm fails to produce an acceptable result, the patient should be retested for each individual antigen. The safest and most definitive way to do this is to repeat the diagnostic testing for each antigen in the vial using IDT. This automatically overcomes any differences between IDT and MQT for exact determination of endpoint, and it will show any disparity between m-RAST/ImmunoCap and their correlation with skin endpoint. Alternatively, if the initial antigen evaluation was by means of an in vitro quantitative test, repeating the in vitro test may reveal a different result (perhaps a seasonal variation) and lead to a revised antigen mix in the treatment vial. If not, then IDT should be performed as noted above. Mabry[9] describes a similar approach called *incremental vial testing*, which is less time- and resource-intensive for evaluation of endpoints via IDT. This process involves educated extrapolations from the initial endpoints. This may save some testing of the progressing dilutions leading to an endpoint. The relevance and accuracy of the method's results still must be shown with the subsequent vial test of the new treatment vial. I refer the more experienced clinician to the cited references for a more complete description.[2,9] No matter what method is used to arrive at a new treatment vial, a vial test result must be acceptable before treatment is started.

Lastly, *if an urticarial or systemic response occurs with a vial test*, a review is necessary of the patient, the history, the diagnostic antigen testing, the mixing and administration, indeed the whole path of diagnosis leading to treatment. Even after correction of any problem(s) and subsequent acceptable results on a vial test, the indication and decision for pursuing immunotherapy should be reconsidered.

◆ Initial Dosing

At this point, all of the patient's treatment vials have produced acceptable vial test results (i.e., 13 mm or smaller wheal). A conservative 5 to 7 days have passed and it is now time to give the initial dose from each vial. When giving any immunotherapy injection, the patient should not be acutely ill or unstable in any way. Vigorous exercise the day of the injection(s) should not be permitted, either pre- or postinjection(s), as this may increase the risk of adverse reaction. The blood pressure should be acceptable and asthmatics should not be in any distress or below their

usual forced expiratory volume in 1 second (FEV_1). The initial dose is 0.05 mL SC of extract from each treatment vial(s), at separate sites if more than one vial is used. Injections are usually made in the posterior portion of the arm(s) over the triceps. If an injection is mistakenly given intramuscularly (IM) rather than SC, the result will be pain and most likely a locally symptomatic induration. The patient should remain in the office to be monitored for 20 to 30 minute after the injection(s). Having patients wait in an area where their activity can be observed, a place in which the nurse can talk with them as necessary, is advisable. When adverse reactions occur, the shorter the time interval between the injection(s) and the onset of symptoms, the greater is the tendency for severity of the reaction. Although some authorities have advocated up to 1 to 2 hours observation, 20 minutes has been shown to be usually adequate and is the currently recommended minimum.[2] If the patient was initially tested with IDT, the amount of antigen given during the testing to produce an endpoint wheal and a subsequent confirming wheal is greater in volume and total concentration of antigen than the 0.05 mL given as the initial treatment dose. This adds another layer of safety in addition to the vial test. Before the patient leaves the office, the nurse should check the size of any local swelling, and note the production of any local reaction or symptoms, to help confirm the appropriateness and safety of the dosing. The patient should be instructed to report any subsequent adverse symptoms, and if need be, to seek emergent help in the rare case of a severe, delayed response. Even if the patient makes no such reports, an inquiry at the time of the next visit should be standard practice.

In the initial escalation scheme, injection sessions subsequent to the initial dosing occur once or twice a week (at least 3 to 4 days apart). In the manner and setting noted above, the subsequent doses are conservatively increased by 0.05 mL per vial, per session, until a dose of 0.50 mL SC per vial is attained. Typically, escalation occurs in this fashion: 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50 mL **(Table 9–1)**.[1] This is a conservative initial escalation scheme that may be used by veteran and novice clinicians alike, ensuring a high standard of safety. With experience, in a nonbrittle, low-reacting, nonasthmatic patient, not in any high sensitivity season, and after all due consideration, a more rapid escalation schedule might be chosen in the initial escalation scheme only. Such a scheme could proceed thusly: 0.05, 0.10, 0.20, 0.30, 0.40, 0.45, 0.50 mL.

Rush immunotherapy is a term applied to a protocol of rapid desensitization over a short period of time, ranging from hours to days depending on the protocol. These methods involve techniques and immunotherapy

Table 9–1 The Initial Treatment Set

Injection	Amount (cc)
1	0.05
2	0.10
3	0.15
4	0.20
5	0.25
6	0.30
7	0.35
8	0.40
9	0.45
10	0.50

From Ward WA. Immunotherapy dosage based on skin endpoint titration. In: Mabry RL, ed. Skin Endpoint Titration. New York: Thieme, 1992:40, with permission.[1]

sequences different from those described in this book.[3] Safety should always be the first priority of the clinician. Any type of rapid or rush escalation scheme saves time and materials, but at the expense of increased risk, which must be acceptable before proceeding.

Some definitions are needed to clarify the direction and expected outcomes of further escalation beyond the initial series of doses. A *symptom-relieving dose* is a dose that generally relieves the allergic symptoms for a period of a week. The *maximally tolerated dose* is a known or predicted dose at which further escalation will produce a significant adverse reaction. The *optimal treatment dose* is a dose that approaches the maximally tolerated dose, is a conservative ideal for maintaining potent immunotherapy, and usually does not have to be changed with fluctuations in patient sensitivity. This optimal treatment dose usually relieves symptoms while producing a local reaction that is no more than 25 to 30 mm in diameter, not present for more than 24 to 48 hours, and is not associated with other local or systemic symptoms. A dose causing a 30-mm local reaction indicates that further advancement at that time may produce adverse reactions. This may signal a *maximally tolerated dose.*

The *maintenance dose* is the dose required for the remainder of the course of immunotherapy to elicit the favorably preserved, immune response for desensitization. This dose (often the optimal dose) is usually beyond the symptom-relieving dose and less than or equal to the maximally tolerated dose. Conservative maintenance immunotherapy uses an optimal treatment dose, whereas more aggressive therapy pushes the maximally tolerated dose. I prefer the optimal treatment dose as a maintenance dose, if possible, as it provides a greater margin of safety with

less need for periodic up- or downregulation.[3] The goal of dose escalation is to establish a true maintenance dose of sufficient antigenic volume and concentration to allow, over a period of time, for the immune changes necessary to effect a prolonged state of desensitization and symptom relief or maximal improvement. Usually this requires the vast majority of the antigen concentrations used in the vials to eventually, and safely, to be mixed from concentrations of dilution No. 1 or concentrates, with an injection interval span of 2 to 3 weeks, and over an average therapy span of 3 to 5 years.[2,3] Symptom relief is always the goal, but in reality, chronic "allergic" rhinitis is not always purely allergic in origin. Therefore, there are situations when nonallergic stimuli will continue to produce less than total relief outcomes. Examples would be of the allergic patient who cannot totally avoid cigarette smoke, or the patient with recalcitrant vasomotor (idiopathic) triggers. Without these exposures or triggers, the patient may have total relief of his/her allergic symptoms with appropriately maintained immunotherapy, but with them, may be only improved. It is possible, although unusual, for the patient to reach a maximally tolerated dose at the end of the escalation of the initial vial. If this occurs, the clinician should reevaluate the diagnosis-to-management pathway, and seek an explanation of this occurrence.

◆ Subsequent Escalation

Having successfully completed the initial escalation scheme with the patient tolerating 0.50 mL SC from the initial treatment vial(s), dose escalation is now continued by mixing treatment vial(s) No. 2 with the same antigens, fivefold stronger than the concentrations used in the first, or initial, treatment vial(s). For example, if dilution No. 2 of antigen A was used in mixing the initial treatment vial, dilution No. 1 of antigen A would be used in mixing treatment vial No. 2. Adding the diluent would be the same as before, and as described elsewhere. Mathematically and pharmacologically, because fivefold dilutions are involved, 0.10 mL of vial No. 2 is the same concentration (only in a different volume) as 0.50 mL of vial No. 1, the initial treatment vial. Therefore, the patient who tolerated 0.5 mL of the initial vial will receive the same amount of antigen in 0.10 mL of the next vial, vial No. 2. However, it is strongly recommended that continuing therapy from vial No. 2 should be preceded by a vial test, and that the test should be initiated in the allergist's office, even if the patient normally gets his/her injections at another physician's office or is on home immunotherapy. Realize that a vial test wheal >13 mm, with no

local or systemic symptoms, could result for any of the possible reasons previously reviewed, or be due to the higher concentrations of antigen and glycerin in vial No. 2. After safety concerns have been satisfied, the clinician may cautiously continue escalation by starting with an injection of 0.05 mL from vial No. 2. Starting with 0.05 mL from vial No. 2 rather than 0.10 mL is another safety measure against potential changes of reactivity in the fivefold, up-concentrated vial No. 2, which is fresher than the preceding vial and could conceivably be slightly more antigenic. The dosing is escalated by 0.05 mL per injection session as described before: 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50 mL.

The transition between subsequent, successive treatment vials (i.e., vial No. 3, vial No. 4, etc., if needed) will be the same in principle. There may be one or more different antigenic vials in the initial treatment set. Each vial may undergo a successive number of remixes into new vials of higher antigenic potency until a maintenance dose for each group of antigens is found and continued. Antigens may be grouped into separate vials of high reactors and low reactors, or as I prefer, into perennial, spring seasonal, fall seasonal, and any other select groups for which the clinician wishes to exert a more controlled, tailored, time-efficient escalation. In the latter case, for example, a spring vial could be advanced during the fall season safely, whereas a bottle of highly reactive antigens consisting of spring and fall pollens may cause an adverse reaction if escalated during the fall season. This wastes time, which could be used to escalate the spring pollen in the bottle. If antigens are divided into high- and low-reactor bottles, as the high reactors are escalated, the changing concentrations will eventually allow the antigens in the initial high-reactor bottle to be combined with those in the low-reactor bottle as their concentrations come closer together. As doses and concentrations are escalated, eventually local reactions or symptom relief will occur.

A local, subcutaneous induration or swelling of 25 mm at the injection site, without any urticaria or systemic symptoms, resolving in 24 to 48 hours, is generally an indication that the maintenance dose for that vial is near. The dose producing such a response may be an optimal treatment dose. A response of 30 mm is an indicator that further escalation may produce an adverse reaction. This probably represents a maximally tolerated dose. Any dose that produces urticaria or a systemic reaction is a nontolerated dose and presents a red flag indicating a need to stop escalation. Always reevaluate the diagnosis-to-management process when a systemic reaction has occurred. The dosage should be reduced to one producing no more than a 25-mm transient swelling and no urticaria or systemic symptoms. The safest way to do this is to vial test the patient again with a new, remixed, error-corrected vial producing an acceptable

result with no systemic symptoms or urticaria. Then start escalation at a dose of 0.05 mL SC.

Symptom relief after an injection (symptom relieving dose) may occur as doses are escalated, with or without the transient 25-mm injection site(s) swelling. The maintenance dose is usually higher than the dose that first produces symptom relief. As the maintenance dose is approached, the patient will usually have symptom relief lasting for a week, plus a transient 25-mm swelling (optimal treatment dose). When this occurs, and the majority of antigen concentrations used to mix the vial(s) are of a No. 2 concentration or more potent (usually No. 1 or concentrate), the maintenance dose has been achieved. As discussed earlier, there are occasions in which total symptom relief is not achieved with immunotherapy alone. When this occurs, and no problem is found with the composition of the immunotherapy, the maintenance dose will be just below the maximally tolerated dose, that is, an optimal treatment dose.

Once the maintenance dose has been established, this dose should be given once a week for a year, that is, throughout all of the seasons. Factors such as seasonal changes, dietary variation, other illnesses, etc., may cause a shift in the patient's sensitivity, requiring some change in the patient's dosing from time to time. After a year of well-tolerated, symptom relieving/improving weekly injection(s), the immunotherapy interval may be increased to 2-week and then to 3-week intervals. If the patient misses a dose and the time interval has been 3 weeks or less, usually there need be no dosage reduction when resuming immunotherapy. If the time since the last dose is up to 6 weeks, the last tolerated dose should be halved, and then escalation may proceed in increasing 0.05-mL increments at the patient's usual interval. If the lapse has been more than 6 weeks, the patient should pass a vial test and then have immunotherapy begun at 0.05 mL. If a patient misses injection(s) for over 3 months or into another season, I advocate retesting.

Once a patient has safely continued to have good results from injections at 2- to 3-week intervals, and has been on therapy for 3 to 5 years, consideration may be given to discontinuing immunotherapy. This is usually done after the patient's historically most significant season has passed with no significant problems. If symptoms return within 2 months of stopping the injections, the patient may be vial tested from the most recent vial(s), and if the result is acceptable, therapy may be restarted at a lower dose (usually the previous maintenance dose). The most conservative approach would be to restart escalation at 0.05 mL per vial(s) from the vial giving the acceptable vial test. If the current vial(s) has expired, and the season has not changed, then a new vial(s) must be made, and a vial test(s) performed. If the vial test is unacceptable, then

the algorithm described earlier should be followed. Longer periods between cessation of therapy and resumption require retesting, and perhaps starting the desensitization process over again.

If the clinician is faithful to the process described in this chapter, he or she may have confidence that the immunotherapy provided will be both conservative and as safe as possible.

◆ Acknowledgments

The author wishes to thank Ms. Karen Stoner, chief librarian of the Decatur Memorial Hospital Systems Medical Library, and Mr. George Smaistrla Jr., administrator for ENTA Allergy, Head & Neck Institute, for their help. Most importantly the author never presumes, and is always thankful for, the patience and support of his wife, Melinda, and his son, Nicholson, with whom his time is divided with Vanderbilt University.

References

1. Ward WA. Immunotherapy dosage based on skin endpoint titration. In: Mabry RL, ed. Skin Endpoint Titration. AAOA Monograph Series. New York: Thieme, 1992
2. Vial preparation and immunotherapy. In: King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF, eds. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2005
3. Haydon RC, Gordon BR. Aeroallergen immunotherapy. In: Krouse JH, Chadwick SJ, Gordon BR, Derebery MJ, eds. Allergy and Immunology—An Otolaryngic Approach. Philadelphia: Lippincott Williams & Wilkins, 2002
4. Blending skin testing and in vitro testing in clinical practice. In: King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF, eds. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2005
5. Gordon BR. Anaphylaxis: prevention and treatment. In: Krouse JH, Chadwick SJ, Gordon BR, Derebery MJ, eds. Allergy and Immunology—An Otolaryngic Approach. Philadelphia: Lippincott Williams & Wilkins, 2002
6. Allergic emergencies. In: King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF, eds. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2005
7. Testing methods for inhalant allergy. In: King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF, eds. Allergy in ENT Practice: The Basic Guide, 2nd ed. New York: Thieme, 2005
8. Fornadley JA. Skin testing in the diagnosis of inhalant allergy. In: Krouse JH, Chadwick SJ, Gordon BR, Derebery MJ, eds. Allergy and Immunology—An Otolaryngic Approach. Philadelphia: Lippincott Williams & Wilkins, 2002
9. Mabry RL. Blending skin endpoint titration and in vitro methods in clinical practice. Otolaryngol Clin North Am 1992;25:61–70

10

Prevention and Management of Anaphylaxis

Bruce R. Gordon

Note: Because emergency treatments often change, do not use this chapter as an inflexible treatment guide. Instead, use multiple reference sources to broaden and constantly update your knowledge.

There are about 500 anaphylaxis deaths annually in the United States,[1] and about one case per 3500 persons per year, with a fatality rate of 3%.[2] Frequent causes are food, insect sting, drugs, and exercise.[3,4] Fortunately, anaphylaxis rarely occurs during allergy management,[5] with major systemic reactions occurring after only 0.005% of immunotherapy injections.[6] This very low reaction rate is largely due to the safety of quantitative testing techniques[7] such as intradermal titration (IDT),[7] in vitro tests,[8,9] the intracutaneous progressive dilution food test (IPDFT),[10] and the use of immunotherapy based on these methods.[11] It is more likely that anaphylaxis treatment knowledge will be used to treat acute asthma, food or drug reactions, and insect stings than reactions from allergy testing or treatment.

◆ Time is Critical

Quick, positive action is needed to manage anaphylaxis. Pumphrey[12] carefully investigated all fatal anaphylaxis cases in the United Kingdom from 1992 to 1999 to evaluate treatment details. He found that anaphylaxis deaths had been underreported, and that half the deaths were iatrogenic, with the rest about equally divided between food and insect stings. In most cases, food reactions caused asthma flares, resulting in respiratory arrest. Hypotensive shock was common with stings (in one half of cases) and iatrogenic anaphylaxis (in one third of cases). Previously unappre-

ciated was how very rapidly anaphylaxis victims progress to respiratory or cardiac arrest. Median times to arrest were 30 minutes for foods, 15 minutes after stings, and only 5 minutes in iatrogenic situations.

◆ Prevention of Reactions

Diagnosis and Treatment

Excessive antigen exposure is the most common reason for anaphylaxis.[11] This can arise from immunotherapy during peak pollen[13] or mold[14] seasons, or with any high allergen exposure.[15] Overdoses also may arise from inexperience,[16] error, skin testing an excessive number of antigens at one time, or by starting immunotherapy at too high a dose. The great advantage of quantitative testing methods is that accurate measurement of the patient's degree of sensitivity to each allergen[17] allows the preparation of a treatment mix and initiation of treatment, with a high degree of confidence that injections will not result in an overdose reaction.[18] The use of glycerin preservative, refrigeration, and dated treatment vials help to reduce variations in potency, which may also be a source of error. During immunotherapy, excess antigen may be administered,[6,14] by either too rapid an escalation or too frequent dosing.[14] When immunotherapy is administered at home or in the office of a physician who is not specially trained in allergy, additional safety measures should be considered.[6] Finally, errors in patient identification, dose calculations, diluting, mixing, or injecting may result in reactions.[6,19,20] These issues are thoroughly discussed in the immunotherapy safety study by Hurst et al.[6]

Potent Antigens

Cottonseed, flaxseed, castor bean, peanut, insect venoms, pollens in season (especially grass), and any allergen the patient suspects of causing previous reactions have a high risk,[20] and testing with these antigens should be performed with caution. Screening tests at a high dilution, or the use of in vitro tests, is recommended before proceeding.[21]

Sensitive Patients

Caution and a conservative approach are urged when dealing with highly sensitive patients,[13,22] such as children,[23] patients with a history of prior

anaphylaxis,[13] those taking a beta-blocking agent,[22] and patients with uncontrolled asthma.[6,15]

In Vivo Safety Test (Vial Test)

A vial test is useful as a safety check before administering any allergy treatment mix.[24] This initial skin test from the treatment vial (before starting dose escalation) must always be done when therapy is based on in vitro testing. Some physicians always use a vial test for the first dose from any vial.

◆ Diagnosis of Reactions

Nonallergic Events

Some ailments resemble anaphylaxis.[2,25,26] These include anxiety, flushing, hypoglycemia, arrhythmia, angina, myocardial infarction, transient ischemic attack, seizure, hereditary angioedema, airway obstruction, and acute pulmonary embolism. If any significant symptoms occur in the hours following antigen exposure **(Fig. 10–1)**, prompt medical evaluation is recommended,[27,28] to establish a diagnosis and render appropriate treatment.

Vasovagal Events

Most allergy-related reactions fall into three categories: vasovagal events, delayed allergic reactions, and immediate allergic reactions. Vasovagal events are common reactions that are not themselves dangerous but that must be quickly diagnosed to differentiate them from anaphylaxis. The predominant features of vasovagal attacks are pale skin, cold sweats, slow pulse, and normal blood pressure (BP) when recumbent. On the other hand, the features of anaphylaxis are usually opposite to those of a vasovagal event. The skin is red or flushed, warm, and dry, and there is a rapid pulse and a low recumbent BP. In addition, anaphylaxis patients often demonstrate itching or respiratory distress early in the reaction, but these are not seen during vasovagal events. Anxious patients can appear to have respiratory distress due to hyperventilation. Close examination of the skin is important, because over 90% of anaphylaxis patients develop skin urticaria, angioedema, or pruritus,[29] and do not generally demonstrate diaphoresis. Cyanosis or pallor may develop

Reactions to Allergy Shots

The techniques we use for testing for the presence and degree of sensitivity to an allergen, and the way in which dosage is advanced, make a reaction to an allergy injection unlikely. However, this information is furnished to make your treatment even safer. Please read it carefully, call us if you have questions, and *keep this sheet where it can be easily found if you need it*.

To treat a possible reaction, you will need an *antihistamine* and *epinephrine*. Please make sure you have these on hand, and nearby before giving your shot. Any antihistamine, either prescription or over-the-counter, will do. Examples are Allegra, Zyrtec, Clarinex, Claritin, ChlorTrimeton, or Benadryl. Epinephrine is available in an automatic injection form called EpiPen or EpiPen Jr. You will receive a prescription to purchase one of these and will be taught how to use it. It is unlikely that you will ever need it, but *it must be available when you receive your allergy shot*. Don't forget to check the expiration date from time to time, and keep it at room temperature (heat and freezing destroy potency).

The combination of an allergy shot with higher than usual allergen exposure may sometimes result in a *local reaction*, which is an area of firmness (not necessarily redness) at the injection site, which is larger than a 50-cent coin, and which persists for at least 24 hours. Redness and/or firmness can also be due to a complicating infection, or to a reaction to glycerin in the mixture. If a local reaction around an injection site occurs, take an antihistamine, and be sure to *report this to the nurse before your next injection, for dosage adjustment if necessary*.

A true *severe reaction* must be treated immediately. It begins within a few minutes to an hour of the injection, usually with intense itching of the throat, nose, and chest membranes. If this occurs, take an antihistamine immediately. If this progresses to any swelling of the face, swelling of the throat, difficulty swallowing or breathing, generalized itching or redness of the body, especially if accompanied with a feeling of distress, *immediately administer one dose of epinephrine*, injecting into the muscle of your thigh. Be certain to wait about 30 seconds after triggering the Epi-Pen before removing the device from your thigh, to allow time for a spring to push the epinephrine injection into your muscle. Put a tourniquet (belt, etc.) above the place where you gave the allergy shot, to slow the absorption of the material into the system. *If it is necessary to administer epinephrine, call 911 and go immediately by ambulance to the Emergency Room*, where you can receive medical attention while contact is made with your doctor.

Fig. 10–1 Sample patient handout.

Table 10–1 Comparison of Signs and Symptoms: Vasovagal Events and Anaphylaxis.

Sign or Symptom	Vasovagal Event	Anaphylaxis
Pulse	Slow	Fast*
Blood pressure (recumbent)	Normal	Usually low
Feeling of impending doom	Absent	May be present
Itching, urticaria, or edema	Absent	Usually present
Skin color/temperature	Pale/cool	Red/warm**
Sweating	Present	Absent
Respiratory distress	Absent†	May be present
Cough or wheeze	Absent	May be present

*May be slow with beta-blockade.
**Cyanosis or pallor may develop subsequently.
†May be tachypneic due to anxiety.

later in anaphylaxis.[1] Some vasovagal patients lose consciousness, experience seizures, or develop bradyarrhythmia, but these patients always recover rapidly when placed in a head-down position. The differential between anaphylaxis and a vasovagal event may be particularly difficult in patients who are taking beta-blockers, or patients with a large local or general allergic reaction and panic or anxiety. **Table 10–1** compares the signs and symptoms of anaphylaxis and vasovagal events.

Anaphylactoid Reactions

Allergic mediators, or substances capable of releasing allergic mediators, may be released without actual allergen exposure, triggering anaphylaxis. This is called an *anaphylactoid reaction*. Common anaphylactoid triggers are scombroid fish poisoning, narcotics, vancomycin, anesthetics, muscle depolarizing drugs, hyperosmolar solutions, and radiologic contrast agents. Contrast agents cause about one anaphylactoid reaction for every 5000 exposures,[25] whereas anaphylactoid reactions during general anesthesia occur in from one in 6000 to one in 20,000 cases.[30] Anaphylactoid reactions present in the same way, and are treated exactly like allergen-induced anaphylaxis.[29]

Delayed Allergic Reactions

Skin test or immunotherapy injection wheals may enlarge or reappear after 6 or more hours,[31] and such delayed reactions may require a reduction in

dosage. Delayed systemic reactions, usually in the form of worsening of preexisting allergic symptoms, also are possible. Delayed systemic reactions require both symptomatic treatment of the event and subsequent dose reduction. Unless asthma is provoked by these late reactions, emergency treatment is seldom necessary. However, especially in the case of reactions to food, in rare instances there may be a delay of up to 6 hours before symptoms worsen to a serious level.[12]

Immediate Allergic Reactions

There are four types of immediate reactions: local, large (severe) local, generalized (systemic), and anaphylaxis. These reactions differ in their degree of severity, and only anaphylaxis is life threatening. Reactions may occur within seconds, minutes, or up to several hours following antigen exposure.[32] As already noted, iatrogenic cases (immunotherapy, skin tests, drugs, anesthesia) are likely to result in cardiopulmonary arrest within minutes.

Local Reactions

Local reactions are frequent normal events during allergy treatment, and are characterized by local itching, erythema, or swelling smaller than a half-dollar coin (3 cm) in diameter.

Large Local Reactions

These reactions vary from silver-dollar–sized (4 cm) indurated areas to swelling of the whole upper arm, and usually indicate an antigen overdose or strong contemporaneous environmental exposure. Successful immunotherapy need not include the production of large local reactions,[33] and when these are encountered, they indicate a need to reduce the antigen dosage.

Generalized (Systemic) Reactions

These reactions may manifest themselves as exacerbation of preexisting allergic symptoms, bronchospasm, urticaria, or angioedema. These reactions correspond to grade I or II in the classification of Müller.[34] They occur when the patient is already experiencing a high antigen exposure, and testing or treatment add sufficient antigen to exceed the symptom-producing threshold. Although generalized reactions usually do not progress to anaphylaxis, they do require symptomatic treatment and

careful observation. Even if anaphylaxis does not occur, a general reaction may initiate a dangerous late-phase asthma flare within 6 to 8 hours.[35]

Anaphylaxis

True anaphylaxis, Müller grades III to IV, may begin like a generalized reaction, and then rapidly evolve to cardiopulmonary collapse. Early marked exacerbation of allergic symptoms, especially nasal, throat, and ocular itching, facial flushing, and throat tightness,[36] are usually accompanied by *tachycardia*, a normally reliable sign of anaphylaxis.[37] Tachycardia may not occur in patients receiving β-adrenergic blocking agents.[38] Other common symptoms of anaphylaxis are wheezing, cough, urticaria, pruritus, angioedema, or a feeling of impending doom ("angor animi"). Less often, confusion, diarrhea, cramps, vomiting, and urinary urgency develop. Severe asthma, oral or laryngeal edema, hypotension, and arrhythmias may precede cardiovascular collapse. Most cases progress to respiratory obstruction or shock,[38] with arrest occurring in as little as 1 minute, unless appropriate measures are rapidly undertaken.[12]

Biphasic Anaphylaxis

In general, the longer the delay from exposure to onset of anaphylaxis, the less severe the reaction. In two studies, the initial symptoms of anaphylaxis symptoms always occurred within 60 minutes of parenteral antigen exposure.[35] However, because of slow absorption of antigens after oral exposure, anaphylaxis symptoms due to drugs or foods may not begin to occur until 6 hours after ingestion of the offending substance.[12,39] At a median time of 8 hours after initial treatment, 5 to 20% of anaphylaxis patients may relapse into protracted late-phase reactions, including oral, laryngeal, or pulmonary edema, hemorrhage, shock, and severe asthma.[39,40] These cases are initially indistinguishable from patients who do not relapse,[41] and because of this possibility, after stabilization, one should always consider hospitalization for observation of patients experiencing anaphylaxis.[38]

◆ Being Prepared to Treat Anaphylaxis

Every allergy office, even one within a hospital, and each patient must be ready to handle the first minutes of anaphylaxis **(Fig. 10-1).** The physician's

responsibility is to make a proper diagnosis rapidly, initiate treatment, and then stabilize the patient for transport. The basic measures are administering epinephrine without delay, ensuring airway support, and instituting cardiopulmonary resuscitation (CPR). Epinephrine must be immediately available, either in commercial kits or prefilled syringes, and all personnel should be trained and authorized in its use. All anaphylaxis patients must be given intramuscular (IM) epinephrine as quickly as possible. Early use of epinephrine was the most critical survival factor in Pumphrey's[12] study, in which only 14% of patients who died from anaphylaxis had received epinephrine before cardiopulmonary arrest.

Second only to administration of epinephrine is the maintenance of an airway. This may require only the use of bronchodilators, but the office staff should be prepared to perform either intubation or tracheotomy, with administration of oxygen under pressure. Three quarters of anaphylaxis victims die from hypoxia due to airway edema or asthma.[42] Thus, equipment and training for establishing an airway are paramount.

Third, because failure to institute CPR when needed is a recognized error,[38] one must consider CPR training for all personnel. Physicians and nursing supervisors should consider obtaining advanced cardiac life support (ACLS) certification.[27] One quarter of anaphylaxis fatalities occur from circulatory failure; therefore, rapid volume replacement, pressor support, and effective CPR are critical. Finally, how extensive other preparations must be depends on the practice's geographic location. Rural practitioners, without nearby hospital facilities, may need to function at an advanced level. Readiness drills before anaphylaxis strikes are useful for evaluating readiness of supplies and personnel, and for maintaining familiarity with emergency plans.

◆ Drug Interactions Complicating Anaphylaxis

Beta-Blockers

Beta-adrenergic blockers[43] affect anaphylaxis adversely in two ways. First, beta-blockade is proallergic, it and reduces the effectiveness of anaphylaxis therapy.[44] In addition, beta-blockade, especially that produced by noncardioselective drugs, may cause a hypertensive crisis due to unopposed β-adrenergic effects of epinephrine.[39] Beta-blockade increases the risk of reactions to radiocontrast material by about threefold,[45] and it probably has similar effects on allergic anaphylaxis. Beta-1 selective beta-blockers are less likely to trigger asthma, but are otherwise still proallergic,[43] as well as interfering with anaphylaxis treatment.

Tricyclic and Monoamine Oxidase (MAO) Inhibitor Antidepressants

Tricyclics block the reuptake of catecholamines.[46] MAO inhibitors prevent degradation of catecholamines.[7,47] In both cases, it is necessary to utilize reduced epinephrine or dopamine doses, and to closely monitor patients for the development of hypertension when such drugs are employed.

◆ Recommended Emergency Drugs and Supplies

The supplies that should be on hand to manage anaphylaxis depend on many factors, especially the distance of the office from hospital care. Several lists of recommended drugs and supplies have been published,[27,29,48,49] but these should be modified to suit the needs of each office, as follows:

1. Monitoring equipment: Every office should have a sphygmomanometer and stethoscope. In addition, one may consider having on hand an oximeter, and an electrocardiograph (ECG)/defibrillator or an automated external defibrillator (AED). Early monitoring of pulse and BP is important in distinguishing a vasovagal reaction from true anaphylaxis. Once epinephrine is given, continuous monitoring of vital signs is critical.
2. Epinephrine 1:1000 (1 mg/cc): This is the single most valuable drug in the management of anaphylaxis.[37] It should be immediately available in the office, as well as in homes where it may be needed.[3,50] At the first suspicion of anaphylaxis, administer epinephrine. A prolonged resuscitation effort or a fatal outcome is generally the result when epinephrine is not used early in the reaction.[1,12,38] The Canadian Laboratory Centre for Disease Control states, "Failure to use epinephrine promptly is more dangerous than using it improperly,"[51] and, according to the United Kingdom Resuscitation Council, "Epinephrine is greatly under-used...and, when given intramuscularly is very safe."[1] However, despite the critical role of epinephrine, it should be used carefully, because administration of too large a dose, or intravenous administration too rapidly or in too concentrated a form can be fatal.[12,52]
    a. Adult use: Prefilled 0.3-cc dual-dose syringes (Ana-Kit, Hollister-Stier, Spokane, Washington) or self-injecting 0.3- or 0.15-cc syringes (EpiPen, EpiPen Jr., Dey Laboratories, Napa, California) of

epinephrine are recommended because they can be used quickly. The usual adult dose is 0.3 to 1.0 cc (0.3 to 1.0 mg) intramuscular (IM). The English consensus recommendation is to use 0.5 cc IM.[1] IM use is always preferred because of more rapid action than with subcutaneous (SC) administration.[1,51,53]

b. Pediatric use: The usual IM pediatric dose of epinephrine is 0.01 cc/kg (up to 0.3 to 0.5 cc maximum).[53] To accurately measure the small doses required for infants, 1:1000 weight per volume (w/v) epinephrine should be diluted 1:10 before administration. Because of variable absorption in this age group,[53] additional epinephrine may be required, although this will require careful monitoring. Epinephrine 1:1000 w/v can also be given intratracheally, 0.1 cc/kg.[46]
c. Reduced doses: Older patients, especially those with arteriosclerosis or hypertension, may not tolerate the usual adult dose of epinephrine. In this group, it may be necessary to start at a dose of 0.2 cc.[27]
d. Beta-blockers: Persons taking beta-blockers may require more epinephrine than usual to counter anaphylaxis, but giving multiple doses to these patients may also cause hypertension. Therefore, careful monitoring is needed in these situations.
e. Inhaled epinephrine: Epinephrine can be administered by metered dose inhaler (over-the-counter brands) provided the patient is able to inspire deeply. Ten to 15 puffs in a child, or $>$20 puffs in an adult, produce blood epinephrine levels similar to those seen with recommended IM doses.[3]
f. Repeated doses: In adults epinephrine is rapidly inactivated. A single dose is clinically effective for only about 3 to 5 minutes. Don't hesitate to repeat epinephrine, with monitoring, every 3 to 5 minutes until the patient is clinically stable.[1,46] In children, the half-life of epinephrine is about 40 minutes.[53] It is necessary to monitor to determine the need for subsequent doses.
g. Shock: In circulatory collapse, epinephrine *(always diluted to 1:10,000 or 1:100,000)* must be given centrally via intravenous (IV)[54] or endotracheal routes.[46] If no airway or IV access has been established, it may be given IM into the tongue, or via a transtracheal puncture. Epinephrine should be administered IV only to treat immediately life-threatening shock. The initial IV dose (children or adults) is 5 μg/kg,[54] up to a maximum adult dose of 1 mg in 10 cc.[46] Give half the calculated dose by *slow* IV push, then *slowly* give the remainder in small amounts while monitoring rhythm and BP. Monitoring is strongly suggested

whenever IV epinephrine is used.[1] British authorities prefer using 1:100,000 solutions, starting at 1 to 2 cc/minute.[42] When treating shock, endotracheal or IM routes may require 2 to 2.5 times greater epinephrine doses than those employed for anaphylaxis alone. IV epinephrine must be used early for the treatment of shock, as animal data suggest that late use is ineffective.[55]

3. Oxygen and ventilation support: Second only to epinephrine, oxygen is a key drug. Low-flow oxygen should be started during initial treatment. If shock develops, the patient is intubated, or CPR is started, then it becomes necessary to give 10 to 15 L/minute[1] to maintain >90% oxygen saturation. Oral edema or laryngeal edema may require cricothyrotomy or tracheotomy. The office where allergy injections are given should be able to support respiration with an Ambu-type bag, masks, oral airways, a laryngoscope (with fresh batteries), endotracheal tubes, and cricothyrotomy instruments such as Nu-Trake and Pedia-Trake (Armstrong Medical Industries, Lincolnshire, Illinois), or tracheotomy instruments.
4. Intravenous supplies: The largest possible IV catheter should be inserted as soon as possible (before shock causes vascular collapse). The office should have available IV catheters, syringes, needles, lidocaine, alcohol wipes, connecting tubing, IV fluids (several liters), tape, tourniquets, and an IV pole. Crystalloid solutions may not be effective in treating anaphylactic shock.[38,42] Therefore, both types of IV solutions are recommended: normal saline or 5% dextrose (D5W), and 5% albumin, 5% plasma protein solution, or a dextran solution. If shock is present, give fluid first, before starting pressor agents, administering ~20 cc/kg of IV fluid as initial therapy in adults or children.[1,54]
5. Suction and catheters: In anaphylaxis, thick secretions may make ventilation or intubation difficult or impossible. When setting up supplies, check that suction catheters fit into the endotracheal and cricothyrotomy tubes, and that suction will reach wherever it is needed, and is strong enough (greater than −120 mm Hg).[46]
6. Bronchodilators: An albuterol inhaler, or equivalent, should be available. Multiple inhalations may be required if the patient is beta-blockaded or has been using β-agonists regularly. Ipratropium (Atrovent) inhaler, or equivalent, may also be helpful, but requires 15 to 30 inhalations. Anticholinergics are not blocked by beta-blockers and are synergistic with inhaled β-agonists.[56]
7. Dopamine: This drug is primarily β-adrenergic at doses below 10 μg/kg/minute. Start treatment at 1 μg/kg/minute IV, and titrate up to

a maximum of 20 μg/kg/minute to support BP. Reduce the initial dose to 0.1 μg/kg/minute if the patient is on MAO inhibitors.[46] *Dopamine must be diluted before IV administration.*

8. Phentolamine: This α-adrenergic blocker is used in 5- to 10-mg IV increments (for children, 1 mg) every 5 to 15 minutes, to control BP in a hypertensive crisis (e.g., beta-blockade).[57]
9. Nitroglycerin: Stock sublingual 0.4-mg tablets. For angina, give one tablet under the tongue every 5 minutes, up to three doses, or until relief occurs.[46]
10. Antihistamines: Treatment should include an H_1 antihistamine, such as diphenhydramine 100 mg IV (child: 12.5 to 100 mg).[51] Alternatively, one may give an oral (PO) antihistamine. Following this, *slowly* (over 5 minutes) give an H_2 IV antihistamine,[39] such as ranitidine 50 mg. Do not administer cimetidine because it interferes with the metabolism of many drugs, including beta-blockers.[58] Both H_1 and H_2 agents are helpful, particularly in beta-blockaded patients,[59] and in refractory anaphylaxis.[42] Always give an H_1 antihistamine before an H_2 antihistamine, to prevent cardiac side effects.
11. Corticosteroids: Steroids take up to 4 to 6 hours to work,[42] but they act to shorten anaphylaxis and can prevent late reactions. An oral dose of 40 to 50 mg of prednisone may be given.[38] For IV administration, *slowly* give dexamethasone 20 mg, or hydrocortisone 500 mg.[1,42,60] If the patient is sulfite allergic, one may substitute IV methylprednisolone 40 mg, unless the patient has a known succinate ester allergy,[36] or allergy to benzyl alcohol. In children, a minimum dose of 0.5 mg/kg methylprednisolone may be given. Corticosteroids in some form should probably be given to every patient with a generalized or anaphylactic reaction,[37] and they should always be administered if severe asthma is present.[61] Because of the risk of preexisting suppression of endogenous cortisol, steroids should also be administered to patients who are already taking systemic corticosteroids or high-dose inhaled steroids.
12. Heparin: In difficult cases of anaphylaxis, consider giving heparin. Heparin adsorbs and inactivates histamine and other allergic mediators,[62,63] releases histaminase, which lowers histamine levels,[64] improves the coagulopathy of anaphylaxis,[65] and is anti-inflammatory.[66] Heparin ameliorates or prevents anaphylaxis in animal models,[67] and it has been used successfully in small clinical trials of acute asthma.[68,69] According to experienced clinicians, it is especially useful in beta-blockaded or refractory anaphylactic

patients. The adult dose is 10,000 units IV, whereas the dose for children is 50 to 75 U/kg. The contraindications in the heparin package insert must be considered before it is used. Low molecular weight heparins have not been tested in anaphylaxis.

13. Aspirin: For suspected coronary insufficiency, give 325 mg PO.

◆ Anaphylaxis Treatment: Sample Protocol

1. Cease administration of allergenic extracts.
2. Assess symptoms, pulse, BP, respirations; evaluate skin color, temperature, and moisture.
3. Quickly deduce type of reaction.
4. Consult other clinicians within office.
5. Always give IM epinephrine, as soon as anaphylaxis diagnosis is made.
6. Confirm diagnosis; continue recording vital signs.
7. Apply tourniquet proximal to allergen injection site.
8. Assess reaction severity and review patient's medical and medication history.
9. Check peak flow, give albuterol inhaler, repeat if not effective.
10. Lower patient's head, loosen clothing.
11. Call for help and notify supervisor physician. Call ambulance, if not already done.
12. If severe hypotension (shock) occurs, give epinephrine 1:10,000 centrally, with monitoring.
13. Request crash cart, defibrillator, suction machine, and oximeter.
14. If continued bronchospasm, give ipratropium inhaler, repeat if not effective.
15. Start 100% oxygen by mask. If oximeter available, keep O_2 saturation $>90\%$.
16. Assign duties; record personnel involved, patient symptoms, vital signs, and treatment given.
17. Establish IV as soon as possible, start IV fluids.
18. If patient beta-blocked, consider heparin IV; repeat epinephrine and monitor for hypertension.
19. If angina occurs, give nitroglycerin. If no relief, give aspirin and start ACLS protocol.
20. If no respirations, begin CPR, bag-mask, intubate, or perform a cricothyrotomy or tracheotomy.

21. If no pulse noted, begin CPR, attach defibrillator or AED.
22. Consider second dose of epinephrine; repeat at least every 3 to 5 minutes, with monitoring, in adults until satisfactory clinical improvement occurs. In children, monitoring is required to determine if subsequent doses are necessary.
23. Check and loosen tourniquet every 5 minutes.
24. Give IV or oral H_1 antihistamine.
25. Give IV (slowly) or oral H_2 antihistamine (not cimetidine).
26. Give IV (slowly) or oral corticosteroid.
27. Reconsider heparin IV, for severe anaphylaxis.
28. If hypotension noted, administer IV fluid, up to 1000 cc every 20 minutes and start second IV.
29. If hypotension persists, mix and begin dopamine IV drip per package insert.
30. If hypotension continues, administer IV colloid solution wide open.
31. If hypertension occurs, turn off dopamine; if persistent, give phentolamine 5 to 10 mg IV, repeat every 5 minutes until BP normal.
32. Transport via ambulance to hospital as soon as possible, communicate with emergency room physician, consider cardiology consult, encourage 24-hour observation.
33. Postcode debriefing of personnel, completion of records, replenish supplies.

◆ Conclusion

Acute anaphylaxis is a rare, potentially fatal, multisystem allergic reaction that every allergy office must be prepared to treat. Key points are (1) reaction prevention; (2) diagnosing the serious reaction; (3) proper staff training; and (4) keeping on hand, readily accessible, and in functioning condition, adequate supplies to provide emergency treatment appropriate to the office locale. Early administration of IM epinephrine is the most crucial step in managing anaphylaxis. The airway must be maintained, oxygen given, circulation supported, and further mediator effects blocked. Cardiopulmonary resuscitation is used whenever respiration or circulation is insufficient. Cardiac monitoring and the capability for defibrillation are helpful in the event of a severe reaction. Similarly, the ability to intubate or create a cricothyrotomy or tracheotomy may be life saving. Stabilized patients should be transported as soon as possible, preferably by ambulance with medical personnel in attendance. Because

of the risk of delayed-onset reactions, and the possibility of multiorgan injury, anaphylaxis patients should be considered for admission to the hospital, and some authorities would make admission mandatory. Patients should be observed for a minimum of 8 hours,[27,40,42] and appropriate specialist consultations should be arranged.

References

1. Chamberlain D, Fisher J, Ward M, and the Project Team of the Resuscitation Council (UK). Consensus guidelines: emergency medical treatment of anaphylactic reactions. Resuscitation 1999; 41:93–99
2. Heffner D. Anaphylaxis. Lippincotts Prim Care Pract 1997;1:220–223
3. Sampson HA. Fatal food-induced anaphylaxis. Allergy 1998;53(suppl 46): 125–130
4. Sorensen HT, Nielsen B, Ostergaard-Nielsen J. Anaphylactic shock occurring outside hospitals. Allergy 1989; 44:288–290
5. Hunsaker DH. Approaches to otolaryngic allergy emergencies. Otolaryngol Clin North Am 1998;31:207–219
6. Hurst DS, Gordon BR, Fornadley JA, Hunsaker DH. Safety of home based and office allergy immunotherapy: a multicenter prospective study. Otolaryngol Head Neck Surg 1999;121: 553–561
7. Mabry RL, ed. Skin Endpoint Titration Manual. Silver Spring, MD: American Academy of Otolaryngic Allergy, 1990
8. Anon JB. Introduction to in vivo allergy testing. Otolaryngol Head Neck Surg 1993;109:593–600
9. Fadal RG. Experience with RAST-based immunotherapy. Otolaryngol Clin North Am 1992;25:43–60
10. King WP. The Intracutaneous Provocative Food Test and Neutralization Treatment. Silver Spring, MD: American Academy of Otolaryngic Allergy, 1989
11. Haydon RC, Gordon BR. Aeroallergen immunotherapy. In: Krouse JH, Chadwick SJ, Gordon BR, Derebery MJ, eds. Allergy and Immunology, an Otolaryngic Approach. Philadelphia: Lippincott Williams & Wilkins, 2002: 151–184
12. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000; 30:1144–1150
13. VanArsdel PP Jr, Sherman WB. The risk of inducing constitutional reactions in allergic patients. J Allergy 1957;28: 251–261
14. Tinkelman DG, Cole WQ, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. J Allergy Clin Immunol 1995;95:8–14
15. Gibofsky A. Legal issues in allergy and clinical immunology. J Allergy Clin Immunol 1996;98:S334–S338
16. Norman PS. Editorial: safety of allergen immunotherapy. J Allergy Clin Immunol 1989;84:438–439
17. Gordon BR. Allergy skin tests and immunotherapy: comparison of methods in common use. Ear Nose Throat J 1990;69:47–62
18. In vivo diagnostic testing and immunotherapy for allergy. Report I, Part II, of the Allergy Panel. Council on Scientific Affairs. JAMA 1987;258:1363–1367
19. King HC. An Otolaryngologist's Guide to Allergy. New York: Thieme, 1990: 175–177
20. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. J Allergy Clin Immunol 1987;79: 660–667
21. Ward WA Jr. Diagnostic skin testing: skin endpoint titration. In: Krause HF, ed. Otolaryngic Allergy and Immunology. Philadelphia: WB Saunders, 1989:133–140

22. Greineder DK. Risk management in allergen immunotherapy. J Allergy Clin Immunol 1996;98:S330–S334

23. Hejjaoui A, Dhivert H, Michel FB, Bosquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract: IV: systemic reactions according to the immuno-therapy schedule. J Allergy Clin Immunol 1990; 85:473–479

24. King HC. An Otolaryngologist's Guide to Allergy. New York: Thieme, 1990:103

25. James JM. Anaphylaxis: multiple etiologies—focused therapy. J Ark Med Soc 1996;93:281–287

26. Wyatt R. Anaphylaxis. Postgrad Med 1996;100:87–99

27. Fader DJ, Johnson TM. Medical issues and emergencies in the dermatology office. J Am Acad Dermatol 1997;36: 1–16

28. Freeman TM. Anaphylaxis: diagnosis and treatment. Prim Care 1998;25: 809–817

29. Kagy L, Blaiss MS. Anaphylaxis in children. Pediatr Ann 1998;27:727–734

30. Flaherty SA. Allergic reaction to antibiotics during anesthesia: a case report. CRNA 1996;7:118–125

31. Mabry RL. Management of allergic emergencies. In: Krause HF, ed. Otolaryngic Allergy and Immunology, Philadelphia: WB Saunders, 1989: 297–301

32. Frew AJ, Kay AB. Eosinophils and T-lymphocytes in late-phase allergic reactions. J Allergy Clin Immunol 1990;85:533–539

33. Turkeltaub PC, Campbell G, Mosimann JE. Comparative safety and efficacy of short ragweed extracts differing in potency and composition in treatment of fall hay fever: use of allergenically bioequivalent doses by parallel line bioassay to evaluate comparative safety and efficacy. Allergy 1990;45: 528–546

34. Müller UR. Insect Sting Allergy: Clinical Picture, Diagnosis and Treatment. New York: Gustav Fischer Verlag, 1990

35. MacIntyre D, Boyd G. Site of airflow obstruction in immediate and late reactions to bronchial challenge with Dermatophagoides pteronyssinus. Clin Allergy 1983;13:213–218

36. Soto-Aguilar MC, deShazo RD, Waring NP. Anaphylaxis: why it happens and what to do about it. Postgrad Med 1987;82:154–170

37. Kniker WT. Anaphylaxis in children and adults. In: Bierman CW, Pearlman DS, eds. Allergic Diseases from Infancy to Adulthood. Philadelphia: WB Saunders, 1988:667–677

38. Fisher MM, Baldo BA. Acute anaphylactic reactions. Med J Aust 1988;149: 34–38

39. Dykewicz MS. Anaphylaxis and stinging insect reactions. Compr Ther 1996; 22:579–585

40. Smit de V, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. J Emerg Med 2005;28: 381–388

41. Brazil E, MacNamara AF. "Not so immediate" hypersensitivity—the danger of biphasic anaphylactic reactions. J Accid Emerg Med 1998;15:252–253

42. Brown AFT. Therapeutic controversies in the management of acute anaphylaxis. J Accid Emerg Med 1998;15: 89–95

43. Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol 1988;81:1–5

44. Javeed N, Javeed H, Javeed S, Moussa G, Wong P, Rezai F. Refractory anaphylactoid shock potentiated by beta-blockers. Cathet Cardiovasc Diagn 1996;39:383–384

45. Cohan RH, Leder RA, Ellis JH. Treatment of adverse reactions to radiographic contrast media in adults. Radiol Clin North Am 1996;34:1055–1076

46. Cummins RO, ed. Advanced Cardiac Life Support 1997–1999 ed. Dallas: American Heart Association, 1997

47. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York: McGraw-Hill, 1996

48. Davis WE, Cook PR, McKinsey JP, Templer JW. Anaphylaxis in immunotherapy. Otolaryngol Head Neck Surg 1992;107:78–83

49. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Diagnosis and management of anaphylaxis: an updated

practice parameter. J Allergy Clin Immunol 2005;115:S483–S523
50. Weiszer I. Allergic emergencies. In: Patterson R, ed. Allergic Diseases Diagnosis and Management Philadelphia: JB Lippincott, 1985:418–439
51. Paulson E. Anaphylaxis: statement on initial management in nonhospital settings. Can Med Assoc J 1996;154: 1519–1522
52. Johnston SL, Unsworth J, Gompels MM. Adrenaline given outside the context of life threatening allergic reactions. BMJ 2003;326:589–590
53. Simons FER, Roberts JR, Gu XC, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998;101:33–37
54. Gavalas M, Sadana A, Metcalf S. Guidelines for the management of anaphylaxis in the emergency department. J Accid Emerg Med 1998;15:96–98
55. Bautista E, Simons FE, Simons KJ, et al. Epinephrine fails to hasten hemodynamic recovery in fully developed canine anaphylactic shock. Int Arch Allergy Immunol 2002;128:151–164
56. Beakes DE. The use of anticholinergics in asthma. J Asthma 1997;34:357–368
57. Calhoun DA, Oparil S. Treatment of hypertensive crisis. N Engl J Med 1990; 323:1177–1183
58. Powell JR, Donn KH. The pharmacokinetic basis for H2-antagonist drug interactions: concepts and implications. J Clin Gastroenterol 1983;5(suppl 1): 95–113
59. Sullivan TJ. Dr. Sullivan's response to Dr. Toogood's editorial. J Allergy Clin Immunol 1989;83:706–707
60. Chapman KR, Verbeek PR, White JG, Rebuck AS. Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma. N Engl J Med 1991;324:788–794
61. Jantz MA, Sahn SA. Corticosteroids in acute respiratory failure. Am J Respir Crit Care Med 1999;160:1079–1100
62. Dolowitz DA, Dougherty TF. Allergy as inflammatory reactions. Ann Allergy 1971;29:410–417
63. Dolowitz DA, Dougherty TF. The use of heparin in control of allergies. Ann Allergy 1965;23:309–313
64. Gang V, Gaubitz W, Gunzer U. Postheparin-diamine oxidase (histaminase) in anaphylaxis. Klin Wochenschr 1975;53:285–287
65. Ferrell WJ, Jabs CM, Robb HJ, Mammen EF. Comparative study of blood clotting factors in anaphylactic and primary and secondary endotoxin shock. Ann Clin Lab Sci 1983;13: 291–298
66. Gervin AS. Complications of heparin therapy. Surg Gynecol Obstet 1975; 140:789–796
67. Dhar HL, Mukherjee B, Sanyal RK. The effect of heparin on the heart in anaphylaxis. Am Heart J 1967;74: 489–495
68. Boyle JP, Smart RH, Shirley JK. Heparin in the treatment of chronic obstructive bronchopulmonary disease. Am J Cardiol 1964;14:25–28
69. Dougherty TF, Dolowitz DA. Physiologic actions of heparin not related to blood clotting. Am J Cardiol 1964; 14:18–24

Appendix 1

Glossary of Common Terms Used in Otolaryngic Allergy

M. Jennifer Derebery

allergy The production of symptoms through immunologic mechanisms by a substance that is not harmful in itself.

anaphylaxis An immunologically mediated, immediate-type, multisystem reaction that is often severe and sometimes lethal.

antibody A protein substance developed in response to, and interacting specifically with, an antigen.

antigen A substance capable of eliciting a response by the immune system, producing a substance (antibody) specific to the challenging substance.

antigen screen A limited number of allergens used in initial testing (in vivo or in vitro) in order to identify allergic individuals most efficiently. An inhalant screen of 12 to 14 antigens is suggested.

antihistamine Drug, used in treating allergy, with an action that opposes the action of histamine.

basophil A leukocyte, the granules of which stain blue, that participates in some types of acute allergic reactions.

beta-blocker A drug, most often used in the management of hypertension and vascular headaches, that blocks β-adrenergic stimuli and may complicate allergy skin testing and immunotherapy.

bevel The slanted portion of a hypodermic needle.

concentrate Antigen, as obtained from the supplier, in an extremely concentrated form, and usually containing 50% glycerin as a preservative.

confirming wheal Wheal that has grown 2 mm larger than first positive wheal; in intradermal dilutional testing (IDT) the confirming wheal is usually 9 mm in diameter.

CLIA Clinical Lab Improvement Act; sets forth requirements for laboratories, including those doing in vitro allergy tests.

corticosteroid A drug with potent antiinflammatory effects, used to alleviate the symptoms of an allergic reaction while providing protection from the late-phase reaction. Also called glucocorticoid.

cromolyn A drug that stabilizes the mast cells, preventing both acute- and late-phase allergic reactions by inhibiting mast cell degranulation and the resulting release of mediators of inflammation.

cross-reactivity The ability of more than one antigen to react with a specific antibody, due to similar or identical antigen-antibody combining sites, called epitopes.

decongestant An α-adrenergic drug, used topically or systemically, to produce shrinkage of congested nasal mucosa.

delayed whealing response Whealing that occurs hours after initial testing. This is especially seen with molds and food allergens.

diluent The antigenically inert substance (most commonly phenolated saline) used for volume adjustment in the preparation of various concentrations of antigenic materials.

ELISA Enzyme-linked immunosorbent assay. An in vitro test using a nonradioactive marker.

endpoint In intradermal dilutional testing, the antigenic concentration at which progressive positive whealing first occurs.

eosinophil A leukocyte, the granules of which stain red, that participates in the allergic reaction, and is found in increased numbers in the peripheral blood and nasal secretions of allergic individuals.

flash response A variant response in IDT in which a series of negative responses is suddenly followed by a large positive wheal (e.g., 5 – 5 – 5 – 13).

fungi A large class of vegetable organisms, which includes molds (mushrooms, rust).

Gell and Coombs reaction Classifications of immune reactions according to the mechanism involved. A type I reaction, the most common, is immediate, immunoglobulin E (IgE)-mediated, and exemplified by anaphylaxis.

glycerin A preservative contained in most antigen concentrate vials, usually in a 50% concentration, to extend the useful life of the biologic material.

glycerin control Application of a 4-mm wheal of 2% glycerin, for comparison with skin reactions obtained with No. 2 antigen concentration (which normally contains 2% glycerin).

histamine A mediator of inflammation that plays an important role in the acute allergic response.

histamine control Creation of a 4-mm wheal using dilute histamine to demonstrate a positive reaction and confirm the presence of an intact capability for a wheal-and-flare response.

hourglass response In IDT, wheals of decreasing size are followed by a clear zone, after which the usual progression appears: 9–7–5–5–7–9. This is most commonly seen if testing is begun at a concentration weaker than No. 6.

hypersensitivity Excessive and abnormal susceptibility to the action of a given agent.

IDT See intradermal dilutional testing.

immunoglobulin Human serum globulin produced as a consequence of antigenic stimulation. Classes are (in decreasing order of amounts in the body), immunoglobulins (Ig) G, A, M, D, and E.

immunotherapy Regular injections with appropriate allergens to produce tolerance in the host through varied immunologic mechanisms. These include an eventual drop in allergen-specific IgE and a rise in IgG, plus alteration of the T1-T2 balance.

inhalant A substance that enters the body via the respiratory tract.

intracutaneous test Another term for intradermal testing.

intradermal dilutional testing (IDT) Testing that is begun with an anticipated nonreacting antigen dilution, continuing with fivefold stronger concentrations to determine the concentration at which progressive whealing occurs.

intradermal testing Injection of a test antigen just under the outermost layer of epidermis to form a wheal.

in vitro testing Testing by laboratory means. For allergy, the common methods are RAST (radioallergosorbent testing) and ELISA (enzyme-linked immunosorbent assay).

in vivo testing Testing for allergies by skin testing methods, such as prick, intradermal, or IDT.

late-phase reaction In a Gell and Coombs type I (anaphylactic) reaction, the phase that follows 4 to 6 hours after the acute-phase reaction.

linear testing Intradermal dilutional testing for a single antigen accomplished by placing wheals using progressively more concentrated antigen strengths until the endpoint is determined.

mast cell A cell found in respiratory and connective tissue that releases preformed and newly formed mediators of inflammation (e.g., histamine) as part of acute allergic reactions.

modified quantitative testing Combining screening using multiple prick tests, with confirmatory intradermal tests employing the dilutions predicted by the prick test results, in order to give quantitative results with increased efficiency.

molds A type of fungi (fungi imperfecta) having septate mycelia. Numerous molds are potential allergens.

MQT See modified quantitative testing.

multiple-dose vial A treatment vial containing sufficient quantity for the withdrawal and administration of several immunotherapy injections.

multiple-prick test A prick-puncture test using a multipronged device for introducing multiple antigens with a single application. One example is the multitest apparatus.

negative control A skin test wheal made using only diluent without added antigen, to rule out primary skin hyperreactivity.

OSHA Occupational Safety and Health Administration. The agency of the U.S. government with the responsibility to ensure safety and healthful work environments.

perennial allergens Allergens that are present virtually year-round (e.g., animals, molds), rather than limited to a specific season.

plateau reaction In IDT, a skin whealing response in which two (or more) of the positive wheals are the same size.

pollen A potential allergen source, composed of fertilizing elements of a flowering plant.

prick test A skin test in which the skin is punctured at a 45-degree angle through a drop of antigen, introducing a small amount into the skin. Also called intracutaneous testing.

prick-puncture test A variant of the prick test in which the puncture through the antigen droplet is vertical to the skin surface. Multiple prick tests are prick-puncture types.

RAST Radioallergosorbent test. An in vitro test using a radioactive marker.

seasonal allergens Allergens that are present during specific periods of the year (e.g., pollens).

SET Skin endpoint titration or serial dilution endpoint titration, the precursor and prototype of IDT (see above).

single-dose vial A treatment vial containing the exact amount for one immunotherapy injection.

standardized extract An allergenic extract in which the biologic potency has been expressed in a form allowing comparison to known standards developed by an overseeing agency.

stock vial A vial of concentrate (see Concentrate).

testing board A collection of relevant antigens in varying concentrations used for skin testing.

titrating the vial Diluting the contents of an antigen-containing treatment vial by fivefold increments, then making test wheals with these concentrations to determine a safe starting point for dosage.

titration A bioassay involving the application of progressively stronger antigen concentration to determine the point at which reactivity is first noted.

TOE Term for three species of fungi: *Trichophyton, Oidiomycetes (Candida)*, and *Epidermophyton;* also used to designate the clinical syndrome due to delayed hypersensitivity to these antigens.

treatment board A collection of relevant antigens in varying concentrations, often mixed using 10% glycerine for stability, used to prepare treatment vials.

vertical testing A screening maneuver in IDT in which testing for several antigens is done simultaneously, starting with the No. 6 concentration, then (if necessary) the No. 4 and No. 2 dilutions to estimate the degree of sensitivity present.

vial test Making a skin wheal using a treatment vial, to determine if the concentration of antigen is appropriate for commencing immunotherapy. This type of test must always precede initial immunotherapy based on in vitro results, and it should be applied before administering the first dose from any new treatment vial.

w/v (weight per volume) concentration Antigen strength expressed as grams of antigen per milliliter of extracting fluid.

well-characterized extract An antigen extract not meeting the criteria for "standardized" status but much better characterized than the typical w/v material.

wheal In allergy, an elevated area on the skin surface, initially produced by an intradermal injection, the ultimate size of which is also affected by cutaneous hypersensitivity and other factors.

◆ Acknowledgment

This glossary is derived from material prepared for courses of the American Academy of Otolaryngic Allergy. I thank the academy for its assistance.

Appendix 2

Aeroallergen Panels

Table A2–1 contains lists of inhalant allergens that are most often associated with clinical allergic rhinitis in the various geographic areas of the United States. Several of the suggested allergens are perennial allergens found in nearly all regions of the United States. Several common fungi (molds) are prevalent almost everywhere and are also included. The final portion of the suggested panel consists of clinically important pollen allergens commonly found in the particular region.

Although each region is quite large, the native plant species are similar across the region. Many plant species are introduced by people in gardens and landscaping. Those plants, especially trees, may change the pattern of predominant pollens over a period of years. This has been noted especially in the southwest and mountain states.

The suggested panels do not list any allergen mixes. Many experts do not favor using mixtures of unrelated species such as mixes with extracts of pollen from several different tree or weed species. This is because extracts from unrelated species dilute the other extracts. Experts in the field do endorse using mixes of related cross-reactive species such as mixtures of northern grasses, dust-mite mixes, and mixes of short and tall ragweed.

Because Americans tend to move to different regions of the country, a person may become sensitized to an allergen or group of allergens in one region of the country then move to a region with different allergens. Certain patients may live a portion of the year in different geographic regions, such as Florida in the winter and a northeast state in the summer. As their physician, you may wish to test them for sensitivity to regional allergens from that area.

There are many ways to divide the United States with regard to allergen prevalence. The system used here is similar to that developed for in vitro testing panels by Pharmacia. In this system, the United States is divided into 17 geographic regions. Northern California is further divided into subregions: the Central Valley and coastal Northern California. Some states, especially in the West, may fall into two or more allergenic regions.

Each regional section on the following pages contains two lists: a screening panel of 14 key allergens and an expanded list of allergens of clinical significance in the region. Additional allergenic extracts are available for physicians who wish to test patients on a broader range of inhalant allergens or foods.

Table A2–1 Aeroallergen Panels*

Region 1—North Atlantic States	
New York, New Jersey, Pennsylvania, Connecticut, Massachusetts, Vermont, Maine, New Hampshire, Rhode Island	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus*
Box Elder (Maple)	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy (Northern grass)	Alternaria (Mold)
Ragweed, Short	*Cladosporium* (Mold)
Lamb's Quarters	Cockroach, German
Mugwort	Birch, White
Histatrol Histamine Positive Control (Central Laboratories, Port Washington, NY)	Negative Control
Expanded Region 1 Panel	
Cottonwood, Eastern	Pigweed, Rough
Alder, White	Burweed Marshelder
Willow, Black	Bermuda Grass
Sycamore	Dock, Yellow
Hickory, Shagbark	*Aspergillus fumigatus*
Ryegrass, Perennial	*Penicillium notatum*
Cedar, Red	*Drechslera*
English Plantain	*Curvularia*
Region 2—Mid-Atlantic States	
Delaware, Maryland, Virginia, North Carolina, District of Columbia	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus*
Hickory, Shagbark	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)
Lamb's Quarters	Cockroach, German
Bermuda Grass	Box Elder (Maple)
Histatrol Histamine Positive Control	Negative Control

(*Continued*)

Table A2–1 (*Continued*)

Expanded Region 2 Panel	
Cottonwood, Eastern	Pigweed, Rough
Pecan Pollen	Burweed Marshelder
Ash, White	Australian Pine (Beefwood)
Cedar, Red	Dock, Yellow
Bahia Grass	*Aspergillus fumigatus*
Ryegrass, Perennial	*Penicillium notatum*
Cocklebur	*Drechslera*
English Plantain	*Curvularia*
Region 3—South Atlantic States	
Georgia, South Carolina, Northern Florida	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus*
Hickory, Shagbark	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
June Grass (Kentucky Bluegrass)	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Bermuda Grass	Johnson Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 3 Panel	
Cottonwood, Eastern	Lamb's Quarters
Pecan Pollen	Burweed Marshelder
Ash, White	Australian Pine (Beefwood)
Cedar, Red	Dock, Yellow
Bahia Grass	*Aspergillus fumigatus*
Ryegrass, Perennial	*Penicillium notatum*
Cocklebur	*Drechslera*
English Plantain	*Curvularia*
Region 4—Subtropical Florida	
Screening Panel	
Australian Pine (Beefwood)	House Dust Mite—*Dermatophagoides pteronyssinus*
Pecan Pollen	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Bermuda Grass	Bahia Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 4 Panel	
Cottonwood, Eastern	Lamb's Quarters
Hickory, Shagbark	Burweed Marshelder
Melaleuca	Queen Palm
Cedar, Red	Dock, Yellow
Johnson Grass	*Aspergillus fumigatus*
Ryegrass, Perennial	*Penicillium notatum*
Cocklebur	*Drechslera*
Ragweed, Tall	*Curvularia*

(*Continued*)

Table A2–1 (*Continued*)

Region 5—Greater Ohio Valley	
Ohio, Indiana, West Virginia, Kentucky, Tennessee	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus*
Box Elder (Maple)	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)
Lamb's Quarters	Cockroach, German
Hickory, Shagbark	Johnson Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 5 Panel	
Cottonwood, Eastern	Pigweed, Rough
Birch, White	Burweed Marshelder
Willow, Black	Walnut, Black (Pollen)
Sycamore	Dock, Yellow
Bermuda Grass	*Aspergillus fumigatus*
Ryegrass, Perennial	*Penicillium notatum*
Cedar, Red	*Drechslera*
English Plantain	*Curvularia*
Region 6—South Central States	
Alabama, Arkansas, Mississippi, Louisiana	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus*
Bermuda Grass	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)
Lamb's Quarters	Cockroach, German
Pecan Pollen	Johnson Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 6 Panel	
Cottonwood, Eastern	Pigweed, Rough
Alder, White	Burweed Marshelder
Willow, Black	Walnut, Black (Pollen)
Sycamore	Dock, Yellow
Hickory, Shagbark	*Aspergillus fumigatus*
Ryegrass, Perennial	*Penicillium notatum*
Cedar, Red	*Drechslera*
English Plantain	*Curvularia*
Region 7—Northern Midwest States	
Michigan, Wisconsin, Minnesota	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus* or Mixed mite
Box Elder (Maple)	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)

(*Continued*)

Table A2–1 (*Continued*)

Lamb's Quarters	Cockroach, German
Mugwort	Birch, White
Histatrol Histamine Positive Control	Negative Control
Expanded Region 7 Panel	
Cottonwood, Eastern	Pigweed, Rough
Alder, White	Burweed Marshelder
Willow, Black	Beech
Sycamore	Dock, Yellow
Hickory, Shagbark	*Aspergillus fumigatus*
Orchard Grass	*Penicillium notatum*
Cedar, Red	*Drechslera*
English Plantain	*Curvularia*
Region 8—Central Midwest States	
Illinois, Missouri, Iowa	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus*
Box Elder (Maple)	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)
Lamb's Quarters	Cockroach, German
Mugwort	Birch, White
Histatrol Histamine Positive Control	Negative Control
Expanded Region 8 Panel	
Cottonwood, Eastern	Pigweed, Rough
Alder, White	Burweed Marshelder
Willow, Black	Mugwort
Sycamore	Dock, Yellow
Hickory, Shagbark	*Aspergillus fumigatus*
Orchard Grass	*Penicillium notatum*
Cedar, Red	*Drechslera*
English Plantain	*Curvularia*
Region 9—Great Plains States	
Kansas, Nebraska, South Dakota, North Dakota	
Screening Panel	
Elm, American	House Dust Mite—*Dermatophagoides pteronyssinus*
Box Elder (Maple)	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)
Lamb's Quarters	Cockroach, German
Firebush—Kochia	Russian Thistle
Histatrol® Histamine Positive Control	Negative Control
Expanded Region 9 Panel	
Cottonwood, Eastern	Pigweed, Rough
Alder, White	Burweed Marshelder
Willow, Black	Mugwort
Mulberry	Dock, Yellow
Bermuda Grass	*Aspergillus fumigatus*

(*Continued*)

Table A2–1 (*Continued*)

Orchard Grass	*Penicillium notatum*
Cedar, Red	*Drechslera*
English Plantain	*Curvularia*
Region 10—Southwestern Grassland States	
Texas, Oklahoma	
Screening Panel	
Elm, Chinese	House Dust Mite—*Dermatophagoides pteronyssinus*
Mountain Cedar	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Ragweed, Short or Mix	*Cladosporium* (Mold)
Lamb's Quarters	Cockroach, German
Pecan Pollen	Bermuda Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 10 Panel	
Cottonwood, Eastern	Pigweed, Rough
Alder, White	Burweed Marshelder
Willow, Black	Sagebrush, common
Mulberry	Dock, Yellow
Johnson Grass	*Aspergillus fumigatus*
Orchard Grass	*Penicillium notatum*
Elm, Fall Blooming	*Drechslera*
English Plantain	*Curvularia*
Region 11—Rocky Mountain States	
Colorado, Wyoming, Utah, New Mexico, Arizona mountains	
Screening Panel	
Elm, Chinese	House Dust Mite—*Dermatophagoides farinae*
Juniper, Western	Cat Hair (Dander)
Oak, White	Dog Epithelium (Dander)
Perennial Ryegrass	*Alternaria* (Mold)
Alder, White	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Bermuda Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 11 Panel	
Cottonwood, Fremont	Brome Grass
Ragweed, Short or Mix	Willow, Black
Scale—Spearscale	Sagebrush, common
Lamb's Quarters	Ash, White
Johnson Grass	*Aspergillus fumigatus*
Box Elder (Maple)	*Penicillium notatum*
Ragweed, Western	*Drechslera*
Firebush—Kochia	*Curvularia*
Region 12—Arid Southwest States	
Southern Arizona, Southeast California desert	
Screening Panel	
Mesquite	House Dust Mite—*Dermatophagoides farinae*
Juniper, Western	Cat Hair (Dander)

(*Continued*)

Table A2–1 (*Continued*)

Oak, White	Dog Epithelium (Dander)
Perennial Ryegrass	*Alternaria* (Mold)
Ash, White	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Bermuda Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Regional Panel	
Cottonwood, Fremont	Pigweed, Rough
Alder, White	Willow, Black
Scale—Spearscale	Sagebrush, common
Saltbush, Annual	Wild Oat Pollen
Johnson Grass	*Aspergillus fumigatus*
Olive Pollen	*Penicillium notatum*
Ragweed, Western	*Drechslera*
Firebush—Kochia	*Curvularia*
Region 13—Southern Coastal California	
Screening Panel	
Cypress, Arizona	House Dust Mite—*Dermatophagoides farinae*
Juniper, Western	Cat Hair (Dander)
Oak, California Live	Dog Epithelium (Dander)
Perennial Ryegrass	*Alternaria* (Mold)
Brome Grass	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Bermuda Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 13 Panel	
Cottonwood, Fremont	Pigweed, Rough
Alder, White	Walnut, Black (Pollen)
Scale—Spearscale	Sagebrush, common
Saltbush, Annual	Wild Oat Pollen
Johnson Grass	*Aspergillus fumigatus*
Olive Pollen	*Penicillium notatum*
Ragweed, Western	*Drechslera*
Firebush—Kochia	*Curvularia*
Region 14A—Central Valley California	
Screening Panel	
Cypress, Arizona	House Dust Mite—*Dermatophagoides farinae*
Juniper, Western	Cat Hair (Dander)
Oak, California Live	Dog Epithelium (Dander)
Perennial Ryegrass	*Alternaria* (Mold)
Brome Grass	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Bermuda Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Central Valley Panel	
Cottonwood, Fremont	Pigweed, Rough
Alder, White	Walnut, Black (Pollen)
Scale—Spearscale	Sagebrush, common
Saltbush, Annual	Wild Oat Pollen

(*Continued*)

Table A2–1 (*Continued*)

Johnson Grass	*Aspergillus fumigatus*
Olive Pollen	*Penicillium notatum*
Ragweed, Western	*Drechslera*
Firebush—Kochia	*Curvularia*
Region 14B—Northern Coastal California	
Screening Panel	
Cypress, Arizona	House Dust Mite—*Dermatophagoides farinae*
Juniper, Western	Cat Hair (Dander)
Oak, California Live	Dog Epithelium (Dander)
Perennial Ryegrass	*Alternaria* (Mold)
Brome Grass	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Bermuda Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Northern California Coastal Panel	
Cottonwood, Fremont	Pigweed, Rough
Alder, White	Walnut, Black (Pollen)
Scale—Spearscale	Sagebrush, common
Saltbush, Annual	Wild Oat Pollen
Johnson Grass	*Aspergillus fumigatus*
Olive Pollen	*Penicillium notatum*
Ragweed, Western	*Drechslera*
Firebush—Kochia	*Curvularia*
Region 15—Intermountain West	
Nevada, Southern Idaho	
Screening Panel	
Cottonwood, Fremont	House Dust Mite—*Dermatophagoides farinae*
Juniper, Western	Cat Hair (Dander)
Elm, Chinese	Dog Epithelium (Dander)
Perennial Ryegrass	*Alternaria* (Mold)
Sagebrush, Common	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Bermuda Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 15 Panel	
Brome Grass	Ash, White
Alder, White	Willow, Black
Scale—Spearscale	Saltbush, Annual
Lamb's Quarters	Cypress, Arizona
Oak, White	*Aspergillus fumigatus*
Box Elder (Maple)	*Penicillium notatum*
Ragweed, Western	*Drechslera*
Firebush—Kochia	*Curvularia*
Region 16—Inland Northwest	
Eastern Oregon and Washington	
Screening Panel	
Cottonwood, Fremont	House Dust Mite—*Dermatophagoides farinae*
Walnut, Black (Pollen)	Cat Hair (Dander)

(*Continued*)

Table A2–1 (*Continued*)

Juniper, Western	Dog Epithelium (Dander)
Ryegrass, Perennial	*Alternaria* (Mold)
Sagebrush, Common	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Brome Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 16 Panel	
Bermuda Grass	Birch, White
Alder, White	Willow, Black
Scale—Spearscale	Saltbush, Annual
Lamb's Quarters	Cypress, Arizona
Oak, White	Aspergillus fumigatus
Wild Oat Pollen	Penicillium notatum
Ragweed, Western	Drechslera
Firebush—Kochia	Curvularia
Region 17—Pacific Northwest	
Western Oregon & Washington	
Screening Panel	
Cottonwood, Fremont	House Dust Mite—*Dermatophagoides farinae*
Walnut, Black (Pollen)	Cat Hair (Dander)
Box Elder (Maple)	Dog Epithelium (Dander)
Timothy Grass	*Alternaria* (Mold)
Sagebrush, Common	*Cladosporium* (Mold)
Pigweed, Rough	Cockroach, German
Russian Thistle	Brome Grass
Histatrol Histamine Positive Control	Negative Control
Expanded Region 17 Panel	
Bermuda Grass	Birch, White
Alder, White	Willow, Black
Scale—Spearscale	Saltbush, Annual
Lamb's Quarters	Cypress, Arizona
Oak, White	*Aspergillus fumigatus*
Wild Oat Pollen	*Penicillium notatum*
Ragweed, Western	*Drechslera*
Firebush—Kochia	*Curvularia*

*Additional allergens are available for further testing.
Aeroallergen panels provided courtesy of ALK-Abello, Inc., 1700 Royston Lane, Round Rock, Texas, telephone 800-325-7354, fax 888-329-2551.

◆ Acknowledgment

This material is supplied by ALK–Abello Antigen Company, Round Rock, Texas, and is reprinted with permission. We appreciate their cooperation and assistance.

Index

Note: Page numbers followed by t and f indicate tables and figures, respectively.