Northwestern University
Allergy-Immunology Syllabus 2012: Residents and Students

Edited By
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# Northwestern University Allergy-Immunology Syllabus 2012: Residents and Students

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About the cover: The cover image is reproduced with permission from Bellanti, JA (Ed). *Immunology IV: Clinical Applications in Health and Disease*, I Care Press, Bethesda, MD, 2012, www.immunologycenter.org. It is a schematic representation of the total immune capability of the host based upon the efficiency of elimination of foreign matter and symbolizes the capacity of the immune system to maintain a balance between the internal and external environments. Nowhere are the expressions of an imbalance of the host’s internal immune response to the external environment better illustrated than in the field of allergy-immunology.
Overview

Paul A. Greenberger, M.D., and Leslie C. Grammer, M.D.

Allergic and immunologic diseases continue to result in frequent visits to physicians’ offices. Allergic rhinitis, rhinosinusitis, asthma, and urticaria form the bulk of these visits, and although the number of fatalities from asthma in the United States has declined, the number of hospitalizations remains unacceptably high. Episodes of anaphylaxis may be encountered in the emergency department, primary care physician’s office, or hospital and for some physicians or health care professionals, it is the very first time that they have been asked to diagnose and treat a patient with this potentially life-threatening condition. Patients who experience recurrent infections may have a treatable deficiency of their adaptive immune system. In this syllabus we hope to aid all physicians and health care professionals in diagnosing and treating commonly encountered allergic–immunologic diseases. We hope you enjoy this journal and will use it as a constant resource.

Also, we would like to extend a special thank you to the fellows and faculty at the Northwestern University Feinberg School of Medicine, Division of Allergy–Immunology who have made this syllabus possible.
An overview of allergens

Rachna Shah, M.D., and Leslie C. Grammer, M.D.

ABSTRACT

Most allergens are proteins or glycoproteins that range in molecular weight from 5000 to 100,000 Da, although polysaccharides and low molecular weight substances also may be allergenic. Common allergens include pollens, fungal spores, house-dust mites, and animal epithelial materials but can also include drugs, biological products, and insect venoms. The allergic response is dependent on the route of exposure. If exposure is to an inhaled aeroallergen, the allergic response will be a respiratory reaction in nature. Ingested or injected exposure gives rise to gastrointestinal, cutaneous, or anaphylactic reactions. Size of pollen determines clinical manifestation of allergy. For example, particles between 20 and 60 μm in diameter can be carried in the wind and cause nasal and ocular symptoms (allergic rhinoconjunctivitis). Particles <7 μm can deposit in the airways and cause symptoms of asthma. Animals produce allergens in forms unique to each species. Cat allergen, most importantly Fel d 1, is found mainly in cat saliva, sebaceous glands in the skin, and in urine of male cats. It is buoyant and “sticky,” which means it easily remains airborne and may last in a home for up to 6–9 months after the source is removed. Cat allergen adheres to clothes and can be found in public places such as schools. Dog allergen, particularly Can f 1, is present in dander, saliva, urine, and serum. There are allergens specific to dog breeds, but all breeds produce allergenic proteins (even poodles and “hairless” dogs).

An allergen is any antigenic substance that can mediate an immediate hypersensitivity reaction with an associated clinical reaction in an individual. Common allergens include pollens, fungal spores, house-dust mites, and animal epithelial materials but can also include drugs, biological products, and insect venoms. Most allergens are proteins or glycoproteins that range in molecular weight from 5000 to 100,000 Da, although polysaccharides and low molecular weight substances also may be allergenic. Little is known, but much research is dedicated to determining the distinguishing facts that make an antigen capable of inducing IgE production (an allergen) in contrast to antigens that induce other immunologic responses (IgG and IgA). Factors that have already been shown to increase immunogenicity of an antigen include molecular size, solubility, stability, conformational fold, and duration of exposure.

Allergens enter the body via inhalation, ingestion, or may be injected. Genetic predisposition and environmental factors determine if an individual will be sensitized to an allergen, and then subsequent allergen exposure of sufficient concentration triggers a physiological response by interacting with specific IgE bound to mast cells and basophils. The ensuing inflammatory cascade elicits a variety of signs and symptoms in the allergic spectrum. The allergic response is dependent on the route of exposure. If exposure is to an inhaled aeroallergen, the allergic response will be a respiratory reaction in nature. Ingested or injected exposure gives rise to gastrointestinal, cutaneous, or systemic reactions.

An allergen is recognized by the International Union of Immunologic Societies as a protein that has allergenicity in at least five individuals. Individual allergens are further divided into major and minor allergens when it comes from the same source, e.g., giant ragweed pollen or cat dander. Major allergens result in an IgE response in >50% of allergic individuals allergic to the specific source, whereas minor allergens cause an allergic response in <50%. Although “minor” is in the name, they still cause a significant allergic response in an individual.

Nomenclature for allergen proteins has been established by the International Union of Immunologic Societies. The standard nomenclature uses the first three letters of the genus, followed by the first letter of the species, and then an Arabic numeral; they are not italicized. For example, cat is Felis domesticus and the allergen protein nomenclature for the primary allergen is Fel d 1.
POLLENS

For pollen to be clinically significant as an aeroallergen, it must be buoyant, present in significant numbers, and be allergenic. Most pollens that cause clinical disease are 20–60 μm in diameter. This small size allows exposure through wind carriage and contact with the respiratory mucosa and conjunctiva. Particles <7 μm tend to deposit in the airways, and those <3 μm may enter the distal airways. Pollen immunogenicity, plant abundance, proximity to living environments, and regional geography determine specific pollens that are responsible for local allergic sensitization.

Grass pollen is the most common cause of allergic rhinitis and asthma worldwide because of the wide distribution of wind-pollinating grasses. Most are 20–25 μm in diameter and, therefore, tend to cause symptoms of rhinitis rather than asthma. Most grasses belong to the same family (Poaceae) and have significant cross-reactivity, with the exceptions of Bermuda and Bahia grass, which are subtropical grasses. Ryegrass (major allergen Lol p1) and Timothy grass (major allergen Phl p1) are among the most important allergenic grasses. Grass pollen is typically released in the afternoon, and in the Midwest, is prevalent in the months of May through July. Many southern areas, such as Florida and southern California, have grass seasons lasting as long as 10–11 months.

Ragweed pollen is the most important cause of allergic rhinitis and pollen asthma in North America. Ambrosia artemisiifolia (short ragweed; major allergen Amb a 1) and Ambrosia trifida (giant ragweed; Amb t 5) are the most important ragweed pollen allergens. Pollen grains are ~16–20 μm in diameter and are notorious for triggering allergic symptoms in the central and eastern United States; Ontario, Canada; and increasing locations in Europe. Weed pollen release depends on seasonal daylight variation and is released typically in the morning during the autumn season in the United States. A single ragweed plant may expel 1 million pollen grains in a single day. It possesses the ability to travel hundreds of miles from its source. In the Chicago area, ragweed pollen is prevalent from August 15 to October 1.

Tree pollen allergens range from 20 to 60 μm in diameter and mostly come from the Angiosperm class. Geography determines which tree families are prevalent in a community, and in contrast to grass pollen, cross-reactivity is uncommon. Tree pollen is a significant cause of allergic disease, and in most of the United States, it is typically released during a short spring season. In Chicago, tree pollination is from late March to late May. However, in Florida and the California lowlands, there are trees with early and late pollens seasons spanning 6 months.

FUNGI

Fungi produce airborne spores and mycelial elements that are believed to contribute significantly to allergic disease throughout the world. These allergens are typically 3–30 μm in diameter. With few exceptions, such as Alternaria in asthma, Aspergillus in allergic bronchopulmonary aspergillosis, and various fungi in allergic fungal sinusitis, the clinical importance of common fungi has been difficult to assess. Alternaria alternata (major allergen Alt a 1) species are common outdoor molds that have been associated with triggering respiratory arrest in patients with asthma. Cladosporium (major allergens Cla h 1, 2) is also a common outdoor mold species, and like Alternaria, it has a seasonal prevalence in the warmer months between spring and autumn. The first hard frost of late autumn decreases spore counts significantly until warm weather returns. In contrast, Aspergillus fumigatus (major allergen Asp f 1) and Penicillium citrinum (Pen c 13,18) species are common indoor molds and may provide allergenic triggers throughout the year. High spore counts in homes are associated with warm, humid environments and may be reduced by air conditioning in the summer, removal of mold in homes with contamination, preventing water damage, and dehumidification if needed.

ENVIRONMENTAL CHANGES

Climate changes due to global warming are expected to increase temperatures by 1–2°C in this century. This will affect vegetation and will likely result in a higher allergic disease burden. The 2006 U.S. Department of Agriculture hardiness zone map showed a shift northward of floristic zones, which influence the type of native vegetation found in a region. This shift exemplifies the effect of global warming on the type of trees and other plants that can survive in a given latitude. In addition, studies have shown increased size and pollen production of ragweed with increased CO₂. This was especially seen in urban areas where CO₂ levels and temperatures were higher than in rural areas.

DUST MITES

Dust mites, particularly Dermatophagoides pteronyssinus (major allergen Der p 1) and Dermatophagoides farinae, ingest human epithelial scales and obtain water from the ambient water in the air. They produce feces that provide a perennial allergen source within homes. Dust mites are small (0.33 mm long), eight-legged animals that are present in pillows, mattresses on box springs, sofas, and carpets (shag much more than low-nap carpets). They thrive in warm, humid conditions and, therefore, peak in the summer months in the United States. The typical allergen size is 1–10 μm in diameter, and its ability to cause allergic respiratory disease is enhanced by intrinsic enzymic activity that
penetrates the respiratory mucosal barrier and promotes inflammation.

**ANIMAL AEROALLERGENS**

Animals produce allergens in forms unique to each species. Dander (desquamated epithelium), saliva, urine, hair, and feathers are the major allergen sources. Cat allergen, most importantly Fel d 1, is found mainly in cat saliva but also in sebaceous glands in the skin and in urine of male cats. Allergen size can be ≤5 μm, allowing cat allergen to reach the small bronchioles, causing symptoms of asthma. It is buoyant and “sticky,” which means it easily remains airborne and may last in a home for up to 6–9 months after the source is removed. Dog allergen, particularly Can f 1, is present in dander, saliva, urine, and serum. There are allergens specific to dog breeds, but all breeds produce allergenic proteins (even poodles and “hairless” dogs). Rodent dander sensitivity occurs in occupational exposure of laboratory workers, but allergenic proteins in rodent urine may also contribute to allergic disease in infested homes.

**COCKROACH**

*Blatella germanica* (German cockroach) and *Periplaneta americana* (American cockroach) are the two most common species of cockroach infesting domestic homes and public buildings. The German cockroach is most prevalent in the United States and has an affinity for warm, humid environments. Increased cockroach infestations have also been noted in the inner cities. Sensitization to cockroach extract, including the best-studied allergens Bla g 1 and Bla g 2, are more common in urban settings. Cockroach protein, like dust-mite allergen, becomes airborne when disturbed and falls quickly.

**HYMENOPTERA**

Hymenoptera venoms are not aeroallergens and are covered in a later chapter and are also discussed in detail in a practice parameter. In brief, the venoms are introduced parenterally by an insect sting from either vespid (yellow jackets, hornets, and wasps) or apids (honeybees). Vespid allergens are largely cross-reactive, but people sensitive to bee venom usually are not sensitive to vespid venom. Fire ants, located in the southeastern United States, also belong to the Hymenoptera order.

**DRUGS**

Medicines often are implicated in triggering undesired immunologic reactions. True drug allergy represents 6–10% of all adverse drug reactions and is overreported by individuals. Most drugs are too small (<1000 Da) to incite allergic sensitization alone. To cause an allergic reaction, a reactive metabolite of the drug must bind to a macromolecular carrier for antigen processing. The drug metabolite in the carrier molecule complex is known as a hapten. This makes skin testing difficult for diagnostic accuracy. Large molecular weight drugs (heterologous antisera, insulin, streptokinase, and l-asparaginase), which are >4000 Da, and medicines that have enough distance between determinants to be bivalent (quaternary ammonium muscle relaxants and aminoglycosides), may provoke an allergic response without forming a hapten–protein complex.

**LATEX**

Natural rubber latex is a product of the rubber tree *Hevea brasiliensis*. Sensitization is present in 75% of patients with spina bifida and 6.5% of the general population. Health care providers and patients with urological problems requiring catheterization are also at increased risk. Clinical manifestations of IgE-mediated disease include allergic rhinitis, asthma, contact urticaria, and anaphylaxis. The incidence of IgE-mediated reactions to latex has declined mostly because of the development of powder-free, low-protein gloves.

**INGESTED ALLERGENS**

Food allergy is common and appears to be increasing; it can be divided into class 1 and class 2. Class 1 food allergy is considered “traditional” and occurs in the gastrointestinal tract. Class 2 food allergy is caused by allergenic sensitization to inhalant allergens that cross-react with food allergens. Class 1 allergens are 10–70 kDa and are heat, acid, and protease stable. Common class 1 allergens are cow’s milk, chicken egg, peanut, soybean, fish, and shrimp. Thirty-five percent of children with moderate to severe atopic dermatitis have an associated food allergy, and 6% of asthmatic children have associated food allergy. Peanut is the most common food allergy in individuals >4 years old. There has been a dramatic increase in the number of children with peanut allergy with one study noting peanut allergy prevalence of 1.4% in 2008 versus 0.8% in 2002 in the United States. Studies are currently looking at environmental factors that may result in this increased prevalence.

Cross-reactivity between members of a food allergen group varies. Cross-reactivity between peanuts and other legumes is 5%, between tree nuts 35%, between different fish 50%, and 75% between members of the shellfish family. Cross-reactivity also occurs between aeroallergens and certain food allergy resulting in class 2 food allergies. This is known as pollen–food syndrome (previously oral allergy syndrome) and manifests as pruritus with or without angioedema of the lips, tongue, palate, and posterior oropharynx. Shared allergen sensitivities have been reported between ragweed and the gourd family (watermelon, cantaloupe, zucchini, and cucumbers) and bananas.
Weed pollens are released mostly in the autumn in the United States. In the upper midwestern United States, tree pollination occurs in mid to late March until May. In the upper midwestern United States, this time is from mid-May to the end of July. Weed pollens are released mostly in the autumn in the United States with ragweed being the major allergen from August 15 to October 1 in the upper midwestern United States.

Global warming has shifted the floristic zones in North America to higher latitudes. Ragweed has increased in size and pollen production because of increased CO₂ and temperature.

Fungal spores and mycelial elements are released preferentially in warm, humid environments. The first hard frost of late autumn decreases outdoor mold spores.

Dust mites thrive in warm, humid conditions and provide allergens through their fecal particles, enhanced by intrinsic enzymic activity.

Cat allergens may last in a home for up to 6 months after the source is removed. It can be isolated from saliva, urine, dander, and from sebaceous glands.

IMMUNOLOGY

- An allergen is typically a protein or glycoprotein that can induce an IgE-mediated immune response with an associated clinical reaction.
- Size of pollen determines clinical manifestation of allergy. Particles between 20 and 60 μm in diameter can be carried in the wind and cause nasal and ocular symptoms. Particles <7 μm can deposit in the airways and cause symptoms of asthma.
- True drug allergy represents ~6–10% of all adverse drug reactions. Skin testing is difficult because most drug allergens are small metabolites of the implicated drug and they must haptenize a carrier protein to induce an immune response.

CLINICAL PEARLS

- Most tree pollens do not have significant cross-reactivity and are released in the spring in the United States. In the upper midwestern United States, tree pollination occurs in mid to late March until May.
- Grass pollen comes from the Poaceae family, has significant cross-reactivity, and is typically released in the late spring and early summer in the United States. In the upper midwestern United States, this time is from mid-May to mid-July.
- Weed pollens are released mostly in the autumn in the United States with ragweed being the major allergen from August 15 to October 1 in the upper midwestern United States.
- Global warming has shifted the floristic zones in North America to higher latitudes. Ragweed has increased in size and pollen production because of increased CO₂ and temperature.
- Fungal spores and mycelial elements are released preferentially in warm, humid environments. The first hard frost of late autumn decreases outdoor mold spores.
- Dust mites thrive in warm, humid conditions and provide allergens through their fecal particles, enhanced by intrinsic enzymic activity.
- Cat allergens may last in a home for up to 6 months after the source is removed. It can be isolated from saliva, urine, dander, and from sebaceous glands.

REFERENCES

Skin tests are used in addition to a directed history and physical exam to exclude or confirm IgE-mediated diseases such as allergic rhinitis, asthma, and anaphylaxis to aeroallergens, foods, insect venoms, and certain drugs. There are two types of skin testing used in clinical practice. These include percutaneous testing (prick or puncture) and intracutaneous testing (intradermal). Prick testing involves introducing a needle into the upper layers of the skin through a drop of allergen extract and gently lifting the epidermis up. Other devices are available for prick testing. Intracutaneous (intradermal) testing involves injecting a small amount of allergen (0.01–0.02 mL) into the dermis. The release of preformed histamine from mast cells causes increased vascular permeability via smooth muscle contraction and development of a wheal; inflammatory mediators initiate a neural reflex causing vasodilatation, leading to erythema (the flare). Prick testing methods are the initial technique for detecting the presence of IgE. They may correlate better with clinical sensitivity and are more specific but less sensitive than intradermal testing. Sites of skin testing include the back and the volar aspect of the arm. Although the back is more reactive, the difference is minimal. By skin testing on the arm, the patient can witness the emergence and often sense the pruritus of the skin test reaction. Because more patients are sensitized (have IgE antibodies and positive skin test reactions) than have current symptoms, the diagnosis of allergy can be made only by correlating skin testing results with the presence of clinical symptoms.
mide, histamine-2 receptor blockers, and tricyclic antidepressants, may affect test results and should be held before testing if possible. Refer to Table 1 for the elimination half-lives ($t\frac{1}{2}$) of several commonly prescribed medications. Short courses of oral corticosteroids will not affect testing results; however, topical corticosteroids may decrease or inhibit skin reactivity. These should not be applied to the test site for at least 1 week before testing. Patients receiving immunotherapy may have decreased skin reactivity. Leukotriene antagonists do not significantly affect skin test reactivity.

Sites of skin testing include the back and the volar aspect of the arm. Although the back is more reactive, the significance of this is minimal. Use of the arm as the test site has the advantage of being able to place a tourniquet above the site should a systemic reaction occur. Skin chosen for testing should be clear of dermatitis.

The skin chosen is cleaned with alcohol. Allergen extracts, positive control (histamine), and negative control (saline or allergen diluent) are placed 2–5 cm apart. One source of skin testing error is placing sites too close together resulting in spread of one allergen extract to another site and inability to accurately record the extent of erythema from two positive sites close together. False negative or positive reactions may occur with insufficient or excessive skin penetration. If prick testing reveals minimal or equivocal reaction to an allergen, one might choose to proceed with intradermal testing with a 100- to 1000-fold dilution of allergen extract.

Standardized extracts should be used to facilitate comparisons between clinicians. Note that use of standardized doses does not always confer equal potency. One study found that the content of major allergen varied significantly among the 12 standardized extracts tested. Extracts should be refrigerated at 4°C. They should contain glycerin to decrease the loss of potency that occurs with time.

Testing should be graded within 15–20 minutes. Several different grading systems exist, one of which is shown in Table 2. The mean diameter of the wheal and erythema are recorded with the presence or absence of pseudopodia. Physicians should quantify the actual size on the data sheet and not solely a grade so that results might be better shared among practitioners. Clinicians also are urged to use a comprehensive data sheet recording the brand of extract, dilutions used, device chosen, mean diameters of wheal and erythema, and specific grading system key.

Interpretation of skin tests may be more difficult in patients with dermatographism. False positive reactions with dermatographism can be distinguished from true positive reactions that are secondary to IgE because the former fade more quickly. Special attention should be paid to the difference between the sizes of the reactions from allergen extracts compared with the negative control. No significant differences in skin test reactivity have been noted for gender. Infants and the elderly, however, may have decreased skin reactivity and thus smaller wheal size. Additionally, darkly pigmented skin can have larger histamine wheals compared with light skin.

**IMMUNOLOGY**

**Skin Test Wheal and Flare Mechanism:**

- Introduction of antigen into the skin causes local mast cell activation via cross-linking of preformed, antigen-specific, membrane-bound IgE.
- The release of preformed histamine from mast cells causes increased vascular permeability via smooth muscle contraction and development of wheal; inflammatory mediators initiate neural reflex vasodilation, leading to development of flare.
CLINICAL PEARLS

- Skin testing is a practical, reliable, and well-tolerated method of establishing IgE-mediated disease.
- Interpretation of skin testing should be done by an experienced practitioner, in the presence of positive and negative controls, and may be confounded by dermatographism or antihistamine use.
- The presence of a positive skin test documents the presence of allergen-specific IgE antibody. Diagnosis of allergy can be made only by correlating skin testing results with the presence of clinical symptoms.

REFERENCES

Allergen immunotherapy: Definition, indication, and reactions

Mary S. Georgy, M.D., and Carol A. Saltoun, M.D.

ABSTRACT

Specific allergen immunotherapy is the administration of increasing amounts of specific allergens to which the patient has type I immediate hypersensitivity. It is a disease modifying therapy, indicated for the treatment of allergic rhinitis, allergic asthma, and hymenoptera hypersensitivity. Specific IgE antibodies for appropriate allergens for immunotherapy must be documented. Indications for allergen immunotherapy include (1) inadequate symptom control despite pharmacotherapy and avoidance measures, (2) a desire to reduce the morbidity from allergic rhinitis and/or asthma or reduce the risk of anaphylaxis from a future insect sting, (3) when the patient experiences undesirable side effects from pharmacotherapy, and (4) when avoidance is not possible. Furthermore, patients may seek to benefit from economic savings of allergen immunotherapy compared with pharmacotherapy over time. Several studies have reported that immunotherapy in children with allergic rhinitis appears to prevent the development of new allergic sensitizations and/or new-onset asthma. Humoral, cellular, and tissue level changes occur with allergen immunotherapy including large increases in antiallergen IgG4 antibodies, a decrease in the postseasonal rise of antiallergen IgE antibodies, reduced numbers of nasal mucosal mast cells and eosinophils, induction of Treg cells, and suppression of Th2 more than Th1 lymphocytes. There is a corresponding increase in IL-10 and transforming growth factor beta. In the United States, allergen immunotherapy is administered by the subcutaneous route in the physician’s office, whereas primarily in some countries in Europe, it is administered for allergic rhinitis and asthma by the sublingual route by the patient at home.


Specific allergen immunotherapy, often called “allergy shots,” has been defined as the administration of increasing amounts of specific allergens to which the patient has type I immediate hypersensitivity.1 The purpose of allergen immunotherapy is to provide protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.2 Although the single best marker that explains immunotherapy’s efficacy is unknown, there are many immunologic changes that occur with immunotherapy (see Table 1).

INDICATION AND DURATION

Immunotherapy is indicated for patients who have clinically significant IgE-mediated allergic rhinitis,3 asthma,4 and hymenoptera sensitivity.5 Specific IgE for appropriate allergens must be documented and symptoms should correlate with exposure to those specific allergens selected for immunotherapy.6–8 Other indications for allergen immunotherapy include inadequate symptom control despite pharmacotherapy and avoidance measures, undesirable side effects from pharmacotherapy, and when avoidance is not possible.8 In addition, immunotherapy may prevent the development of new sensitizations and/or new-onset asthma.9 The relative contraindications to allergen immunotherapy include severe or uncontrolled asthma, significant cardiovascular disease, and β-blocker use.10 Immunotherapy is not currently approved for food allergy11 or chronic urticaria and/or angioedema.12 However, the most recent immunotherapy practice parameter suggests an expanded indication, atopic dermatitis in subjects with aeroallergen sensitization.13 Multiple controlled studies have shown that immunotherapy is effective treatment for allergic rhinitis due grass, ragweed, and birch pollen.8 Immunotherapy with house-dust mite vaccines is an effective treatment for both allergic asthma and allergic rhinitis. Studies favoring allergen immunotherapy in patients with asthma have been published for grasses, trees (birch),
Table 1  Immunologic changes with immunotherapy

<table>
<thead>
<tr>
<th>Antibody changes</th>
<th>Cellular changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in allergen-specific IgG</td>
<td>Decreased mediator release from mast</td>
</tr>
<tr>
<td>(specifically IgG2)</td>
<td>cells, basophils, and eosinophils</td>
</tr>
<tr>
<td>Early increase and late decrease</td>
<td>Reduction of tissue mast cells and</td>
</tr>
<tr>
<td>in serum-specific IgE</td>
<td>eosinophils</td>
</tr>
<tr>
<td>Decrease in seasonal rise of</td>
<td>Induction of regulatory T cells and</td>
</tr>
<tr>
<td>specific IgE</td>
<td>suppression of Th2 &gt; Th1 cells</td>
</tr>
<tr>
<td>Increased secretion of IL-10 and</td>
<td>Increased secretion of IL-10 and TGF-β</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Decrease in histamine-releasing factors</td>
</tr>
</tbody>
</table>

Source: Adapted from Refs. 8 and 17.

TGF-β = transforming growth β.

SCIT IN PREGNANCY

Allergen immunotherapy is effective in the pregnant patient and may be continued during pregnancy if maintenance doses are well tolerated. According to the allergen immunotherapy practice parameters of 2011, the last highest achieved dose is temporarily used as a maintenance dose until delivery. However, if the patient is not experiencing allergic reactions from immunotherapy, the dosage can be increased as if she were not pregnant.

SUBLINGUAL IMMUNOTHERAPY

Sublingual immunotherapy (SLIT) is commonly used in Europe but not currently Food and Drug Administration approved in the United States. SLIT is administered either as a rapidly dissolving tablet containing allergen extracts or in liquid form administered with a dropper; dosages studied are 20–400 times the total dose used in a course of SCIT. The regimen typically starts with a rapid build-up phase and then the treatment is taken either daily or three times per week. The exact mechanism of action of SLIT remains to be elucidated, but SLIT may reduce symptoms and rescue medication use by 30–40%. However, SLIT is ~2/3 as effective as SCIT. The most common adverse event reported is local itching and swelling and systemic side effects are relatively rare.

CLINICAL PEARLS

- Specific allergen immunotherapy is indicated for the treatment of allergic rhinitis, allergic asthma, and hymenoptera hypersensitivity. Allergen immunotherapy is currently not indicated for the treatment of eczema, food allergy, or chronic urticaria.
- Systemic reactions to immunotherapy usually occur within 30 minutes of treatment. The faster the onset
of symptoms of a systemic reaction, the more severe the reaction is likely to be.

- SCIT is contraindicated in severe asthma.
- SLIT, although not currently approved for use in the United States, has been shown to be more effective than placebo and safer than SCIT.

REFERENCES

Chapter 4

Stinging insect allergy and venom immunotherapy

Alan P. Koterba, M.D., and Paul A. Greenberger, M.D.

ABSTRACT

The Hymenoptera order is divided into three families: Apids, Vespidae, and Formicidae. Apids include the honeybee, bumblebee, and sweat bee, which are all docile and tend to sting mostly on provocation. The Africanized killer bee, a product of interbreeding between the domestic and African honeybee, is very aggressive and is found mostly in Mexico, Central America, Arizona, and California. The yellow jacket, yellow hornet, white (bald)-faced hornet, and paper wasp all belong to the Vespidae family. The Formicidae family includes the harvester ant and the fire ant. When a "bee" sting results in a large local reaction, defined as >5 in. and lasting >24 hours, the likelihood of anaphylaxis from a future sting is ~5%. For comparison, when there is a history of anaphylaxis from a previous Hymenoptera sting and the patient has positive skin tests to venom, at least 60% of adults and 20–32% of children will develop anaphylaxis with a future sting. Both patient groups should be instructed about avoidance measures and carrying and knowing when to self-inject epinephrine, but immunotherapy (IT) with Hymenoptera venom is indicated for those patients with a history of anaphylaxis from the index sting and not for patients who have experienced a large local reaction. IT is highly effective in that by 4 years of injections, the incidence of subsequent sting-induced anaphylactic reactions is 3%. This incidence may increase modestly after discontinuation of injections but has not been reported >10% in follow-up.


An anaphylactic (systemic) reaction to a stinging insect occurs in 0.3–3.0% of the general population. Most reactions occur in those subjects who are <20 years of age, but fatalities tend to occur in adults. Hymenoptera anaphylaxis accounts for at least 40–50 deaths/year in the United States. The most common culprit is the yellow jacket.

CLASSIFICATION

There are nine flying insects in the Hymenoptera order that are known to cause anaphylactic reactions. They are divided into three families: Apidae, Vespidae, and Formicidae. The Apids include the honeybee, bumblebee, and sweat bee, which are all docile and tend to sting mostly on provocation. The Africanized killer bee (found mostly in Mexico, Central America, Arizona, and California) is a product of interbreeding between the domestic and African honeybee and is very aggressive. The yellow jacket, yellow hornet, white (bald)-faced hornet, and paper wasp all belong to the Vespidae family. Yellow jacket nests are located in the ground or in rock gardens and yellow jackets tend to be attracted to garbage, open soda cans, punch bowls, and picnic tables. The hornets are commonly found in shrubs, whereas paper wasps nest in the eaves of homes or inside of walls. The Formicidae family includes the harvester ant and the fire ant. They are found in the southeast/southwestern United States and are capable of causing systemic allergic reactions. The sting causes a painful, erythematous reaction followed by a wheal. Within 4 hours, a clear pustule forms. The fluid can become cloudy and the pustule can last some 3–10 days. The pustule is often mistaken for cellulitis although secondary infections may occur. Immunotherapy (IT) is indicated in patients who are skin test positive to fire ant whole-body extract.

TYPES OF REACTIONS

There are five types of sting reactions: normal, local, rare, toxic, and anaphylactic. A normal reaction is characterized by mild erythema (<2 in.), swelling, and pain. It is transient in nature and limited to the area of the sting. Treatment consists of cold compresses and analgesics. A large local reaction (>5 in.) and lasting >24 hours has as high as a 7–17% incidence in the general population. Local reactions are characterized by extensive erythema and swelling and can last be-
between 1 and 10 days. It is important to distinguish large local reactions from an anaphylactic reaction. A large local reaction is contiguous along a joint line (i.e., entire arm swelling) whereas an anaphylactic reaction skips contiguous joint lines (i.e., sting on the hand and hive on the lip). The treatment for large local reactions is analgesics, ice, and, rarely, prednisone (not evidence based). Individuals who develop large local reactions tend to have a similar reaction on a subsequent sting. The risk of anaphylaxis is low in these individuals (<5%) and therefore does not require IT. Rare reactions include serum sickness for which IT may be indicated. In serum sickness, there is urticaria, arthralgias, malaise, and fever about 7 days after an insect sting. There is a risk of anaphylaxis with a repeat sting in these individuals so IT should be considered when skin testing is positive. Neurological, nephritic, vasculitic, and encephalitic-like reactions are other rare reactions that have been reported to occur up to 2 weeks after the implicated sting. Toxic reactions occur after multiple simultaneous stings resulting in hypotension, cardiovascular collapse, and possibly death. IT is indicated for toxic reactions when patients have positive skin test results.

TESTING

The immediate-onset (anaphylactic) reactions are mediated by IgE antibodies to particular venom. This results in mast cell activation leading to mediator release with cutaneous and systemic signs/symptoms of anaphylaxis. Sixty percent of adult subjects and 20–32% of children with a history of anaphylaxis from a previous sting will have anaphylaxis with a repeat sting. Moreover, IT for these individuals provides protection from anaphylaxis in 97% of re-stings. Thus, IT is indicated for patients with a history of anaphylaxis and positive skin tests (showing venom-specific IgE antibody). Testing should be done at least 3 weeks after the suspected anaphylactic event because it may take 2–3 weeks for venom-specific IgE to become detectable. Some patients have a convincing history of anaphylaxis but negative skin testing. This may represent a nonimmunologic reaction or perhaps a loss of reactivity when there is a remote history of a sting reaction. If the initial skin is negative then repeat skin testing is advisable after 3–6 months. Some have argued that in vitro testing is advised in this setting, but the administration of IT should be with an extract that causes a positive skin test. Children <16 years of age with history of a cutaneous systemic reaction (hives/angioedema) do not necessarily require venom IT (VIT) because it is less likely they will experience severe anaphylactic shock with future stings. In particular cases, it may be appropriate to treat a child who has experienced acute urticaria and angioedema who has positive skin tests. Baseline tryptase levels have been found to be elevated (>11 ng/mL) in a subset of patients with known venom hypersensitivity. Interestingly, some of these patients were found to have occult indolent systemic mastocytosis or monoclonal mast cell activation syndrome. In addition, venom-associated anaphylaxis may be the presenting finding of indolent systemic mastocytosis or the monoclonal mast cell activation syndrome.

VIT DOSING AND SCHEDULES

Skin testing is administered using five Hymenoptera venom protein extracts—honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp (Table 1). Typically, testing starts with a prick test at 0.01 μg/mL if the reaction was very severe with subsequent intradermal testing at 0.0001, 0.001, 0.1, and 1.0 μg/mL. For fire ants, whole-body extracts are used for skin testing. In most cases, IT is administered with all of the venoms that tested positive. Therapy for VIT begins at 0.05 μg with incremental doses every week until a maintenance dosage of 100 μg (300 μg if mixed vespid is achieved). Once the patient has reached maintenance, they can gradually convert to monthly injections in their 1st year and then perhaps every 6–8 weeks during the subsequent 3 years or until the skin test becomes negative. VIT decreases risk of re-sting reaction in adults from 60 to 3%. A patient having undergone or still undergoing VIT is still at risk of developing an anaphylactic (systemic) reaction if stung, so they should always carry an epinephrine autoinjector. The rate of systemic reactions to VIT is 3–12% per course of IT, which is similar to aeroallergen IT.

### Table 1 Indications for VIT in patients with positive skin tests

<table>
<thead>
<tr>
<th>Reaction</th>
<th>VIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Normal” transient pain, swelling</td>
<td>No</td>
</tr>
<tr>
<td>Extensive local swelling (large local)</td>
<td>No</td>
</tr>
<tr>
<td>Mild anaphylaxis generalized urticaria</td>
<td>No*</td>
</tr>
<tr>
<td>if &lt;16 yr old</td>
<td>Yes</td>
</tr>
<tr>
<td>if &gt;16 yr old</td>
<td>Yes</td>
</tr>
<tr>
<td>Moderate/severe anaphylaxis</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxic reaction</td>
<td>Yes</td>
</tr>
<tr>
<td>Indolent systemic mastocytosis</td>
<td>Yes#</td>
</tr>
<tr>
<td>Mast cell activation syndrome</td>
<td>Yes#</td>
</tr>
</tbody>
</table>

*Controversial.

#In some patients, an argument can be made even to treat patients with negative skin tests to venom with IT.

VIT = venom immunotherapy.
TREATMENT

Avoidance is a major therapeutic intervention in preventing death from these insects. Measures include wearing long-sleeved light-colored clothing, shoes and hats, being cautious in picnic areas, covering food, avoiding drinking from open beverage cans, and not wearing perfume or cologne. Fire ant mounds are orange in color and can be found underground for up to 80 ft. Thus, there is a case for wearing shoes or hard sandals and avoiding areas where there are fire ant mounds. Along with teaching self-administration of the epinephrine autoinjector, it is important to emphasize the need to carry an epinephrine autoinjector at all times regardless of if the patient has received VIT or not.\textsuperscript{12–14} It is also advisable to let the patient know that anytime they do use an epinephrine autoinjector, they should go to the hospital to get further evaluation. Acute medical therapy for systemic reactions includes the normal treatment for anaphylaxis including epinephrine, \textsubscript{H}\textsubscript{1}-receptor antagonists, corticosteroids, and supportive therapy for shock. Discontinuation of VIT usually occurs after 4–5 years despite a persistently positive skin test or when skin tests become negative after 4 years of injections.\textsuperscript{2} The most recent practice parameter states that VIT should be continued for at least 3–5 years.\textsuperscript{15} This is based on evidence that despite the persistence of a positive skin test response, 80–90\% of patients will not have a systemic reaction to an insect sting if VIT is stopped after 3–5 years; however, one might consider indefinite IT in the patient with severe anaphylaxis.

IMMUNOLOGY

- IgG antibodies are capable of blocking \textit{in vitro} venom-induced histamine release from basophils of allergic patients.
- Passively administered immunoglobulin from bee-keepers provides temporary immunity from venom anaphylaxis in sensitive patients.
- The concentration of IgG produced is proportional to amount of exposure to venom.

CLINICAL PEARLS

- Appropriately treat anaphylactic reactions to venom stings as indicated such as with epinephrine.
- Teach patients avoidance measures such as wearing light-colored clothing, no perfumes, and not walking barefoot in the grass.
- Classification of an allergic reaction helps determine when IT is necessary.
- The “number needed to treat”\textsuperscript{16} for an adult patient receiving IT for a history of anaphylaxis to stinging insects and positive skin tests is 2 (1/0.60–0.03) or 1/0.57 derived from 1/risk of anaphylaxis in untreated group-risk of anaphylaxis in treated group. This is a remarkably low number. For children where the risk of a repeat anaphylactic reaction after IT is \textasciitilde20\%, the “number needed to treat” is 1/0.20–0.03 or 6, also a very low number.

REFERENCES

Allergic rhinitis

Ashraf Uzzaman, M.D., and Rachel Story, M.D.

ABSTRACT

Rhinitis is a symptomatic inflammatory disorder of the nose with different causes such as allergic, nonallergic, infectious, hormonal, drug induced, and occupational and from conditions such as sarcoidosis and necrotizing antineutrophil cytoplasmic antibodies positive (Wegener’s) granulomatosis. Allergic rhinitis affects up to 40% of the population and results in nasal (ocular, soft palate, and inner ear) itching, congestion, sneezing, and clear rhinorrhea. Allergic rhinitis causes extranasal untoward effects including decreased quality of life, decreased sleep quality, obstructive sleep apnea, absenteeism from work and school, and impaired performance at work and school termed “presenteeism.” The nasal mucosa is extremely vascular and changes in blood supply can lead to obstruction. Parasympathetic stimulation promotes an increase in nasal cavity resistance and nasal gland secretion. Sympathetic stimulation leads to vasoconstriction and consequent decrease in nasal cavity resistance. The nasal mucosa also contains noradrenergic noncholinergic system, but the contribution to clinical symptoms of neuropeptides such as substance P remains unclear. Management of allergic rhinitis combines allergen avoidance measures with pharmacotherapy, allergen immunotherapy, and education. Medications used for the treatment of allergic rhinitis can be administered intranasally or orally and include oral and intranasal H1-receptor antagonists (antihistamines), intranasal and systemic corticosteroids, intranasal anticholinergic agents, and leukotriene receptor antagonists. For intermittent mild allergic rhinitis, an oral or intranasal antihistamine is recommended. In individuals with persistent moderate/severe allergic rhinitis, an intranasal corticosteroid is preferred. When used in combination, an intranasal H1-receptor antagonist and a nasal steroid provide greater symptomatic relief than monotherapy. Allergen immunotherapy is the only disease-modifying intervention available.

tion and an increase in nasal cavity resistance. The nasal mucosa also contains the noradrenergic noncholinergic system, but the contribution to clinical symptoms of neuropeptides such as substance P remains unclear.

PATHOPHYSIOLOGY

Allergic rhinitis is an immunoglobulin E (IgE)-mediated (or a type I, immediate⁵) reaction to the protein or glycoprotein component of inhaled Aeroallergens⁶ including pollens, molds, animal danders, dust-mite fecal particles, and cockroach residues.⁷ In the occupational setting, small molecular weight chemicals can act as haptens that associate with self-proteins to form complete allergens.⁸ On inhalation, the allergen deposits in the nasal mucosa. After deposition, antigen-presenting cells in the nasal epithelial mucosa phagocytose and process the allergen and subsequently present the processed antigen to CD4⁺ T cells in local lymph nodes. The allergen-stimulated T cells proliferate in a Th2 pathway and release cytokines including IL-3, IL-4, IL-5, IL-13, and others. These cytokines lead to local and systemic production of IgE antibodies by plasma cells. These antibodies bind to mast cells and basophils. This process is referred to as sensitization. On reexposure, the allergen is recognized by IgE antibodies, which are bound to mast cells and basophils. The recognition and subsequent binding leads to degranulation of mast cells and basophils that release preformed mediators including histamine and enzymes such as tryptase and chymase. There is also rapid de novo synthesis of other mediators such as cysteinyl leukotrienes (leukotriene D₄) and prostaglandin D₂ (PGD₂). The mediators lead to vasodilation of arteriolar venous Anastomosis, plasma leakage from blood vessels, increased secretion of mucous, and stimulation of afferent nerves with consequent occlusion of the nasal passages. Histamine produces pruritus, rhinorrhea, and sneezing and leukotrienes and PGD₂ are associated with the development of nasal congestion. This comprises the early or immediate-phase response. Cytokines released during the immediate-phase response mediate a cascade of events over the next 4–8 hours, referred to the late-phase response. Clinical symptoms in early and late response are similar, but nasal predominates during the late phase. Mediators released at the postcapillary endothelial cells, during the early phase response, promote the expression of adhesion molecules that assist in migration of eosinophils, neutrophils, and basophils and, eventually, macrophages and CD4⁺ Th2 cells into the superficial lamina propria of the nasal cavity. These cells become activated and produce more mediators that are similar to those involved in the early response phase except for mast cell–derived tryptase, chymase, and PGD₂.⁹

On repeated exposure to an allergen, the nasal mucosa becomes more sensitive and there is a progressive decrease in the amount of allergen required to elicit symptoms, a phenomenon referred to as priming. Additionally, the priming effect may lead to increased sensitivity of the nasal mucosa to nonallergenic triggers such as cigarette smoke and strong odors.

DIFFERENTIAL DIAGNOSIS

The constellation of nasal symptoms in individuals with allergic rhinitis may also be present in persons with rhinitis from other causes. The occurrence of associated ocular symptoms—itching, redness, and tearing—make allergy a more likely cause of rhinitis. Allergic rhinitis must be distinguished from other causes of rhinitis that may present with similar symptoms. Vasomotor rhinitis or nonallergic rhinitis without eosinophilia primarily manifests as nasal congestion and rhinorrhea and less commonly with nasal itching and sneezing. Symptoms occur in response to nonallergic triggers such as changes in temperature or relative humidity, strong odors, cigarette smoke, and alcohol ingestion. Nonallergic rhinitis with eosinophilia syndrome is characterized by perennial nasal symptoms and primarily manifests as nasal congestion and is less frequently associated with nasal itching and sneezing, rhinorrhea, and loss of smell. It is unusual in the pediatric population. The nasal smears show 5–20% eosinophils and the skin-prick test and specific IgE levels to environmental allergens are negative. Nasal symptoms may result from hormonal changes such as those that occur during puberty, pregnancy, and with thyroid disorders. Symptoms associated with pregnancy usually occur in the second trimester and typically resolve within 2 weeks of delivery. Rhinitis can develop due to the administration of intranasal and oral medications. Rebound nasal congestion often occurs after discontinuing an intranasal adrenergic decongestant spray used for >4–7 days. This is referred to as rhinitis medicamentosa. Oral antihypertensive agents such as angiotensin-converting enzyme inhibitors and β-blockers may cause nasal symptoms. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen also cause rhinitis in some individuals. Repeated nasal administration of cocaine or amphetamines can lead to rebound nasal congestion. Ingestion of ethanol in alcoholic beverages causes vasodilatation of nasal blood vessels resulting in nasal congestion. Gustatory rhinitis is characterized by rhinorrhea and is associated with ingestion of hot and spicy food. Atrophic rhinitis is characterized by atrophy of the nasal mucosa, nasal dryness, and foul-smelling nasal crusts often associated with a constant sense of malodor. It may be primary, because of infection, or secondary, associated with nasal surgery, irradiation, or trauma. Acute viral
upper respiratory tract infections typically manifest with nasal symptoms, although nasal pruritus is typically absent and constitutional symptoms are often present.11

CLASSIFICATION AND DIAGNOSIS

The Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines classify allergic rhinitis as intermittent or persistent. If one or more of the symptoms of rhinitis such as nasal itching, rhinorrhea, sneezing, and congestion are present for <4 days of the week or for <4 consecutive weeks, the disease is classified as intermittent. If symptoms occur for >4 days of the week and are present for >4 weeks, the disease is classified as persistent. Intermittent and persistent rhinitis are further categorized into mild or moderate/severe disease based on the severity of the symptoms and quality-of-life outcomes. Rhinitis is categorized as mild if the individual does not have sleep disturbance, there is no impairment of daily activities and leisure and/or sports, there is no impairment of school or work, and symptoms are not troublesome. The disease may be classified as moderate/severe if one or more of the aforementioned are present.12 The ARIA classification has largely replaced classifying allergic rhinitis as seasonal for individuals who have symptoms only during particular pollen (tree, grass, and weed) or mold seasons, or perennial for those with year-round symptoms typically caused by pet dander, house-dust mites, cockroaches, and mold in some climates.

On physical exam, the nasal mucosa is commonly pale and boggy, the turbinates are swollen, and clear nasal secretions are often present. The diagnosis is established by performing a thorough history and physical exam and correlating the patient’s history with skin-prick test or allergen-specific serum IgE antibody results.12 A number of measures may provide an objective measure of the severity of rhinitis and have been used clinically. These include visual analog scale and objective measures of nasal obstruction such as acoustic rhinometry and rhinomanometry.

TREATMENT

Management of allergic rhinitis combines allergen avoidance measures with pharmacotherapy, allergen-specific immunotherapy, and education.

Many environmental allergens are known to be associated with allergic rhinitis. House-dust mite is an important cause of allergic rhinitis and avoidance measures have been shown to improve symptoms. There is some benefit of using impermeable covers to encase mattresses, pillows, box springs, and beddings. Some reduction of symptoms has been reported with washing linen in hot water (120°F) and replacing carpets with hardwood floors. Patients allergic to animals with dander benefit from avoidance at home; however, they may encounter these allergens in school, at work, and in public transportation. Regular washing of the pet and use of high-efficiency particulate air filters in households with pets has been shown to be of some benefit in reducing symptoms in sensitized individuals, but removal of the pet from the home is more effective. Moisture control and repair of areas allowing water intrusion in the household will help prevent growth of indoor mold.

The second step in treatment of allergic rhinitis involves pharmacotherapy. Physicians must take into account safety, efficacy, cost-effectiveness, patient preference, severity of symptoms, and compliance when recommending medications. Medications used for the treatment of allergic rhinitis can be administered intranasally or orally and include oral and nasal H1-receptor antagonists, intranasal and systemic corticosteroids, intranasal anticholinergic agents, and leukotriene receptor antagonists. Oral and intranasal decongestants effectively treat nasal congestion, but intranasal decongestants should only be used short term (<5–7 days) because rhinitis medicamentosa may occur. The choice of pharmacotherapy is usually dictated by the severity and chronicity of symptoms. For intermittent mild rhinitis, an oral or intranasal antihistamine is recommended. In patients with intermittent moderate/severe symptoms or in those with persistent mild symptoms an oral or intranasal antihistamine or an intranasal steroid is recommended. In individuals with persistent moderate/severe disease an intranasal corticosteroid is preferred. An intranasal H1-receptor antagonist may be added to control symptoms. When used in combination, a topical antihistamine and a nasal steroid provides greater symptomatic relief than monotherapy.13,14 Leukotriene receptor antagonist can also be used and are particularly beneficial for individuals with allergic rhinitis and asthma, which may have an allergic component. Symptom control should be reviewed 2–4 weeks after initiating treatment and if symptoms persist, medications should be adjusted. If rhinorrhea is the troubling symptom, an anticholinergic agent may be added; and if nasal congestion is the disturbing symptom a short course of oral steroids may be used. For ocular symptoms, an intraocular H1-receptor antagonist sometimes in combination with a mast cell stabilizer may be used.

Allergen-specific immunotherapy15 should be considered if symptoms are not adequately controlled by avoidance and pharmacotherapy or in individuals who can not tolerate pharmacotherapy. Specific allergen immunotherapy has been shown to modify the natural history of allergic diseases, may prevent future sensitization to new environmental allergens, and has been shown to reduce asthma when initiated early.16
IMMUNOLOGY

- Allergic rhinitis is a Th2-mediated immune response.
- Synthesis of allergen-specific IgE is dependent on activation of CD4+ helper T cells and their secretion of IL-4 and IL-13.
- Mast cells and basophils express a high-affinity receptor for the Fc portion of the IgE antibody called FcεRI.
- Mast cells are activated by cross-linking of FcεRI receptors on mast cells by binding of multivalent antigens.

CLINICAL PEARLS

- Commonly occurring symptoms of allergic rhinitis are nasal itching, congestion, sneezing, and rhinorrhea.
- Sympathetic stimulation leads to decrease in nasal cavity resistance; parasympathetic stimulation has the opposite effect.
- Symptoms consist of an immediate response and a delayed response; nasal congestion is the predominant symptom in delayed phase response.
- The ARIA guidelines classify allergic rhinitis into intermittent and persistent.
- Management combines allergen avoidance measures with pharmacotherapy, allergen-specific immunotherapy, and patient education.

REFERENCES

Nonallergic Rhinitis

Rachna Shah, M.D., and Kris G. McGrath, M.D.

ABSTRACT

Nonallergic rhinitis represents a non–IgE-mediated group of disorders that share the symptoms of nasal congestion, rhinorrhea, sneezing, and/or postnasal discharge but not pruritus that characterizes allergic rhinitis. Nonallergic rhinitis may be divided into two broad categories, inflammatory and noninflammatory etiologies. The inflammatory causes include postinfectious (viral and bacterial), rhinitis associated with nasal polyps, and nonallergic rhinitis with eosinophilia, where eosinophils are present in nasal smears but skin testing for aeroallergens is negative. The noninflammatory causes include idiopathic nonallergic rhinitis (formerly referred to as vasomotor rhinitis or colloquially as an “overreactive nose”); rhinitis medicamentosa, which is medication-induced rhinitis; hormone related (pregnancy); systemic disease related (severe hypothyroidism); and structural defect related (deviated septum, head trauma causing cerebrospinal fluid rhinorrhea). The classic symptoms of idiopathic nonallergic rhinitis are nasal congestion, postnasal drip, and sneezing triggered by irritant odors, perfumes, wine, and weather changes. The diagnosis of rhinitis begins with a directed history and physical exam. Examination of the nasal cavity with attention to appearance of the septum and inferior turbinates is recommended. Skin testing for seasonal and perennial aeroallergens is helpful in establishing the presence or absence of IgE antibodies and to help differentiate nonallergic from allergic rhinitis. Topical H1-receptor antagonists (antihistamines), nasal sprays, intranasal steroids, intranasal anticholinergics, and oral decongestants are options for pharmacotherapy. It is important to inquire about hypertension, arrhythmias, insomnia, prostate hypertrophy, or glaucoma to prevent undesirable side effects associated with the oral decongestant pseudoephedrine.


Nonallergic rhinitis represents a non–IgE-mediated group of disorders that share the symptoms of nasal congestion, rhinorrhea, sneezing, and/or postnasal discharge. Symptoms are almost identical to allergic rhinitis, except there is absence of skin test reactivity to common aeroallergens.1 An estimated 19 million persons in the United States suffer from pure nonallergic rhinitis.2 Women are more likely than men to have nonallergic rhinitis, and age of onset after age 40 years is more likely associated with nonallergic rhinitis.3

The pathogenesis of nonallergic rhinitis is incompletely understood. One theory is based on the concept of entopy, which is localized allergy in the nose without positive skin prick or serum IgE specific to the allergen.4 Other studies have looked at nociceptive nerve dysfunction in the nose resulting in nonallergic rhinitis.4 Nasal mucosa of patients with nonallergic rhinitis showed an equal number of CD4+ as those found in patients with allergic rhinitis and nasal lavage showed increase eosinophils in patients with nonallergic rhinitis as compared to controls.4

Nonallergic rhinitis may be divided into two broad categories, inflammatory and noninflammatory etiologies.5 Table 1 represents a differential diagnosis based on this classification.

Vasomotor rhinitis, also referred to as idiopathic, nonallergic noninfectious rhinitis, is the most common of these disorders and manifests with symptoms of perennial nasal congestion, rhinorrhea, and postnasal drip. Unlike allergic rhinitis, nasal pruritus is rare. Classic “nonallergic” triggers include irritants such as smoke, perfumes, chemicals, weather change, and cold air.6 Subclassifications of vasomotor rhinitis include gustatory rhinitis (rhinitis provoked by eating, especially hot or spicy foods) and exercise induced.

In nonallergic rhinitis with eosinophilia syndrome (NARES), eosinophils are found in nasal cytology; however, skin testing for aeroallergens is negative.3 Some 5–20% eosinophils are observed on nasal smear.3 The etiology for this condition is unknown. NARES usually manifests in middle-aged adults and is very uncommon in children. Patients may complain of sneezing paroxysms, copious amounts of clear rhinorrhea, nasal pruritus, and anosmia.2,7
Primary atrophic rhinitis occurs in young to middle-aged adults who present with nasal congestion and foul smelling, thick dry crusts in the nares. This disease, of unknown etiology, occurs rarely in western countries and is more prevalent in developing countries with warm climates. Secondary atrophic rhinitis may result from granulomatous disease, nasal irradiation, aggressive nasal surgery, and trauma. It is less severe and progressive than primary atrophic rhinitis.

Infectious rhinitis or rhinosinusitis may present with purulent nasal secretions, fever, and/or headache among other symptoms. Most commonly, this condition follows an acute viral rhinosinusitis. “Beefy red” turbinates on physical exam are classically seen in rhinitis medicamentosa. This syndrome refers to overuse of topical α-adrenergic agents such as phenylephrine and oxymetazoline or associated with cocaine use. Use of these medications for 5–7 days may result in rebound congestion on stopping the medication. Other medications that may cause symptoms of rhinitis include angiotensin-converting enzyme inhibitors, phosphodiesterase type 5 inhibitors (sildenafil), nonsteroidal anti-inflammatory drugs, and gabapentin.

Nasal congestion and rhinorrhea are common during pregnancy. It is sometimes related to organic conditions such as allergic rhinitis or sinusitis. Vasomotor rhinitis of pregnancy is sometimes referred to as “pregnancy rhinitis.” It occurs in approximately one-fifth of pregnant women and presents as nasal congestion in the last 6 weeks of pregnancy and resolves within 2 weeks of delivery. Historically, women taking oral contraceptives or hormone replacement therapy occasionally reported nasal congestion and rhinorrhea. The risk associated with current low-dose hormone medications is unknown.

It is important to consider conditions that mimic nasal congestion and rhinitis. Anatomic abnormalities, such as a deviated septum, nasal tumors, and foreign bodies, especially in young children, are other causes of nasal obstruction. Cerebrospinal fluid rhinorrhea can present with symptoms of rhinitis, but the drainage usually occurs from one side of the nasal passage and usually with the presence of a significant basal skull fracture, trauma, or surgery. Systemic diseases associated with rhinitis include severe hypothyroidism, diabetes mellitus, and granulomatous diseases such as necrotizing (ANCA⁺; Wegener’s) granulomatous vasculitis or midline lethal granuloma.

The diagnosis of rhinitis begins with a directed history and physical exam. Careful attention should be paid to the onset, duration, triggers of symptoms, and response to pharmacotherapy. Examination of the nasal cavity with attention to appearance of the septum and inferior turbinates is recommended. Skin testing for seasonal and perennial aeroallergens is helpful in establishing the presence or absence of IgE antibodies.

**Table 1  Classification scheme of nonallergic rhinitis**

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Noninflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious rhinosinusitis</td>
<td>Rhinitis associated with nasal polyposis</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
</tr>
<tr>
<td>NARES</td>
<td></td>
</tr>
<tr>
<td>Rhinitis associated with nasal polyposis</td>
<td></td>
</tr>
<tr>
<td>Topical drugs</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
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<tr>
<td>Oxymetazoline</td>
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<tr>
<td>Topical illicit agents</td>
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<tr>
<td>Cocaine</td>
<td></td>
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<tr>
<td>Systemic drugs</td>
<td></td>
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<tr>
<td>Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers</td>
<td></td>
</tr>
<tr>
<td>β-adrenergic blockers</td>
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<tr>
<td>Clonidine</td>
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<tr>
<td>Hydralazine</td>
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<tr>
<td>Hydrochlorothiazide</td>
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<tr>
<td>Guanethidine</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors (Sildenafil and Tadalafil)</td>
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<tr>
<td>Prazosin</td>
<td></td>
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<tr>
<td>Methyldopa</td>
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<tr>
<td>NSAIDS and aspirin</td>
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<tr>
<td>Reserpine (historical)</td>
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<tr>
<td>Psychotropic drugs</td>
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<tr>
<td>Thoridazine</td>
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<tr>
<td>Risperidone</td>
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<tr>
<td>Chlordiazepoxide-amitriptyline</td>
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<tr>
<td>Ovarian hormonal agents</td>
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<tr>
<td>Oral contraceptives (high dose and older generation)</td>
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<tr>
<td>Hormone replacement therapy</td>
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<tr>
<td>Hormone-induced vasomotor instability</td>
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<td>Pregnancy</td>
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<tr>
<td>Rhinitis associated with systemic disease</td>
<td></td>
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<tr>
<td>Severe hypothyroidism</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Rhinitis associated with structural defects</td>
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<td>Deviated septum</td>
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<td>Head trauma resulting in cerebrospinal fluid rhinorrhea</td>
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NARES = nonallergic rhinitis with eosinophilia; NSAIDs = nonsteroidal anti-inflammatory drugs.
and to help differentiate nonallergic from allergic rhinitis. Rhinoscopy may be of value if an anatomic or pathological entity is suspected but not visualized on speculum exam. CT scans can help diagnose unsuspected rhinosinusitis or nasal polyps.

The treatment for nonallergic rhinitis is generally empirical. Topical antihistamine nasal sprays, intranasal steroids, and oral decongestants are the mainstays of therapy. Topical antihistamines, e.g., azelastine hydrochloride or olopatadine hydrochloride, decrease postnasal drip and congestion. When used in combination, a topical antihistamine and a nasal steroid provides greater symptomatic relief than monotherapy. Oral decongestants, such as pseudoephedrine, help with symptoms of congestion if side effects are tolerated. It is important to take a thorough history regarding hypertension, arrhythmias, insomnia, prostate hypertrophy, or glaucoma to prevent serious side effects associated with pseudoephedrine. Nasal ipratropium bromide, an anticholinergic agent, can help treat rhinorrhea associated with nonallergic rhinitis, gustatory rhinitis, and cold air–induced rhinitis. Cessation of cigarettes, marijuana smoking, cocaine use, and topical nasal decongestants should be recommended.

Patients with rhinitis medicamentosa attributable to overuse of topical β-adrenergic agonist medications should be weaned off these agents over 7–10 days while using an intranasal steroid. The patient may require a short course of oral prednisone tapered over 7–10 days. NARES is treated with intranasal steroids. Topical antihistamines might be added to improve symptoms. Treatment of rhinitis associated with a systemic disease should be directed at the underlying disease process. Management of atrophic rhinitis may include nasal saline irrigation and antibiotics. Some patients with either anatomic abnormalities or suspected foreign body should be referred to otolaryngology for further management.

In summary, nonallergic rhinitis constitutes a heterogeneous group of disorders with a common set of symptoms including nasal congestion, rhinorrhea, sneezing, and postnasal drip. Idiopathic nonallergic rhinitis is the most common of these conditions. Patient education, oral decongestants, intranasal steroids, and intranasal antihistamines are mainstays of treatment.

**IMMUNOLOGY**

- It has been reported that patients with nonallergic rhinitis have an equal number of CD4 T cells in comparison with patients with allergic rhinitis.
- It has been shown that the nasal lavage from patients with nonallergic rhinitis have increased eosinophils compared with normal controls.

**CLINICAL PEARLS**

- Nonallergic rhinitis affects 19 million people in the United States and is more prevalent in women than men.
- The classic symptoms of nonallergic rhinitis are nasal congestion, postnasal drip, and sneezing triggered by irritant odors, perfumes, wine, and weather changes.
- The mainstay for treatments are intranasal steroids, intranasal antihistamines, and oral decongestants. When used in combination, intranasal steroids and intranasal antihistamines showed increased symptom relief in comparison with monotherapy.

**REFERENCES**

Nasal polyps

Mary S. Georgy, M.D., and Anju T. Peters, M.D.

ABSTRACT

Nasal polyps are inflammatory outgrowths of paranasal sinus mucosa caused by chronic mucosal inflammation that typically arise from the middle meatus and ethmoid region. The main symptoms of nasal polyps are perennial nasal congestion, nasal obstruction, and anosmia or hyposmia. Unlike patients with chronic rhinosinusitis (CRS) without nasal polyps who present with headache and facial pain, patients with nasal polyps typically do not complain of those symptoms. Nasal polyps appear as semitranslucent, pale gray growths in the nasal cavity in contrast to pink or erythematous adjacent mucosa. Nasal polyps occur more frequently in patients with persistent asthma, aspirin-exacerbated respiratory disease (AERD), CRS, and cystic fibrosis. Children with nasal polyps should be evaluated for cystic fibrosis. Churg-Strauss syndrome and ciliary dyskinesia also may be associated with nasal polyps. Nasal polyps have increased numbers of activated eosinophils, mast cells, and IgE. Staphylococcal superantigens may play a role in the Th2 type of chronic eosinophilic inflammation observed in nasal polyps. Dysfunction of the epithelial barrier in nasal polyps causing reduced levels of antimicrobial proteins has been described. Topical nasal steroids are the treatment of choice. They significantly decrease polyp size, nasal congestion, rhinorrhea, and increase nasal airflow. Short courses of oral steroids may be needed to reduce polyp size followed by maintenance therapy with intranasal steroids. Surgery is reserved for cases when polyps cause severe obstruction, recurrent sinusitis, and for patients who have failed medical therapy. Aspirin desensitization may decrease the requirement for polypectomies and sinus surgery in patients with AERD.

nasal polyps and nonallergic late-onset asthma is significantly linked more to polyps compared with allergic asthma.\textsuperscript{1,2} Recent studies, however, suggest that \textasciitilde 50\% of patients with nasal polyps are atopic.\textsuperscript{10} Nasal polyps may be visualized by nasal speculum; however, rhinoscopy may be required in some patients. CT scans are used to investigate the extent of the disease and are necessary before planning sinus surgery.\textsuperscript{11} Topical nasal steroids are the chronic treatment of choice. They significantly decrease polyp size, nasal congestion, rhinorrhea, and increase nasal airflow.\textsuperscript{1} Short courses of oral steroids may be needed to reduce polyp size followed by maintenance therapy with intranasal steroids.\textsuperscript{1} Surgery is reserved for cases when polyps cause severe obstruction, recurrent sinusitis, and for patients who have failed medical therapy.\textsuperscript{12} Unfortunately, nasal polyps may recur after surgical polypectomy. For patients with AERD, functional endoscopic sinus surgery is less effective than patients without aspirin intolerance. However, aspirin desensitization (performed by an experienced practitioner and in a monitored setting) has been reported to decrease the requirement for polypectomies and sinus surgery.\textsuperscript{1}

**IMMUNOLOGY**

- Nasal polyps have increased numbers of activated eosinophils, mast cells, and IgE. Polyps from China have been found to have increased numbers of neutrophils in contrast to European polyps that tend to be eosinophilic.
- Th2 type of inflammation is observed in nasal polyps.
- Staphylococcal superantigens may play a role in the Th2 type of chronic eosinophilic inflammation observed in nasal polyps.
- Defect in the epithelial barrier has been shown in nasal polyps.

**CLINICAL PEARLS**

- Nasal polyps typically arise from the middle meatus and ethmoid region.
- Main symptoms of nasal polyps are congestion, nasal obstruction, and hypo/anosmia.
- Intranasal steroids and intermittent oral steroids are the mainstay of medical therapy.
- Functional endoscopic sinus surgery may be needed if patients with nasal polyps fail medical therapy.

**REFERENCES**

Rhinosinusitis

Mary S. Georgy, M.D., and Anju T. Peters, M.D.

ABSTRACT

Rhinosinusitis is defined as inflammation of one or more of the paranasal sinuses and affects ~16% of the population. Acute rhinosinusitis is defined as symptoms lasting <4 weeks and subacute rhinosinusitis is between 4 and 8 weeks. Chronic rhinosinusitis (CRS) is defined as symptoms lasting >8–12 weeks. CRS is divided into three groups: CRS with nasal polyps, CRS without nasal polyps, and allergic fungal rhinosinusitis. The sinus cavities are lined with pseudostratified ciliated columnar epithelial cells interspersed with mucous goblet cells. Cilia continuously sweep the mucous toward the ostial openings and are important in maintaining the proper environment of the sinus cavities. The frontal, maxillary, and anterior ethmoid sinususes drain into the ostiomeatal unit of the middle meatus. The posterior ethmoid sinuses and superior sphenoid sinususes drain into the sphenoethmoid recess of the superior meatus. Most acute sinus infections are caused by viruses and, therefore, it is not surprising that the majority of patients improve within in 2 weeks without antibiotic treatment. A bacterial infection should be considered if symptoms worsen or fail to improve within 7–10 days. Amoxicillin, trimethoprim-sulfamethoxazole, or doxycycline are first-line therapy. The Joint Task Force on Practice Parameters for Allergy and Immunology suggests assessing response to symptoms after 3–5 days of therapy and continuing for an additional 7 days if there is improvement. Combining an intranasal corticosteroid with an antibiotic reduces symptoms more effectively than antibiotics alone.

(Rhinosinusitis is one of the most common medical complaints and affects ~16% of the population.1 Rhinosinusitis is defined as inflammation of one or more of the paranasal sinuses. Acute rhinosinusitis is defined as up to 4 weeks of symptoms; subacute rhinosinusitis is defined as symptoms persisting between 4 and 8 weeks duration; and chronic rhinosinusitis (CRS) is defined as symptoms lasting at least 8–12 weeks.2 CRS is divided into three groups, CRS with nasal polyps (CRSwNP), CRS without nasal polyps (CRSsNP), and allergic fungal rhinosinusitis (AFRS).2

The sinus cavities are lined with pseudostratified ciliated columnar epithelial cells interspersed with mucous goblet cells. Cilia continuously sweep the mucous toward the ostial openings and are important in maintaining the proper environment of the sinus cavities. The frontal, maxillary, and anterior ethmoid sinususes drain into the ostiomeatal unit of the middle meatus. Posterior ethmoid sinususes and superior sphenoid sinususes drain into the sphenoethmoid recess of the superior meatus. Narrowing or complete obstruction of the ostia by various anatomic or inflammatory causes impairs the ventilation of the sinuses, resulting in mucus accumulation, impaired mucociliary function, and decreased oxygenation that may promote infections. There are multiple predisposing factors for the development of rhinosinusitis (Table 1). Anatomic pathology such as a deviated nasal septum or nasal polyps may compromise the opening of the ostia. The inflammation associated with both allergic and nonallergic rhinitis may increase the risk of rhinosinusitis.3 Infection is a major contributor to the development of rhinosinusitis, which is predominately caused by viruses. The transition from viral to bacterial rhinosinusitis occurs in 0.5–2% of cases.2 Bacterial rhinosinusitis should be suspected when symptoms persist beyond 7 days.1 Organisms commonly found in acute bacterial rhinosinusitis include Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.4 The role of infection in CRS is less certain, but studies have identified the same organisms found in acute rhinosinusitis, as well as, Pseudomonas aeruginosa, Staphylococcus aureus, coagulase-negative staphylococci, Gram-negative enteric bacteria, and various anaerobes.1,2 Rhinosinusitis is associated with certain medical conditions (Table 1). For example, the incidence of rhinosinusitis is higher among individuals with asthma5;
and increasing severity of asthma is associated with advancing severity of CRS. Nasal polyps are rare in the general population; however, 20–33% of CRS cases are associated with nasal polyps. Certain systemic conditions such as ANCA-necrotizing granulomatosis (Wegener’s), cystic fibrosis, cilia dysmotility syndromes, and various immunodeficiencies are associated with the risk of developing rhinosinusitis. In addition, defects in the local innate immune system might predispose to sinus infections.

AFRS is CRS with the following characteristics: (1) allergic mucin that is thick and light tan to brown to dark green in color, (2) fungal hyphae in the mucin but not invasive, and (3) evidence of IgE-mediated fungal allergy (i.e., positive skin tests). Patients with AFRS are differentiated immunologically from CRS patients by having increased total IgE and fungal-specific IgE. AFRS is usually associated with nasal polyps and symptoms are similar to other forms of CRS (see later in text). The symptoms are caused by intense allergic inflammation directed against colonized fungi.

Symptoms of acute rhinosinusitis commonly include frontal or maxillary head pain, fever, and mucopurulent or bloody nasal discharge (Table 2). Fever is less common in children who more commonly present with cough, nasal discharge, and halitosis. CRS presents with similar symptoms, but facial pain/pressure, headache, and postnasal drip are more common.

On physical examination, mild percussion of the maxillary or frontal sinuses may elicit pain or tenderness. Mucopurulent nasal discharge, erythema, and edema of the nasal turbinates may be visualized, but these findings are nonspecific. Evaluation of the nasal passageways may also reveal evidence of anatomic pathology associated with rhinosinusitis such as a deviated septum, enlarged inferior turbinates, or nasal polyps. Postnasal drainage may be present on examination of the oropharynx. Finally, an evaluation for conditions associated with rhinosinusitis such as otitis media or asthma is warranted.

In most cases, acute rhinosinusitis is diagnosed by clinical history and physical examination. However, sinus imaging may be warranted for patients with rhinosinusitis unresponsive to an initial course of antibiotics or if the patient presents with symptoms or signs consistent with extrasinus involvement (see later in text). Computed tomography (CT) is the standard radiological method for identifying sinus pathology. Evidence of air–fluid levels, mucosal thickening, or opacification of the sinus cavities on imaging are consistent with but not specific for rhinosinusitis.

Laboratory tests are recommended in specific cases only. Given the association between allergic rhinitis and rhinosinusitis, skin testing may be performed, especially in patients with frequent or recurrent rhinosinusitis. Nasal cytology may help differentiate between allergic rhinitis and other forms of rhinitis such as vasomotor rhinitis or nonallergic rhinitis with eosinophil syndrome, but this is not commonly performed in the clinical setting. If cystic fibrosis is suspected, a sweat chloride test should be performed. When the diagnosis is suspected, ciliary function studies should be performed to evaluate for diseases such as Kartagener syndrome. Recurrent rhinosinusitis associated with recurrent lower airway disease warrants evalua-
tion for common variable immunodeficiency or specific antibody deficiency.10

As mentioned previously, most acute sinus infections are caused by viruses and, therefore, it is not surprising that the majority of patients improve within 2 weeks without antibiotic treatment.2 Therefore, antibiotics should be reserved for patients whose symptoms may suggest a bacterial etiology. However, symptoms of bacterial rhinosinusitis do not typically differ from a viral etiology. Symptoms that may suggest a bacterial rhinosinusitis include fever, general malaise, unilateral frontal headache, beginning of complications (see later in text), or patients at risk (immunodeficiency, advanced age, etc.).3 In addition, a bacterial infection should be considered if symptoms worsen or fail to improve within 7–10 days.1 Increasing penicillin resistance to the main bacterial pathogens associated with rhinosinusitis should be considered when choosing an antibiotic. In patients who are not at risk of resistant organisms, amoxicillin is first-line therapy. Other first-line alternatives include trimethoprim-sulfamethoxazole or doxycycline. If there is a lack of response to first-line antibiotics, then the antibiotic should be switched to one with broader coverage. Second-line antibiotics include amoxicillin-clavulanic acid, cephalosporins, and macrolides.1 Another antibiotic class that is used to treat rhinosinusitis is fluoroquinolones but should be reserved for patients who have failed other treatments. Practice parameters by the Joint Task Force on Practice Parameters for Allergy and Immunology suggest assessing response in symptoms after 3–5 days of therapy and continuing for an additional 7 days if there is improvement. However, if there is no response, then the antibiotic should be changed.11 Other treatments include topical steroids, sinus irrigations, and topical nasal vasoconstrictors. However, patients should be advised not to use topical nasal vasoconstrictors for a prolonged period given risk of rhinitis medicamentosa. Finally, surgical intervention may be necessary in patients who fail medical therapy.1

The role of antibiotics for the treatment of CRS is questionable.3 It is imperative to identify contributing factors such as allergic rhinitis, structural abnormalities, immunodeficiency, tobacco smoke, and environmental or occupational factors.1 According to the 2008 Working Group on CRS in Adults, antibiotics should be reserved for patients with purulent sinus drainage.12 The length of antibiotic treatment is controversial, but prolonged antibiotic treatment for 3–6 weeks may be more effective than shorter courses.1 As in acute rhinosinusitis, other treatments include topical steroids and sinus irrigations. A short course of oral steroids may be beneficial in treating CRS especially CRSwNP. Further evaluation is warranted in patients who fail to respond to medical therapy and surgical intervention may be necessary.

In AFRS, surgery is usually necessary to establish the diagnosis and remove the thickened mucus.2 After surgical intervention, oral corticosteroids are usually prescribed with a gradual taper to the lowest dose necessary to control symptoms.2 In addition, topical corticosteroid nasal sprays are used to control inflammation.2

The sinus cavities surround vital structures in the skull, and thus serious complications may occur if the infection invades adjacent structures. Inadequately treated rhinosinusitis may result in periorbital cellulitis, subperiosteal infections (Pott’s puffy tumor), cavernous sinus thrombosis, meningitis, and brain abscesses, although these complications are very uncommon. If there is any evidence of serious complications, immediate evaluation is necessary.

In summary, rhinosinusitis is one of the most common presenting complaints in the United States. The blockage of the ostiomeatal complex by inflammation or anatomic variations is a major pathogenic factor in the development of rhinosinusitis. Frequently, inflammation related to a viral infection is the precipitating cause for the development of bacterial rhinosinusitis. Certain other factors such as asthma or nasal polyps are also associated with a higher incidence of rhinosinusitis. Imaging and various laboratory tests are ordered in only specific situations. Antibiotics may be used for the treatment of acute rhinosinusitis and CRS, although the treatment success may vary with the latter.

**IMMUNOLOGY**

- Patients with recurrent rhinosinusitis should be evaluated for immunodeficiencies.
- CRS is characterized by basement membrane thickening, goblet cell hyperplasia, subepithelial edema, and mononuclear infiltration.
- The predominant inflammatory cell in tissue of patients with CRSwNP differs from CRSsNP; eosinophils predominate in CRSwNP and neutrophils predominate in CRSsNP.

**CLINICAL PEARLS**

- Rhinosinusitis is inflammation of the paranasal sinus cavities.
- Acute rhinosinusitis is defined as symptoms lasting <4 weeks, subacute rhinosinusitis is between 4–8 weeks, and CRS is defined as symptoms lasting >8–12 weeks.
- Viral upper respiratory infection is a major contributing factor in the development of acute rhinosinusitis. The majority of the cases resolve with supportive care and do not require antibiotics.
- Rhinosinusitis is associated with other conditions such as allergic rhinitis, asthma, and nasal polyps.
- CT scan of the sinuses is not recommended for the diagnosis of acute rhinosinusitis. CT scan of the sinuses is indicated for certain cases such as chronic, refractory, or recurrent rhinosinusitis.

REFERENCES
Asthma classification

Alan P. Koterba, M.D., Ph.D., and Carol A. Saltoun, M.D.

ABSTRACT

Asthma is a chronic inflammatory disorder of the airways resulting physiologically in hyperreactivity and clinically in recurrent episodes of wheezing, chest tightness, or coughing. Airway inflammation, smooth muscle contraction, epithelial sloughing, mucous hypersecretion, bronchial hyperresponsiveness, and mucosal edema contribute to the underlying pathophysiology of asthma. Diagnostic tests such as methacholine or mannitol challenges or spirometry (pre- and postbronchodilator responses) help to identify such underlying pathophysiology via assessments of bronchial hyperreactivity and lung mechanics but are imperfect and ultimately must be viewed in the context of a patient’s clinical presentation including response to pharmacotherapy. The National Asthma Education and Prevention Program Expert Panel Report (2007) classifies asthma into either intermittent or persistent, and the latter is either mild, moderate, or severe. Some patients change in either direction from intermittent to persistent asthma. In addition, patients with asthma may be classified as allergic (IgE mediated), nonallergic (often triggered by viral upper respiratory tract infections or no apparent cause), occupational, aspirin-exacerbated respiratory disease, potentially (near) fatal, exercise induced, and cough variant asthma. In the latter, the patients have a nonproductive cough that responds to treatment for asthma but not with antibiotics, expectorants, mucolytics, antitussives, beta-2-adrenergic agonists, treatment for acid reflux, or rhinosinusitis. Thus, cough variant asthma is in the differential diagnosis of chronic cough.

Because of its complex pathophysiology, asthma is difficult to define simplistically. The American Thoracic Society and the National Asthma Education and Prevention Program (NAEPP) define asthma in different ways but both concur that it is a chronic inflammatory disorder of the airways resulting physiologically in hyperreactivity and clinically in recurrent episodes of wheezing, chest tightness, or coughing. Airway inflammation, smooth muscle contraction, epithelial sloughing, mucous hypersecretion, bronchial hyperresponsiveness, and mucosal edema are all responsible for the underlying pathophysiology of asthma. Diagnostic tests such as methacholine or mannitol challenges or spirometry (pre- and postbronchodilator responses) help to identify such underlying pathophysiology via assessments of bronchial hyperreactivity and lung mechanics but are imperfect and ultimately must be viewed in the context of a patient’s clinical presentation. Once a diagnosis is made, however, asthma is usually classified according to etiology or severity.

Allergic asthma may occur at any time but is most common between 4 and 40 years of age. Allergic asthma implies a temporal relationship that exists between clinical reactivity and allergen exposure. As discussed in another article of this journal, patients inhale allergens such as pollen, mold, house-dust mite, and animal proteins that trigger asthma symptoms by dimerizing (bridging) the high-affinity IgE receptors located on mast cells in the lungs. Both early and late-phase reactions contribute to the disease state. Positive skin tests for these allergens may corroborate the diagnosis but should be interpreted within the clinical context.

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Copyright © 2012, OceanSide Publications, Inc., U.S.A.
ence relief when at work, away from their pet. These patients may display the chronic airway inflammatory changes that only resolve after prolonged pharmacotherapy and months of allergen avoidance. With all these scenarios, it is not surprising that ≥75% of patients with persistent asthma may have an allergic component. Allergen avoidance is, therefore, the safest, most cost-effective therapy for allergen-induced asthma.

Nonallergic asthma is not associated with an allergic cause. Allergen-specific IgE is not detected and there is no temporal relationship between allergen exposure and symptoms. It is typically exacerbated by upper respiratory tract or sinus infections, gastrointestinal reflux, and irritant exposures such as tobacco smoke, crying, or cold air. These same factors may also worsen other types of asthma. Nonallergic asthma is most common in patients <4 years or >40 years of age and may be persistent or intermittent.

Mixed asthma describes patients with a combination of allergic and nonallergic asthma. For instance, a mixed asthma patient might display perennial asthma symptoms that worsen during the months of their ragweed allergy but have no positive skin test for a perennial allergen.

Occupational asthma may be either allergic or nonallergic and is estimated to account for as high as 5–10% of all adult-onset asthma. The longer a patient remains exposed to the culprit allergen or chemical, the more likely they are to have long-term or irreversible disease. Abnormal pulmonary function tests and increased bronchial hyperresponsiveness are also associated with a worse prognosis. Multiple causes of occupational asthma exist including plicatic acid in western red cedar, metal salts, pharmaceutical agents, animal or plant proteins, and industrial chemicals such as tolune diisocyanate, phthalic and trimellitic anhydride, and polyvinyl chloride. Prompt removal of the patient from exposure to the causative agent is optimal. Occupational asthma is further discussed in another chapter of this syllabus.

Exercise-induced asthma may exist in symptomatic patients with persistent asthma or as the only manifestation of mild asthma. Symptoms including cough, wheeze, shortness of breath, and chest pain or discomfort typically occurring 8–15 minutes after onset of exercise in cold, dry environments. Exercise-related respiratory symptoms limit physical activities and negatively impact daily lives. The mechanism of bronchoconstriction is not understood completely, although inflammatory mediators released in response to heat and water loss have been postulated. The diagnosis is usually clinical with a convincing history and an appropriate response to short-acting bronchodilators, although a ≥10% decline in forced expiratory volume in 1 second (FEV1) after an exercise challenge test can be helpful.

Nonpharmacologic treatment includes warming up, covering the nose and mouth in cold weather, improved physical conditioning, and exercising in warm, moist environments. Pharmacologic therapy usually includes an inhaled short-acting bronchodilator 10–20 minutes before exercise. Use of additional agents such as long-acting β-agonists (formoterol more than salmeterol because of shorter onset of action) or leukotriene receptor antagonists also may be of benefit. Inhaled corticosteroids taken regularly can help reduce symptoms of exercise-induced asthma.

Cough variant asthma presents with the primary symptoms of paroxysmal cough without wheeze and may occur after upper respiratory tract infections, exercise, allergic triggers, or nonspecific triggers. Diagnosis and subsequent treatment of this condition are often delayed because of alternate or coexisting causes of cough-like gastrointestinal reflux, rhinitis, and rhinosinusitis. Further complicating the diagnosis, the patient’s FEV1 may be normal on office spirometry. The cough is usually refractory to treatment with antibiotics, expectorants, antitussives, and β2-adrenergic agonists but often responds to inhaled steroids and, if necessary, oral steroids.

Aspirin-induced asthma (aspirin-exacerbated respiratory disease [AERD]) is characterized by severe bronchoconstriction, lacrimation, and rhinorrhea within minutes or up to 3 hours after ingestion of aspirin or other nonselective nonsteroidal anti-inflammatory medications. However, acetaminophen, nonacetylated salicylates such as salsalate, and cyclooxygenase 2 inhibitors appear to be safe in these patients. Aspirin sensitivity occurs in 5–10% of patients with moderate-to-severe asthma and in up to 20–30% of patients with asthma who have nasal polyposis and chronic rhinosinusitis. These latter two conditions are further discussed in other articles of this journal. Patients with the triad of asthma, nasal polyposis, and aspirin sensitivity are classified as having AERD. These patients tend to have more severe asthma and usually present with aspirin sensitivity in the third or fourth decade of life. It has been reported that the overexpression of leukotriene C4 (LTC4) synthase and the consequent higher production of inflammatory and bronchoconstrictive leukotrienes such as LTD4 may play a role in the underlying pathogenesis. Aspirin desensitization of AERD patients has provided benefit in asthma control, reduced frequency of sinus infections, and need for polyp removal surgery. Aspirin-sensitive patients requiring aspirin for ischemic heart disease also may be desensitized. When considering aspirin desensitization, benefits must be weighed against risks, including gastrointestinal complications, and strategies for their management.
Patients categorized with potentially (near) fatal asthma, discussed further in another article of this journal, must have a history of asthma resulting in one of the following: intubation, respiratory acidosis or failure, two or more episodes of pneumothorax or pneumomediastinum, or two or more episodes of acute severe asthma (status asthmaticus) despite appropriate therapy with oral corticosteroids. Malignant potentially fatal asthma describes a patient with potentially fatal asthma who is noncompliant with medications or follow-up. Sometimes depot methylprednisolone may be necessary to prevent hospitalizations and help guarantee that the patient receives a needed course of corticosteroid therapy. Both classifications of potentially fatal and malignant potentially fatal asthma may be applied to any other type of patient with asthma and may further serve to remind the health care provider to treat these patients aggressively, especially in the face of an exacerbation.

Vocal cord dysfunction is an asthma mimic that is increasingly recognized in patients with suspected asthma. The diagnosis is identified when there is a flattened inspiratory flow volume loop or direct visualization of vocal cord adduction on inspiration during laryngoscopy. Treatment consists of breathing maneuvers that can be taught with the assistance of a speech therapist. In some patients, deep-seated psychopathology such as physical or sexual trauma has occurred but is not revealed in the course of treatment of asthma. It is important to note that steroids (inhaled or oral) provide no benefit with this disorder and patients often go unrecognized for long periods of time unnecessarily treated with steroids.

As mentioned previously, asthma is a heterogeneous disease and is not easily defined or categorized. Attempts have been made to classify asthma based on phenotype. There are three asthma phenotypes that have been identified in children: transient wheezer, nonatopic wheezer, and atopic wheezer (discussed in different article). The phenotypic spectrum of asthma in adults includes an eosinophilic, neutrophilic, and severe asthmatic phenotype although they are still not well defined.

It also has been proposed that asthma be recognized by the endotype or distinct subtype such as AERD or allergic bronchopulmonary aspergillosis with distinct pathophysiological processes instead of by phenotype.

The types of asthma discussed previously are not mutually exclusive, and often patients have components of several different categories. As a result, appropriate asthma treatment is often determined by the severity of asthma. The NAEPP classifies asthma severity according to frequency of clinical symptoms and objective measurements of lung function. Specifically, patients are classified into four categories based on daytime symptoms, nocturnal symptoms, and FEV$_1$ before therapy. Patients should always be placed in the category that describes their worst parameter.

Patients with mild intermittent asthma may be distinguished from the other three categories because they do not require daily, anti-inflammatory asthma therapy. These patients have daily symptoms less than two times per week, nighttime symptoms less than two times per month, and an FEV$_1$ of >80%.

Patients with mild persistent asthma display daily-time symptoms more than twice a week (but not daily), nighttime symptoms more than twice a month (but less than once a week), and an FEV$_1$ of >80% while moderate persistent asthmatic patients have daily daytime symptoms, nighttime symptoms more than once per week, or an FEV$_1$ between 61 and 79%. Patients with severe persistent asthma display continuous symptoms, frequent nighttime awakenings, or an FEV$_1$ of <60%. The NAEPP applies these same categorizations to children <5 years of age but does not include the FEV$_1$ determinations given the difficulty in obtaining such measurements in younger children.

Over time, patients may be reclassified into different asthma severity categories, but most should be well controlled once they are placed on appropriate therapy. It is important to routinely assess asthma control on each clinic visit. Once therapy is initiated the goal should be to minimize asthma symptoms, functional impairments, and the risk of exacerbations. Therapy should be adjusted based on the degree of control. A stepwise algorithm has been published by the National Institutes of Health/NAEPP to guide the course of therapy.

IMMUNOLOGY

- The early phase symptoms of allergic asthma occur after allergen-specific IgE binds the high-affinity IgE receptor on the surface of lung mast cells.
- The overexpression of LTC$_4$ synthase may contribute to aspirin-induced asthma associated with large increases in LTD$_4$ production, which can be measured as its metabolite, LTE$_4$.

CLINICAL PEARLS

- An awareness of the asthma classification scheme helps guide diagnosis and treatment.
- Mild intermittent asthma patients may be treated with albuterol alone.
- Consider allergen immunotherapy in patients who have mild-to-moderate allergic asthma.
- Patients with cough variant asthma may have normal spirometry but may require inhaled corticosteroids or prednisone for 1–2 weeks to relieve their persistent cough.
REFERENCES


Pediatric asthma: Principles and treatment

Rachel G. Robison, M.D., and Rajesh Kumar, M.D.

ABSTRACT

Approximately one-half of children with asthma present with symptoms before 3 years of age. The typical history describes recurrent episodes of wheezing and/or cough triggered by a viral upper respiratory infection, activity, or changes in weather or seasons. When symptoms occur after a viral respiratory infection, children with asthma often take longer than the usual week to recover fully from their respiratory symptoms. Wheezing and coughing during exercise or during laughing or crying and episodes triggered in the absence of infection suggest asthma. A trial of bronchodilator medication should show symptomatic improvement. The goal of asthma therapy is to keep children “symptom free” by preventing chronic symptoms, maintaining lung function, and allowing for normal daily activities. Avoidance of triggers identified by history, such as second-hand cigarette smoke exposure and allergens identified by skin-prick testing, can significantly reduce symptoms. According to the National Asthma Education and Prevention Program 2007 report (Expert Panel Report 3 [EPR-3]. Guidelines for the diagnosis and management of asthma: Summary report 2007. J Allergy Clin Immunol 120:S94–S138, 2007.), if impairment symptoms are present >2 days/week or 2 nights/mo, the disease process is characterized as persistent, and in all age groupings, inhaled corticosteroids (ICS) are recommended as the preferred daily controller therapy. Other controller medications such as cromolyn must be given three to four times a day and provides less efficacy than ICS. Montelukast is approved for children ≥12 months old and is often used for its ease of daily oral dosing. Long-acting beta2-adrrenergic agonists should not be used as monotherapy (i.e., should only be used with ICS).

Asthma is the most common chronic disease of childhood, and approximately one-half of children with asthma present with symptoms before 3 years of age. However, nonasthmatic wheezing and cough are also common in pediatrics and frequently create a diagnostic challenge to the practitioner.

Physicians must balance the importance of identifying asthma for therapy early in the course of disease with the responsibility to consider what else may cause the child’s respiratory symptoms. To diagnose asthma in a child, one must be familiar with a differential diagnosis for wheezing and episodic cough, as shown in Table 1. The history is of utmost importance in the diagnosis of childhood asthma. The typical history describes recurrent episodes of wheezing and/or cough triggered by a viral upper respiratory infection, activity, or changes in weather or seasons. When symptoms follow a viral respiratory infection, children with asthma often take longer than the usual week to recover fully from their respiratory symptoms. Wheezing and coughing during exercise or during laughing or crying and episodes triggered in the absence of infection suggest asthma. A trial of bronchodilator medication should show symptomatic improvement. Asking about prior emergency room visits, hospitalizations, or systemic steroid courses often reveals the frequency and severity of these episodes. A history of second-hand smoke exposure, gastroesophageal reflux, or sinusitis may identify the primary cause of respiratory symptoms, but frequently these also are triggers of underlying asthma. A personal or immediate family history of atopic disease, such as allergic rhinitis, food allergy, or eczema, increases the likelihood a child will have persistent wheezing, especially if symptoms present in the 1st year of life.

Between asthma exacerbations, typical physical exam findings may be normal or may have subtle signs such as increased chest anterior–posterior diameter, prolongation of the expiratory phase of the respiratory cycle, or decreased air entry. When acutely symptomatic, the child may not be hypoxic but is usually tachypneic with symmetric bilateral expiratory wheezing. Physical signs of overt respiratory distress are often
less prominent in older children and teens compared with infants and younger children. Because the physical exam is often normal between exacerbations, a complete exam should be used to rule out diseases that mimic asthma. The presence of persistent focal findings on repeat exams should not be attributed solely to asthma and deserves further investigation.

Traditional pulmonary function testing is difficult to perform in young children and is generally not recommended in children <5 years of age. However, other tests may prove useful when evaluating respiratory disease. At least one baseline chest x ray should be performed to rule out a structural chest abnormality. Additional studies may be ordered to rule out different diagnoses or factors complicating asthma, such as gastroesophageal reflux, microaspiration, sinusitis, cystic fibrosis, sickle cell disease, tuberculosis, or immunodeficiency. As discussed in another article of this journal, skin-prick testing to environmental allergens documents the presence of sensitization and guides avoidance therapy in atopic children. After the age of 5 years, traditional pulmonary function testing may be helpful to document airway resistance, flow volume loops, and lung volumes. Methacholine challenge may be helpful to document airway responsiveness but is not specific for asthma alone.

The goal of asthma therapy is to keep children “symptom free” by preventing chronic symptoms, maintaining lung function, and allowing for normal daily activities. Avoidance of triggers identified by history, such as second-hand cigarette smoke exposure and allergens identified by skin-prick testing, can significantly reduce symptoms and should be addressed at each physician encounter. In 2007, The National Asthma Education and Prevention Program published updated clinical practice guidelines for the medical treatment of asthma with a new focus on impairment and risk as the two key domains of severity and control of asthma. The updated guidelines address children in three groups separated by age: 0–4 years of age, 5–11 years of age, and youths ≥12 years of age. In assessment of severity, if impairment symptoms are present ≥2 days/week or ≥2 nights/mo, the disease process is characterized as persistent, and in all age groupings, inhaled corticosteroids (ICSs) are recommended as the preferred daily controller therapy. The addition of a risk assessment provides recommendations for therapy in children who may be at higher risk for exacerbation but have low levels of impairment between exacerbations. Recommendations in this case include considering daily long-term therapy initiation especially in children aged 0–4 years with risk factors for persistent asthma and more than four episodes of wheezing in the past year lasting more than 1 day. Similarly, children aged 0–4 years with two exacerbations requiring oral corticosteroids in the past 6 months and children aged 5–11 years or youths ≥12 years of age with two or more exacerbations requiring corticosteroids in the past year would meet risk criteria to start or step up long-term controller therapy.

### Table 1: Differential diagnosis of asthma in children

<table>
<thead>
<tr>
<th>Infants</th>
<th>Toddlers</th>
<th>Older children (also consider toddlers’ diagnoses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis</td>
<td>Viral airway infection, bronchiolitis, and croup</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Pneumonia and pertussis</td>
<td>Pneumonia and pertussis</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Gastroesophageal reflux</td>
<td>Other infectious processes, including pertussis and croup</td>
</tr>
<tr>
<td>Aspiration, foreign body</td>
<td>Aspiration, foreign body</td>
<td>Pneumonia, including <em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Cystic fibrosis</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Epiglottitis</td>
<td>Epiglottitis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Anaphylaxis</td>
<td>Immunodeficiency syndromes</td>
</tr>
<tr>
<td>Immunodeficiency syndromes</td>
<td>Immunodeficiency syndromes</td>
<td>Ciliary dyskinesia syndromes</td>
</tr>
<tr>
<td>Ciliary dyskinesia syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subglottic stenosis (also prior intubation)</td>
<td>Vascular ring, other extrinsic airway compression</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Laryngotraceomalacia</td>
<td>Tracheoesophageal fistula</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Laryngeal web</td>
<td>Bronchopulmonary defects</td>
<td>Other infectious processes, including pertussis and croup</td>
</tr>
<tr>
<td>Immunodeficiency syndromes</td>
<td>Immunodeficiency syndromes</td>
<td>Pneumonia, including <em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td>Ciliary dyskinesia syndromes</td>
<td></td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor, compressing airway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic inhalation</td>
</tr>
</tbody>
</table>

Table 1: Differential diagnosis of asthma in children

<table>
<thead>
<tr>
<th>Adolescents</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</td>
<td>Sinusitis</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Pneumonia, including <em>Mycoplasma pneumoniae</em></td>
<td>Vocal cord dysfunction</td>
</tr>
<tr>
<td>Pneumonia, including <em>Mycoplasma pneumoniae</em></td>
<td>Habit or psychogenic cough</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Tuberculosis</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>Habit or psychogenic cough</td>
<td>Human immunodeficiency virus</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Anaphylaxis</td>
<td>Tumor, compressing airway</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Tumor, compressing airway</td>
<td>Toxic inhalation</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Toxic inhalation</td>
<td></td>
</tr>
<tr>
<td>Tumor, compressing airway</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Allergy and Asthma Proceedings**
The type, amount, and dosing of medication therapy for asthma is determined by the initial assessment of asthma severity and ongoing categorization of control. In general, low-dose ICS is the preferred medication for treatment of mild persistent disease. Alternative medications in all ages include cromolyn and leukotriene receptor antagonists (montelukast). Nedocromil (if available) and theophylline are included as alternatives in children >5 years of age. Cromolyn must be given three to four times a day and provides less efficacy than ICS. Montelukast is approved for children ≥12 months old and is often used for its ease of daily oral dosing. Of note, the Food and Drug Administration (FDA) has instituted labeling of montelukast after re-evaluation of asthma in children 5–11 years of age, it is equally acceptable to use low-dose ICS in combination with anti-inflammatory effects.

For patients with moderate persistent disease, it is preferred to start with a medium-dose ICS in children ≤4 years of age. However, for moderate persistent disease in children 5–11 years of age, it is equally acceptable to use low-dose ICS in combination with either montelukast or a long-acting β-agonist (LABA) or to start the patient at a medium dose of ICS. In children >12 years of age, addition of LABA to low-dose ICS is preferred over addition of montelukast in the National Asthma Education and Prevention Program guidelines. However, LABAs carry a black box warning for possible contribution to asthma-related deaths and a new advisory was issued by the FDA in 2010 regarding LABA use.

Although some FDA recommendations are considered controversial, it is well accepted that LABAs should not be used as a monotherapy (i.e., should only be used in conjunction with ICSs) and should not be used in patients with adequate asthma control on low-to medium-dose ICS. The beneficial effects of LABA use should be weighed against the risk of exacerbation by the health care professional, and these risks and benefits should always be discussed with parents before initiation of therapy. In children, asthma education should include the regular reinforcement of proper delivery device technique. For metered-dose inhalers, this must include a valved holding chamber to ensure consistent medication delivery to the airways. Dry-powder inhaler devices do not require a valved holding chamber, but instruction on proper technique is equally important.

Many parents are hesitant to administer inhaled steroids for fear of side effects. Poor adherence to controller therapy is one of the largest barriers in consistent asthma care, so physicians must take time to address the benefit: risk ratio of ICSs with the family. To date, the only significant ICS side effect identified in children is an initial decrease in growth velocity resulting in ~1-cm difference in height from peers after 1 year of use. This difference does not progress after the initial year of therapy, and some studies suggest a decrease in height difference over time. Studies in even younger age groups over 2 years show similar effects on short-term growth, although effects on long-term growth with dosing in the 1st years of life are still not known. Studies of bone mineral density in children have shown a small decrease in bone mineral accretion in boys, but not in girls with cumulative use of ICS indicating a small potential for decreasing bone mineral density in boys through puberty. Epidemiological evaluations of cataract incidence have not been conclusive in finding an increased risk with ICS use alone. Despite these potential adverse effects, parents should understand that poor asthma control may lead to severe and potentially life-threatening exacerbations and more frequent systemic steroid use, which can also suppress growth with additional unwanted side effects.

Parents frequently ask, “Will my child outgrow asthma?” Most children who wheeze in infancy will not have persistent wheezing in later childhood. Known risk factors for persistent wheezing include smoke exposure, family history of asthma or atopy, and personal history of atopic markers (such as allergic rhinitis, eczema, or increased eosinophil counts). The subset of children who have persistent wheezing have normal initial infant pulmonary functions but will show decreased forced expiratory volume in 1 second compared with peers by 6 years of age. Longitudinal data also reveal that decreased pulmonary function in middle childhood may persist into adult life and may be correlated with severity. Therefore, early disease severity may correlate with a decreased chance of quiescent asthma or “outgrowing asthma,” later in life. Hence, airway remodeling appears to occur early in life as has been suggested by biopsy studies in preschool children and may prove to be an important prognostic factor for asthma.

IMMUNOLOGY

- Bronchoalveolar lavage fluid from wheezing children has increased numbers of lymphocytes, polymorphonuclear cells, macrophages, and monocytes compared with normal controls. Leukotriene B₄, leukotriene C₄, and prostaglandin E₂ also are increased.
- Even in young preschool children with recurrent wheezing, there is evidence for eosinophilic infiltration and basement membrane thickening on biopsy.
- There is some evidence to suggest that there may be a deficit in interferon production in airway epithelium of asthmatic individuals.
CLINICAL PEARLS

- Childhood wheezing and cough are common and do not always represent asthma.
- The physician should be familiar with an age-appropriate differential diagnosis of asthma and what history and physical exam markers predict a risk for persistent wheezing.
- ICSs are preferred first-line controller therapy in childhood persistent asthma. The only consistent side effect shown in children is an initial decrease in growth velocity, which does not appear to be progressive. More data are needed to evaluate the long-term safety profile of inhaled steroids in young preschool children.
- Asthma trigger avoidance, medication compliance, and medication administration technique should be reviewed at interval physician encounters. Valved holding chambers should be used with metered-dose inhaler medicines in children.

REFERENCES

Chapter 11

The infant and toddler with wheezing

Rachel Glick Robison, M.D., and Anne Marie Singh, M.D.

ABSTRACT

Recurrent wheezing is common in young infants and toddlers with 27% of all children having at least one wheezing episode by the age of 9 years. The initial wheezing episodes in young children often are linked to respiratory infections due to viral pathogens such as respiratory syncytial virus, rhinovirus, human metapneumovirus, and influenza virus. Bacterial colonization of the neonatal airway also may be significant in the late development of recurrent wheeze and asthma. Some 60% of children who wheeze in the first 3 years of life will have resolution of wheezing by age 6 years (“transient early wheezers”). Children who are “transient early wheezers” have reduced lung function, which remains low at age 6 years, although wheezing has ceased when compared with children who have never wheezed. In contrast, “nonatopic wheezers” represent 20% of wheezing toddlers <3 years of age. These children have more frequent symptoms during the first year of life and may continue to wheeze through childhood, although typically, episodes become less frequent by early adolescence. Lung function in “nonatopic wheezers” is slightly lower than in control subjects from birth to 11 years of age, but they do not have bronchial hyperreactivity on methacholine challenge. The third phenotype refers to “atopic wheezing” or wheezing associated with IgE sensitization. This phenotype accounts for the last 20% of wheezing children <3 years of age. These “atopic wheezers” have normal lung function in infancy; however, lung function is reduced by age 6 years and bronchial hyperreactivity typically is observed.


Recurrence is a common issue in young infants and toddlers with 27% of all children having at least one wheezing episode by the age of 9 years. Early childhood wheezing accounts for frequent emergency room visits and 3% of all hospitalizations among children. However, these infants and toddler wheezers represent a heterogeneous phenotype, and it can be challenging to characterize these patients because of multiple phenotypes within this age group. With an increase in asthma prevalence over the past 20 years, the complicated nature of the early presentation of wheezing deserves special attention.

WHEEZING PHENOTYPES

Although cross-sectional analyses will identify many wheezers in this age group, longitudinal follow-up has led to a description of three common early life phenotypes: transient early wheezing, nonatopic persistent wheezing, and IgE-associated/atopic persistent wheezing.

The Tucson Children’s Respiratory Study followed over 1200 newborns for the development of wheezing and asthma. These authors found that 60% of children who wheeze in the first 3 years of life will have resolution of wheezing by age 6 years. Children with this phenotype are referred to as having transient early wheezing, the most prevalent phenotype of early wheezing. Transient early wheezers tend to wheeze with lower respiratory tract infections and often have no family history of asthma or allergen sensitization. Interestingly, those with transient early wheezing are noted to have reduced lung function that remains low at age 6 years although wheezing has ceased when compared with children who have never wheezed. In contrast, nonatopic wheezing represents 20% of wheezing toddlers <3 years of age. These children have more frequent symptoms during the first year of life and may continue to wheeze through childhood, although typically, episodes become less frequent by early adolescence. Lung function in nonatopic wheezers is slightly lower than in control subjects from birth to 11 years of age, but they do not have bronchial hyperreactivity on methacholine challenge. These findings are thought to be secondary to alterations in regulation of airway motor tone. The final phenotype refers to atopic wheezing or wheezing associated with IgE sensitization. This phenotype accounts for the last 20% of wheezing children <3 years of age. Symptoms in...
atopic wheezers often begin after age 1 year and are associated with early food or aeroallergen sensitization. These atopic wheezers have normal lung function in infancy; however, lung function is reduced by age 6 years and bronchial hyperreactivity is often observed.1

RESPIRATORY TRACT INFECTIONS AND EARLY WHEEZING

Often, the initial wheezing episodes in young children are linked to respiratory infections due to viral pathogens. Common pathogens associated with wheezing include respiratory syncytial virus, rhinovirus, human metapneumovirus, influenza, and others. The importance of viral pathogens in the development of asthma has been studied in several cohorts. Children hospitalized with respiratory syncytial virus are at increased risk for the development of asthma. Using newer advanced molecular techniques in children at high risk for asthma development, symptomatic infant rhinovirus illnesses were the most significant predictor of subsequent development of asthma at age 6 years.3 Bacterial colonization of the neonatal airway also may be significant in the late development of recurrent wheeze and asthma.4

Only a small subset of children who wheeze early in life will develop persistent asthma, and parents often seek anticipatory guidance regarding future asthma risk. To address this question, an active area of research involves identifying predictors for which children are at a higher risk to go on to develop asthma. The first asthma predictive index was developed based on observations made in the Tucson Children’s Respiratory Study. This index had a positive predictive value of 47.5–51.5% for the development of asthma between ages 6 and 13 years and a negative predictive value of 91.6%.5 A modified asthma predictive index was used in a cohort of children at high risk for development of persistent asthma in the Prevention of Early Asthma in Kids study as shown in Table 1.5 A child defined to be at risk has recurrent episodes of wheezing with one major criteria (parental history of asthma, physician-diagnosed atopic dermatitis, or sensitization to at least one aeroallergen) or two of three minor criteria (sensitization to milk, egg, or peanut; wheezing unrelated to viral illness; and/or serum eosinophilia ≥4%). Most ongoing research has now adopted this modified asthma predictive index for classification of children at risk for continued wheezing.

### APPROPRIATE TO THE INFANT AND TODDLER WITH EARLY WHEEZING

A detailed medical history should be obtained in any child with recurrent wheezing. Special attention should be given to the timing and pattern of wheezing episodes and if any symptoms of cough and limitation occur outside of viral illness. Wheezing associated with feeding, failure to thrive, or that has little response to β2-adrenergic agonist therapy should encourage the provider to consider other diagnoses. Evaluation of infants and toddlers with recurrent wheezing should include assessment of comorbid gastroesophageal reflux, microaspiration, and feeding disorders. A complete examination should be performed with focus on the upper and lower respiratory tracts and chest. A normal examination in between wheezing episodes does not exclude the diagnosis of recurrent wheezing or asthma.

Therapy for the infant and toddler with recurrent wheezing should be tailored to the patient based on the 2007 National Asthma Education and Prevention Program guidelines.6 Children ages 0–4 years with intermittent wheeze with symptoms and need for short-acting β2-adrenergic agonist therapy ≤2 days/week may be symptomatically treated with short-acting β2-adrenergic agonist therapy. Low-dose inhaled corticosteroids (ICSs) are the preferred therapy for children with persistent symptoms >2 days per week in this age group. Physicians should consider risk when assessing disease severity and consider a step up in care in patients with two or more exacerbations in 6 months requiring oral corticosteroids or in those with four or more episodes of wheezing per year lasting >1 day who have risk factors for persistent asthma.

Although ICSs appear to help with symptom and exacerbation control, data do not support that their use alters the natural course of asthma development.7 Although treatment with ICSs did decrease symptoms and exacerbations, it had no effect on the future development of asthma symptoms or lung function in the 3rd treatment-free year. In a similar vein, Childhood Asthma Management of Program data revealed that neither budesonide nor nedocromil is better than placebo in terms of effects on lung function, but inhaled budesonide improved control of asthma symptoms

<table>
<thead>
<tr>
<th>Table 1 Modified asthma predictive index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Parental history of asthma</td>
</tr>
<tr>
<td>Physician-diagnosed atopic dermatitis</td>
</tr>
<tr>
<td>Allergic sensitization to one or more aeroallergen</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Allergic sensitization to milk, egg, or peanut</td>
</tr>
<tr>
<td>Wheezing unrelated to viral illness</td>
</tr>
<tr>
<td>Serum eosinophils ≥4%</td>
</tr>
</tbody>
</table>

Source: Adapted from Ref 5.
better than placebo or nedocromil. Most recently, in a subset of children with recurrent wheezing episodes, daily low-dose ICS was not superior to an intermittent high-dose regimen in reducing asthma exacerbations.

In summary, recurrent wheezing in infants and toddlers is common and represents a heterogeneous phenotype. This variability in presentation and time course distinguishes early childhood wheezing from adult asthma. Evaluation of patients in this age group requires a thorough history and physical with particular focus on risk factors for persistence of wheezing. Through critical assessment of the impact on quality of life and of risk factors for disease progression, informed and appropriate guidance and treatment can be provided to the families of these children.

**IMMUNOLOGY**

- Children with a strong family history and/or evidence of allergic sensitization are at highest risk for persistent asthma. These children may have systemic immune dysregulation (increased Th2 and decreased regulatory and Th1 responses) related to their asthma development.
- Lower respiratory tract infection early in life may impact the early development of the pulmonary system leading to an increased risk of asthma.
- Host-specific factors, such as antiviral responses, genetic predisposition in combination with development and environment are particularly important in this age group.

**CLINICAL PEARLS**

- The majority of children (60%) with wheezing before age 3 years will have resolution of wheezing by age 6 years.
- Children who are at high risk of persistent asthma include those with history of parental asthma, personal history of atopy and allergen sensitization, wheezing outside of illness, and elevated blood eosinophils.
- Although early treatment with ICSs improves symptoms and reduces exacerbations, it does not appear to affect the natural history and progression of asthma.

**REFERENCES**

Chapter 12

Asthma: Principles of treatment

Tara F. Carr, M.D., and Anju T. Peters, M.D.

ABSTRACT

The goals of treatment are prevention of fatalities, hospitalizations, and emergency department visits, along with achieving good long-term control of asthma, with reduction of symptoms, maintenance of normal activity level, prevention of exacerbations, and accelerated loss of pulmonary function (forced expiratory volume in 1 second [FEV₁]) as well as avoiding harm from therapies. Treatment often is initiated based on severity of symptoms, physical examination findings, and, for some patients, the FEV₁ or peak expiratory flow rates. Comorbidities such as gastroesophageal reflux disease and laryngopharyngeal reflux, rhinitis or rhinosinusitis, sleep apnea, recurrent infections, smoking, and substance abuse should be addressed. Two treatment modalities are indicated only for individuals with allergic asthma: allergen-specific immunotherapy, commonly known as allergy shots, and omalizumab. Allergen immunotherapy is effective in decreasing symptoms and medication use in selected patients with mild-to-moderate allergic asthma. In addition, patients receiving allergen immunotherapy for allergic rhinitis may have a decreased risk of developing asthma. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody indicated for persistent moderate-to-severe allergic asthma, has been shown to improve asthma-related quality of life, decrease clinically significant exacerbation rates, number of courses of oral corticosteroids, and reduce the severity of exacerbations. It is administered every 2–4 weeks subcutaneously, and improvement should be ascertained after 4–6 months.


Proper treatment of asthma requires an accurate diagnosis of the type of asthma (allergic versus nonallergic) as well as its severity.1 Once a diagnosis is established, coexisting conditions that affect asthma severity such as rhinosinusitis and gastroesophageal reflux disease (GERD) should be identified and treated. Allergen avoidance is the first step in the management of allergic asthma. In addition, nonallergic triggers of asthma must be avoided in individuals with both allergic and nonallergic disease. Avoidance of triggers is frequently inadequate for the management of asthma, and medications often are required. Medical therapy varies based on the type and severity of asthma. Treatment of acute severe asthma (status asthmaticus) will be discussed in a later article of this journal.2

ALLERGIC VERSUS NONALLERGIC ASTHMA

Allergic Asthma

Indoor allergens such as molds (fungi), dust mites, pet dander, and cockroach are most closely associated with increases in asthma symptoms and severity.1 Allergen avoidance is an essential component of treatment. Mold growth from water damage in the home or workplace of an allergic asthmatic patient should be remediated. Dust-mite covers on the mattress and pillows and washing bedding will decrease exposure to dust-mite antigens. If a patient with asthma is allergic to their pet, it is strongly recommended that they limit exposure to the pet and ideally find a new home for the pet. Cockroach eradication is recommended if cockroach infestation is a problem.

Allergic bronchopulmonary aspergillosis is an immunologic reaction to Aspergillus fumigatus that will be the focus of a later article in this journal.3 It may be present in any patient with asthma who is allergic to this fungus. All patients with persistent asthma should have skin tests for A. fumigatus, and if positive, an appropriate evaluation should be performed.

Nonallergic Asthma

Patients with both allergic and nonallergic asthma commonly react to nonallergic triggers. Cold air, infections, and irritants such as diesel exhaust, indoor and
outdoor air pollution, perfume, and tobacco smoke often trigger asthma. Simple measures such as avoiding tobacco smoke and perfume or other odors can decrease symptoms. Unfortunately, many common triggers such as upper respiratory infections are difficult to avoid. Influenza is frequently more severe in patients with asthma. Therefore, it is recommended that all patients with asthma receive the influenza vaccination. Administration of the antipneumococcal polysaccharide vaccine also is recommended for all patients with asthma who are ≥19 years of age for the prevention of invasive pneumococcal disease.¹

### CONCOMITANT MEDICAL CONDITIONS

Rhinosinusitis and GERD are common triggers of asthma and/or cough. There is a detailed discussion of the diagnosis and management of acute and chronic rhinosinusitis in another article in this journal.⁵

GERD is known to trigger and exacerbate asthma.¹ A thorough history will often elicit symptoms of GERD. However, because GERD can be silent, a trial of lifestyle modification and pharmacotherapy with a proton-pump inhibitor may be of benefit in asymptomatic patients with difficult to control asthma primarily when symptoms consist of both nocturnal cough and heartburn. Lifestyle modification includes weight loss, low-fat diet, decreased caffeine and alcohol intake, raising the head of the bed 6 in., and avoiding meals for 3 hours before reclining. Oral steroids may exacerbate GERD symptoms.

### INITIATION OF THERAPY

Because asthma symptoms frequently persist despite avoidance measures, medications often are needed. The goal of treatment is prevention of fatalities, hospitalizations, and emergency department visits, along with long-term control of asthma, with reduction of symptoms, maintenance of normal activity level, prevention of exacerbations, and prevention of loss of pulmonary function. Treatment is initiated based on severity of symptoms, physical examination findings, and, for some patients, depending on the forced expiratory volume in 1 second (FEV₁) or peak expiratory flow rates. Table 1 contains details of asthma severity classification as recommended by the 2007 National Asthma Education and Prevention Program Expert Panel Report 3 (see Day, Intermittent asthma); Table 2 contains details of asthma control assessment (see Day, Well controlled). Table 3 highlights the recommended stepwise approach to therapy based on severity and symptom control.⁶

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**Table 1** Guidelines for the classification of asthma severity (persons ≥12 yr of age)

<table>
<thead>
<tr>
<th>Symptom Frequency</th>
<th>PEF or FEV₁</th>
<th>Interference with Normal Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
<td><strong>Night</strong></td>
<td></td>
</tr>
<tr>
<td>Intermittent asthma</td>
<td>≤2/wk</td>
<td>≤2 nights/mo</td>
</tr>
<tr>
<td>Mild persistent asthma</td>
<td>&gt;2/wk, &lt;1/day</td>
<td>3–4 nights/mo</td>
</tr>
<tr>
<td>Moderate persistent asthma</td>
<td>Daily</td>
<td>&gt;1 night/wk, not every night</td>
</tr>
<tr>
<td>Severe persistent asthma</td>
<td>Throughout the day</td>
<td>Often 7 times/wk</td>
</tr>
</tbody>
</table>

*Source: Adapted from Ref. 6.*

**Table 2** Guidelines for the classification of asthma control (persons ≥12 yr of age)

<table>
<thead>
<tr>
<th>Symptom Frequency</th>
<th>PEF or FEV₁</th>
<th>ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
<td><strong>Night</strong></td>
<td></td>
</tr>
<tr>
<td>Well controlled</td>
<td>≤2 days/wk</td>
<td>≤2 nights/mo</td>
</tr>
<tr>
<td>Not well controlled</td>
<td>&gt;2 days/wk</td>
<td>1–3 nights/wk</td>
</tr>
<tr>
<td>Very poorly controlled</td>
<td>Throughout the day</td>
<td>≥4 nights/wk</td>
</tr>
</tbody>
</table>

*Source: Adapted from Ref. 6.*

ACT = asthma control test, a commonly used, validated questionnaire for assessing asthma control; PEF = peak expiratory flow; FEV₁ = forced expiratory volume in 1 s.
Commonly used asthma medications including those recommended by the National Asthma Education and Prevention Program Expert Panel Report 3 will be reviewed briefly. References for more comprehensive reviews are included. Table 4 includes examples of medications in each class.

### Inhaled Rapid-Acting $\beta_2$-Adrenergic Agonists

Short-acting $\beta_2$ adrenergic agonists (SABAs) are bronchodilators indicated for breakthrough symptoms that occur despite daily controller medications or during an exacerbation. If these medications are needed >2 days a week or 2 nights a month, an increase in daily controller medication is recommended. Albuterol is the most commonly used medication in this class. Its bronchodilator effects begin within 5 minutes of use, peak within 60 minutes, and last up to 6 hours. The maximum recommended dose is 2 puffs every 4 hours. If a higher dose of $\beta_2$-adrenergic agonist is required, patients should be instructed to increase their inhaled corticosteroid (ICS) dose, begin an oral cortico-

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**Table 3  Stepwise approach to asthma management for patients ≥12 years of age**

<table>
<thead>
<tr>
<th>Step 1 (intermittent only)</th>
<th>Preferred Medication</th>
<th>Alternative Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA as needed</td>
<td>Cromolyn, LTRA, theophylline</td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS</td>
<td>Low-dose ICS + either LTRA, theophylline or zileuton</td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS + LABA or medium-dose ICS</td>
<td>Medium-dose ICS + either LTRA, theophylline or zileuton</td>
<td></td>
</tr>
<tr>
<td>Medium-dose ICS + LABA</td>
<td>Medium-dose ICS + LABA and consider omalizumab</td>
<td></td>
</tr>
<tr>
<td>High-dose ICS + LABA</td>
<td>High-dose ICS + LABA + oral corticosteroid and consider omalizumab</td>
<td></td>
</tr>
<tr>
<td>High-dose ICS + LABA + oral corticosteroid and consider omalizumab</td>
<td>For all patients; SABA as needed for symptoms, address environmental control, and manage comorbidities</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Adapted from Ref. 6.

SABA = short acting $\beta_2$-agonist; LABA = long acting $\beta_2$-agonist; ICS = inhaled corticosteroid; LTRA = leukotriene receptor antagonist.

**Table 4  Commonly used asthma medications**

<table>
<thead>
<tr>
<th>Class of Medication</th>
<th>Examples (generic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled short-acting $\beta_2$-agonists</td>
<td>Albuterol and levalbuterol</td>
</tr>
<tr>
<td>ICSs</td>
<td>Beclomethasone dipropionate MDI, budesonide DPI and Respules, ciclesonide MDI, fluticasone DPI, and mometasone DPI</td>
</tr>
<tr>
<td>(LABA)</td>
<td>Salmeterol, formoterol</td>
</tr>
<tr>
<td>Combination ICS and LABA</td>
<td>Fluticasone at 100, 250, or 500 $\mu$g with salmeterol at 50 $\mu$g</td>
</tr>
<tr>
<td></td>
<td>Budesonide at 80 and 160 $\mu$g with 4.5 $\mu$g of formoterol</td>
</tr>
<tr>
<td></td>
<td>Mometasone at 100 and 200 $\mu$g with 5 $\mu$g of formoterol</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>Prednisone and methylprednisolone</td>
</tr>
<tr>
<td>LTRAs and 5-lipoxygenase inhibitors</td>
<td>Montelukast, zafirlukast, and zileuton</td>
</tr>
</tbody>
</table>

**ICS = inhaled corticosteroids; LABA = long acting $\beta_2$-agonist; LTRAs = leukotriene receptor antagonists; MDI = metered-dose inhaler; DPI = dry powder inhaler.**

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**MEDICATIONS**

Commonly used asthma medications including those recommended by the National Asthma Education and Prevention Program Expert Panel Report 3 will be reviewed briefly. References for more comprehensive reviews are included. Table 4 includes examples of medications in each class.

**Inhaled Rapid-Acting $\beta_2$-Adrenergic Agonists**

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costeroid, and/or call their health care professional for advice; sometimes emergency department evaluation is needed. Common side effects of $\beta_2$-adrenergic agonists include tremors, tachycardia, and palpitations. Asthma fatalities have been associated with excessive use of SABAs. The deaths are most likely caused by inadequate treatment of the underlying asthma. Thus, physicians should monitor closely the amount of SABAs they prescribe for each patient. In addition to treating acute symptoms of asthma, SABAs are effective for prophylaxis of exercise-induced asthma.

**Inhaled Corticosteroids**

ICSs are the first-line treatment for persistent asthma. ICSs reduce inflammation and improve asthma symptom scores, lung function, and quality of life. They also reduce the need for oral steroids, acute care visits, and hospitalizations. The most common ICS side effects are infrequent and include oral candidiasis and voice change (hoarseness). Proper inhaler technique, mouth rinsing, and gargling can decrease the incidence of thrush. Systemic side effects from ICSs are thought to be dose dependent. ICSs are not believed to cause an increase in cataracts/glaucoma or a decrease in bone mineral density when administered in recommended doses. There is evidence that high-dose ICS can cause clinically evident effects on the hypothalamic-pituitary-adrenal axis in susceptible individuals. Thus, patients should be treated with the lowest dose of ICS that controls their asthma symptoms and lung function.

**Long-Acting $\beta_2$-Adrenergic Agonist**

LABAs produce bronchodilation for ~12 hours. Addition of an LABA to ICS improves lung function and asthma control in patients with moderate-to-severe persistent asthma. The administration of a LABA may allow for a reduced dose of ICS. LABAs should not be used in the absence of an ICS because there are reports of death when used as monotherapy for asthma, especially in African Americans. Per 2010 Food and Drug Administration restrictions, LABAs only should be used long term in patients whose asthma cannot be adequately controlled on other asthma controller medications, should be used for the shortest duration of time required to achieve control of asthma symptoms, and should be discontinued, if possible, once asthma control is achieved.

**Oral Corticosteroids**

Oral corticosteroids have potent anti-inflammatory effects and are the most effective drugs for the treatment of asthma. Long-term, high-dose oral corticosteroids have many adverse side effects including loss of bone density, weight gain, hyperglycemia, cataracts, and hypothalamic-pituitary-adrenal axis suppression. Therefore, their use is recommended for patients with moderate or severe persistent disease that is not controlled with other medications, for short-term use in acute exacerbations in patients with asthma, and as a diagnostic therapeutic trial for cough, improvement of dyspnea, or airways obstruction. Fear of side effects should not limit the use of systemic corticosteroids in the appropriate setting because they may be lifesaving for many patients. Every-other-day dosing may decrease side effects in patients requiring long-term steroid therapy. Most adult patients with an asthma flare are treated with prednisone at 0.5–1.0 mg/kg per day for 5 days; the dose in children is 1–2 mg/kg per day; however, despite recommended dose ranges, observed practice patterns are variable.

**Leukotriene Receptor Antagonists, Leukotriene Biosynthesis Inhibitor**

Leukotrienes are implicated in the inflammation and bronchoconstriction of asthma, including aspirin-intolerant asthma. LTRAs block the effects of LTD$_4$ and are approved for use in asthma. LTRAs are not the preferred medication for mild persistent asthma because a systematic review of the literature found them to be less effective than ICSs. In addition, they are not as effective as LABAs when combined with ICS in moderate and severe persistent asthma. However, because LTRAs have almost no side effects, a therapeutic trial is appropriate if a patient has adverse effects from LABAs or in an attempt to decrease ICS dose. A response to montelukast or zafirlukast occurs within days to 4 weeks of initiating these medications.

Zileuton is an oral leukotriene synthesis inhibitor of 5-lipoxygenase that inhibits from 26 to 86% of leukotriene production. Reversible elevations of transaminases occur and baseline and subsequent monitoring of liver function tests is recommended. Two treatment modalities are indicated only for individuals with allergic asthma: allergen-specific immunotherapy, commonly known as allergy shots, and omalizumab. Immunotherapy is effective in decreasing symptoms and medication use in select patients with mild-to-moderate allergic asthma. In addition, patients receiving immunotherapy for allergic rhinitis may have a decreased risk of developing asthma. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody currently indicated for moderate-to-severe allergic asthma, has been shown to improve asthma-related quality of life, decrease clinically significant exacerbation rates and number of courses of oral corticosteroids, and reduce the severity of exacerbations.
CLINICAL PEARLS

• Avoidance is the cornerstone of management in allergic asthma.
• Accurate diagnosis of the type of asthma as well as its severity is essential for proper treatment.
• Coexisting conditions that affect asthma must be identified and treated.
• Medical therapy will vary based on the type and severity of asthma.
• Oral corticosteroids can be lifesaving and fear of side effects should not deter their use in appropriate patients.

REFERENCES
Potentially (near) fatal asthma (PFA) defines a subset of patients with asthma who are at increased risk for death from their disease. The diagnosis of PFA should motivate treating physicians, health professionals, and patients to be more aggressive in the monitoring, treatment, and control of this high-risk type of asthma. A diagnosis of PFA is made when any one of the following are present: (1) history of endotracheal intubation from asthma, (2) acute respiratory acidosis (pH < 7.35) or respiratory failure from acute severe asthma, (3) two or more episodes of acute pneumothorax or pneumomediastinum from asthma, (4) two or more episodes of acute severe asthma despite the use of long-term oral corticosteroids and other antiasthma medications. There are two predominant phenotypes of near fatal exacerbations, the “subacute” exacerbation and the “hyperacute” exacerbation. The best way to “treat” acute severe asthma is 3–7 days before it occurs (i.e., at the onset of symptoms or change in respiratory function) and to optimize control of asthma by decreasing the number of symptomatic days and days/night requiring rescue therapy and increasing baseline respiratory status in “poor perceivers.” PFA is treated with a multifaceted approach; physicians should appreciate limitations of pharmacotherapy including combination inhaled corticosteroid/long-acting beta-agonist products as well as addressing nonadherence, psychiatric, and socioeconomic issues that complicate care.

the hospital, and lower PEF rates. The ability to identify adults and children at high risk for death from their asthma allows physicians to intervene with more aggressive treatment and hopefully prevent fatalities. The majority (80–85%) of near fatal asthma exacerbations are “subacute” with symptom progression over days to weeks. “Hyperacute” exacerbations with acute respiratory failure within 2 hours are much less common and may be associated with massive allergen exposure or possibly emotional distress. Airway remodeling, considered present when the FEV1/forced vital capacity ratio is 75% after 1 year of antiasthma medications, was found to be a risk factor for near fatal asthma attacks. Other reported risk factors include repeated hospitalizations, multiple emergency room visits, previous intubations, a history of hypercapnia, use of more than two canisters a month of β2-agonist, medical comorbidities, and sensitivity to Alternaria species. A complete list is published elsewhere.

![Table 1](image1)

<table>
<thead>
<tr>
<th>Some physician factors associated with suboptimal management of PFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to appreciate the limitations of β2-agonists, ICS, ICS/LABA combinations, leukotriene modifiers, theophylline, or their additive effects in severe asthma</td>
</tr>
<tr>
<td>Fear of prednisone or failure to initiate prednisone or increase the dosage when indicated for an asthma exacerbation, such as during an upper respiratory tract infection</td>
</tr>
<tr>
<td>Poor understanding of the diagnosis, treatment, and control of severe life-threatening asthma</td>
</tr>
<tr>
<td>Failure to recognize the clinical implications of a quiet chest in an acutely dyspneic patient</td>
</tr>
<tr>
<td>Lack of availability</td>
</tr>
<tr>
<td>Prescription of excessively demanding regimens</td>
</tr>
<tr>
<td>Failure to achieve asthma control</td>
</tr>
<tr>
<td>Failure to refer to an allergist immunologist for consultation</td>
</tr>
</tbody>
</table>

Source: Ref. 1.

ICS = inhaled corticosteroids; LABA = long-acting β-agonist; PFA = potentially (near) fatal asthma.

2nd week. Optimal treat regimens for these patients remain under investigation.

PFA is treated with a multifaceted approach, and some fatalities can be prevented if patients are managed effectively. The previous chapter details the appropriate diagnosis and evaluation of a patient with asthma, avoidance measures, treatment of coexisting medical conditions that affect the severity of asthma, and treatment with medications, immunotherapy, or an immunomodulator based on asthma severity. Patients with PFA often require alternate-day oral steroids to control their disease with occasional courses of daily prednisone during exacerbations. Nonadherence must be addressed directly by the managing physician; psychiatric evaluation and management should be used, if necessary. If patients are nonadherent despite psychiatric intervention or refuse psychiatric care, judicious use of depot corticosteroids should be considered such as 40–80 mg of depot methylprednisolone administered as a deep intramuscular injection. Though long-acting parenteral corticosteroids have a higher incidence of steroid side effects than alternate-day oral steroids, they can be lifesaving in nonadherent patients with PFA.

PULMONARY PEARLS

- “Subacute” near fatal exacerbations are associated with airway plugging from tenacious mucus, epithelial damage, mucosal edema, and predominately eosinophilic infiltrate.
- “Hyperacute” near fatal exacerbations lack mucus plugging and are associated with a predominately neutrophilic infiltrate.
- Hyperinflation (elevated functional residual capacity and residual volume) after acute severe asthma persists up to 6 weeks, even after FEV1 and PEF have returned to normal.
Patients with PFA have increased prominence of centrilobular findings on high-resolution CT indicative of intrabronchiolar mucoid impaction, peribronchiolar inflammation, or bronchiolar wall remodeling compared with patients with mild-to-severe asthma. This may be in part from differential expression of proteoglycans and small airway remodeling.

**CLINICAL PEARLS**

- PFA identifies patients with asthma at increased risk of death from their disease.
- There are two predominant phenotypes of near fatal exacerbations, the “subacute” exacerbation and the “hyperacute” exacerbation.
- Patients with PFA should be treated aggressively to avoid a fatality. In fact, the best way to “treat” acute severe asthma is 3–7 days before it occurs (i.e., at the onset of symptoms or change in respiratory function).
- Nonadherence may be an issue in PFA.
- Poor perceivers are patients who tolerate a reduction in FEV1 without a sense of dyspnea. They have impaired responses to hypoxemia but do increase their respiratory rate during times of hypercapnia.

**REFERENCES**

Acute severe asthma (status asthmaticus)
Rachna Shah, M.D., and Carol A. Saltoun, M.D.

ABSTRACT

Acute severe asthma, formerly known as status asthmaticus, is defined as severe asthma unresponsive to repeated courses of beta-agonist therapy such as inhaled albuterol, levalbuterol, or subcutaneous epinephrine. It is a medical emergency that requires immediate recognition and treatment. Oral or parenteral corticosteroids should be administered to all patients with acute severe asthma as early as possible because clinical benefits may not occur for a minimum of 6–12 hours. Approximately 50% of episodes are attributable to upper respiratory infections, and other causes include medical nonadherence, nonsteroidal anti-inflammatory exposure in aspirin-allergic patients, allergen exposure (especially pets), irritant inhalation (smoke, paint, etc.), exercise, and insufficient use of inhaled or oral corticosteroids. The patient history should be focused on acute severe asthma including current use of oral or inhaled corticosteroids, number of hospitalizations, emergency room visits, intensive-care unit admissions and intubations, the frequency of albuterol use, the presence of nighttime symptoms, exercise intolerance, current medications or illicit drug use, exposure to allergens, and other significant medical conditions. Severe airflow obstruction may be predicted by accessory muscle use, pulsus paradoxus, refusal to recline below 30°, a pulse >120 beats/min, and decreased breath sounds. Physicians' subjective assessments of airway obstruction are often inaccurate. More objective measures of airway obstruction via peak flow (or forced expiratory volume in 1 second) and pulse oximetry before oxygen administration usually are helpful. Pulse oximetry values >90% are less commonly associated with problems although CO₂ retention and a low PaO₂ may be missed.

A

Cute severe asthma, formerly known as status asthmaticus, is defined as severe asthma unresponsive to repeated courses of β-agonist therapy such as inhaled albuterol, levalbuterol, or subcutaneous epinephrine. It is a medical emergency and requires immediate recognition and treatment.

PREDISPOSING FACTORS

Approximately 50% of patients diagnosed with acute severe asthma have a concomitant respiratory tract infection. Other exacerbating factors leading to this life-threatening condition in asthmatic patients include medical noncompliance, nonsteroidal anti-inflammatory exposure in aspirin-allergic patients, allergen exposure (especially pets) in severely atopic individuals, irritant inhalation (smoke, paint, etc.), exercise, and insufficient use of inhaled or oral corticosteroids.

PATHOLOGY AND IMMUNOLOGY

Autopsy evaluation of patients who die from asthma have shown anatomic changes that include airway narrowing, extensive plugging of the airways with mucus and inflammatory infiltrates, hyperinflation, and atelectasis. Pulmonary infiltrates contain mostly eosinophils, neutrophils, plasma cells, and lymphocytes. Bronchial lavage analyzed from intubated patients with acute severe asthma and stable asthma showed a significant increase in neutrophils in patients with severe acute asthma. There was, however, no significant difference in bronchoalveolar lavage eosinophil count between severe acute asthma and stable asthma. Cytokine and chemokine profiles showed an increase in proinflammatory cytokines, eosinophil recruitment (IL-5 and RANTES), and remodeling (IL-11).

Genetic polymorphisms also can be associated with severity of asthma. IL-4 is a cytokine that is responsible for B-cell class switching from IgM to IgE. The IL4*-589T allele has been noted to be a risk factor for life-threatening asthma. The B16-Arg/Arg allele at the 16th amino acid residue of the β2-adrenergic receptor is associated with decline in pulmonary function with routine use of β2-adrenergic agonists.
**PATIENT ASSESSMENT**

The patient history should be focused on acute severe asthma. Appropriate questions would elicit information about the patient’s past or current use of corticosteroids, hospitalizations, emergency room (ER) visits, intensive-care unit admissions and intubations, the frequency of albuterol use, the presence of nighttime symptoms, exercise intolerance, current medications or illicit drug use, exposure to allergens, and other significant medical conditions.

The physical exam should focus on assessing the severity of the patient’s asthma and possible causative or complicating conditions such as pneumonia, pneumothorax, pneumomediastinum, or atelectasis. Severe airflow obstruction may be predicted by accessory muscle use, pulsus paradoxus, refusal to recline below 30°, and a pulse >120 beats/min. The presence or degree of wheezing is less valuable as a predictor of severe airflow obstruction.

Physicians’ subjective assessments of airway obstruction are often inaccurate. More objective measures of airway obstruction *via* peak flow (or forced expiratory volume in 1 second) and pulse oximetry before oxygen administration usually are helpful. Pulse oximetry values >90% are less commonly associated with problems although CO₂ retention and a low PaO₂ may be missed. If there are any doubts, an arterial blood gas should be obtained to assess a patient’s true stage of severity (see Table 1). Other indications for obtaining an arterial blood gas include a peak flow <45% of predicted and declining peak flow or oxygen saturation despite treatment.

**DIAGNOSTIC TESTS**

Diagnostic testing should be tailored to the individual situation and generally will include a complete blood count with differential (especially in febrile patients and those with a productive cough), chest x ray, EKG, electrolytes (with a focus on the potassium level given both steroids and β₂-adrenergic agonists may lower serum levels), peak flow rate (pre- and postbronchodilator therapy), arterial blood gas, and serum theophylline concentration (when relevant).

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**Table 1 Arterial blood gas stages in acute severe asthma patients**

<table>
<thead>
<tr>
<th>Stage</th>
<th>pH (nl 7.35–7.43)</th>
<th>pCO₂ (nl 35–40 mmHg)</th>
<th>pO₂ (nl 90–100 mmHg)</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Respiratory alkalosis</td>
<td>↓</td>
<td>Normal</td>
<td>Asthma exacerbation</td>
</tr>
<tr>
<td>II</td>
<td>Respiratory alkalosis</td>
<td>↓↓</td>
<td>↓</td>
<td>Common emergency room finding</td>
</tr>
<tr>
<td>III</td>
<td>Normal</td>
<td>Normal</td>
<td>↓↓</td>
<td>Impending respiratory failure</td>
</tr>
<tr>
<td>IV</td>
<td>Respiratory acidosis</td>
<td>↑↑</td>
<td>↓↓↓</td>
<td>Impending respiratory arrest</td>
</tr>
</tbody>
</table>

All patients who have acute severe asthma should be admitted to the hospital or specialized treatment units. Those patients at increased risk for respiratory failure, such as those displaying a stage III or IV arterial blood gas, should be monitored in the intensive care unit and intubated if necessary. The goal of acute therapy is not to restore patients to their baseline pulmonary function, which may take days to weeks. The goal is to stabilize them as quickly as possible, maintain adequate oxygenation, and improve bronchial obstruction with a minimum of side effects.

Short-acting β₂-adrenergic agonists such as albuterol (most commonly), levalbuterol, pirbuterol, or terbutaline represent the first-line treatment for acute severe asthma, especially because they provide almost four times more bronchodilatation than methylxanthines or anticholinergics. Salmeterol, a long-acting bronchodilator, has a later onset of action (20 minutes) and formoterol (5 minutes) are not recommended for the acute treatment of asthma. Levalbuterol, the (R)-enantiomer of albuterol that does not contain the nonbronchodilating and possibly proinflammatory (S)-isomer, has been shown to provide equal bronchodilation with fewer β₂-adrenergic–mediated side effects than racemic albuterol. In addition, levalbuterol may also be a cost-saving medication, because early ER use of levalbuterol versus racemic albuterol in acute severe asthma leads to fewer hospitalizations. Interestingly, those patients admitted to the hospital for acute severe asthma had no change in hospital course or days until discharge if given levalbuterol versus racemic albuterol.

Different methods of albuterol administration—*via* metered-dose inhaler, dry powder inhaler, and nebulizer—provide the same benefit if given properly and in the same dosage, which is 7.5 mg in an hour for the nebulizer treatment. Metered-dose inhalers combined with a spacer may provide this same improvement in forced expiratory volume in 1 second more quickly and with fewer side effects. In adults, nebulized albuterol treatments are generally dosed at 2.5 or 5 mg (0.15 mg/kg per dose in children) and can be given every 20 minutes for three doses. Then, 2.5–10 mg (0.15–0.3
mg/kg up to 10 mg in children) may be given every 1–4 hours as needed or 10–15 mg/hour (0.5 mg/kg/hour in children) may be given continuously via nebulizer. Intramuscular epinephrine should be given in situations where the asthma attack is part of an anaphylactic reaction or administration of aerosolized albuterol is either ineffective or not possible. Give 0.3–0.5 mg of a 1/1000 dilution in an adult (0.01 mg/kg up to 0.3 mg in a child) every 20 minutes for three doses.

Oral or parenteral corticosteroids should be given to all patients with acute severe asthma as early as possible because clinical benefits may not occur for 6–12 hours. The recommended minimum doses for methylprednisolone are 80 mg in one or two divided doses a day for adults and 1–2 mg/kg in two divided doses (maximum, 60 mg/day) in children. This dosage should be continued until the peak flow reaches 70% of predicted. Duration of therapy with corticosteroids after the acute attack should be 3–10 days. Consensus has not been established as to the exact dosing of corticosteroids after an acute attack.

MAGNESIUM SULFATE

Hypermagnesemia can cause the relaxation of respiratory smooth muscle whereas hypomagnesemia may cause its contraction. Although there is insufficient evidence to support the widespread use of i.v. magnesium in acute asthma, it is an evidence B recommendation by the Expert Panel Report 3 in patients who are having a severe, life-threatening asthma exacerbation. If one chooses to administer magnesium, 1 dose of magnesium sulfate at 2 g i.v. in adults and 25 mg–2 g in children, should be given after 1 hour of conventional therapy has been administered. Side effects, such as muscle weakness, should be monitored.

OTHER TREATMENTS

Hypoxemic patients should receive enough supplemental oxygen to keep their saturations above 90% (95% in children), and sedatives should be avoided to avoid any respiratory depressant effects. Antibiotics should only be given when the clinical setting supports their use—even purulent sputum and fever may be from viral infections.

Most patients with acute severe asthma recover when treated appropriately. On discharge, it is recommended that patients be educated about their medications and the life-threatening risks of asthma and scheduled for an outpatient follow-up appointment, preferably within a week.

IMMUNOLOGY

- Genetic factors such as IL4*-589T allele and B16-Arg/Arg allele may be associated with severity of asthma.
- The airways of patients with severe asthma show infiltration by eosinophils, neutrophils, degranulated mast cells, and occlusion of the bronchial lumen by mucus.
- Significant increase in bronchoalveolar lavage neutrophil count is seen in patients with acute severe asthma versus stable asthma.
- Increased proinflammatory cytokines, eosinophil recruitment (IL-5 and RANTES) and remodeling (IL-11) have been found in patients with acute severe asthma versus stable asthma.

CLINICAL PEARLS

- When obtained in the setting of a hypoxemic asthmatic patient, an arterial blood gas that reveals a normal pH and CO₂ indicates impending respiratory failure.
- Short-acting β₂-adrenergic agonists and oral or i.v. corticosteroids should be administered to patients with acute severe asthma. Observe for hypokalemia and hyperglycemia.
Magnesium sulfate and Heliox can be used if life-threatening symptoms of acute severe asthma are present but are not a substitute for early intubation.

REFERENCES
Lessons learned from clinical trials of asthma

Bradley R. Sabin, M.D., Pedro C. Avila, M.D., Leslie C. Grammer, M.D., and Paul A. Greenberger, M.D.

ABSTRACT

The preponderance of clinical data suggest that inhaled corticosteroids (ICSs) are the preferred therapy for the long-term management of asthma, whereas oral or parental corticosteroids and short-acting beta₂-adrenergic agonists remain the mainstay treatment of acute exacerbations. Allergen and tobacco avoidance are tenets to the practice of allergy–immunology and are beneficial in the treatment of asthma. Failure to avoid animal danders or fungi to which a patient with asthma is allergic is a risk factor for a fatal attack. First introduced in the 1970s, ICSs are the mainstay of pharmacotherapy to control airway inflammation and bronchial hyperresponsiveness in children and adults with asthma. ICSs reduce symptoms, exacerbations, hospitalizations, and deaths while improving quality of life and lung function. When used in combination with an ICS, essentially all clinical trials have indicated that long-acting beta₂-adrenergic agonists are effective and safe. Leukotriene modifiers (LTMs) are effective in the treatment of persistent asthma, exercise-induced asthma, and aspirin-induced asthma, but, in general, are less efficacious than ICSs when used as monotherapy to control asthma symptoms. Nevertheless, some patients respond to LTMs better than ICSs so a personalized approach to asthma pharmacotherapy is recommended. Not only is conventional (subcutaneous) allergen immunotherapy effective in patients with allergic asthma, immunotherapy (subcutaneous or sublingual) administered for rhinoconjunctivitis in children has been shown to reduce the development of asthma.

Numerous clinical investigations have been published regarding the care of patients with asthma. Interpretation and understanding of select trials are critical to the practice of evidence-based medicine by the allergist–immunologist.

EVIDENCE REGARDING THE LONG-TERM MANAGEMENT OF ASTHMA

Quick-Relief Medications

Short-acting beta₂-adrenergic receptor agonists (SABAs) are the most effective medication for rapid relief of acute bronchoconstriction but are not effective for the long-term control of asthma. In the beta-Agonist for Mild Asthma trial, 255 patients aged 12–55 years with mild asthma showed no benefit or deleterious effects when assigned to inhaled albuterol (Alb) q.i.d. for 16 weeks compared with as-needed therapy.¹ The beta-Adrenergic Response by Genotype trial reported that patients homozygous for arginine as opposed to glycine in the 16th amino acid of the beta₂-receptor had a decrement of their morning peak expiratory flow (PEF) rate of 10 L/min compared with placebo when taking scheduled Alb q.i.d.¹ Admittedly, this change is small. Preferably, SABAs should be used intermittently for relief of asthma symptoms.

Long-Term Control Medications

Inhaled Corticosteroids. First introduced in the 1970s, inhaled corticosteroids (ICSs) have become the mainstay of pharmacotherapy to control airway inflammation and bronchial hyperresponsiveness in children and adults with asthma. ICSs reduce symptoms, exacerbations, hospitalizations, and deaths while improving quality of life (QOL) and lung function. In 1991, Haahltela et al. found that compared with terbutaline (Ter), adults (n = 103) with mild asthma treated with 600 μg of inhaled budesonide (Bud) had improved airway hyperresponsiveness, asthma symptoms, and morning PEF.¹ Although a 3-year follow-up suggested reduced efficacy if initiation of Bud was delayed by 2 years,¹ a 13-year follow-up evaluation of these subjects showed no difference in symptom severity and lung function whether or not initiation of Bud therapy was delayed in patients with recent onset of mild asthma.² The Inhaled Steroid Treatment as Regular
Therapy in Early Asthma study described a larger patient population (n = 7241) and wider age range (5–66 years) over 3 years. The key conclusion was that initiation of Bud within 2 years of the diagnosis of asthma was superior to placebo regarding asthma control and risk for severe asthma exacerbations. The Childhood Asthma Management Program research group study included 1041 children (aged 5–12 years) for 4–6 years and showed superiority of Bud at 200 μg b.i.d. compared with nedocromil and placebo regarding forced expiratory volume in 1 second (FEV₁; only at year 1 not year 4), symptoms, and exacerbation rate. It is important to note that in the 1st year of ICS therapy, growth in children was reduced by 1.1 cm in the Childhood Asthma Management Program research group study and 1.3 cm in Inhaled Steroid Treatment as Regular Therapy in Early Asthma study. However, a long-term follow-up of children treated with Bud suggests that they reach normal adult height.

ICS in combination with a bronchodilator is also efficacious if used on an as-needed basis in addition to maintenance daily therapy (this approach is not approved by the Food and Drug Administration [FDA]). The Symbicort Maintenance and Reliever Therapy trial compared Bud/formoterol (For) at 80/4.5 μg b.i.d. and as needed with Bud/For at 80/4.5 μg bid + Ter as needed and Bud at 320 μg b.i.d. + Ter as needed in 2760 patients aged 4–80 years over 2 years. Bud/For maintenance and reliever showed decreased exacerbation risk by 46% and improved symptoms and lung function compared with the other two groups. A retrospective analysis of five studies with similar designs showed equivalent control of asthma in all groups and supported the decreased exacerbation rate in the maintenance and reliever group. Additionally, the Improving Asthma Control Trial investigated Bud at 200 μg as a 10-day course as needed rather than daily in 225 adults with mild persistent asthma followed for 1 year. Despite mild worsening in markers of airway inflammation, as-needed Bud provided equivalent outcomes to daily Bud regarding QOL, symptoms, and FEV₁. Of note, research subjects received 10 days of scheduled treatment with prednisone, Bud, and zafirlukast at the beginning and end of the study. The Beclomethasone Plus Salbutamol Treatment trial examined the combination of beclomethasone dipropionate + Alb at 250/100 μg used as needed in 455 adults with mild persistent asthma and found no-inferiority regarding PEF and exacerbation and a lower cumulative dose of ICS compared with daily ICS therapy. Questions remain if ICSs used on an as-needed basis are effective to prevent severe exacerbations and deaths, and use of an ICS in this fashion has not been FDA approved.

Long-Acting β₂-Agonists. The use of a long-acting β₂-agonists (LABA) as monotherapy to maintain asthma control is contraindicated. In the Salmeterol or Corticosteroids trial 164 patients with mild intermittent asthma controlled on inhaled triamcinolone (Tri) were randomized to placebo, continuation of Tri or salmeterol (Sal) at 42 μg b.i.d., and at 16 weeks inflammation worsened and the risk of treatment failure and exacerbations increased in the Sal group. These data were supported by the Salmeterol ± Inhaled Corticosteroids trial, which showed that in 175 adults with moderate persistent asthma controlled with Tri/Sal, the Tri could not be weaned off without an increase in treatment failure rate from 13.7 to 46.3%. In the Salmeterol Multicenter Asthma Research Trial, Sal at 42 μg b.i.d. or placebo was added to usual asthma care in 26,355 patients, but the trial was stopped early because of an increase in respiratory-related deaths in the Sal group (24 versus 11) largely accounted for by events in the African American population; particularly those who were not using an inhaled corticosteroid. In response, the FDA placed a boxed warning alerting physicians that LABAs may increase the risk of asthma-related deaths.

When used in combination with an ICS, many trials have established LABAs to be effective and safe. The Formoterol and Corticosteroids Establishing Therapy trial evaluated the addition of For at 12 μg b.i.d. to Bud (100 and 400 μg b.i.d.) in 852 patients with asthma and an FEV₁ > 50% and showed that adding For to low-dose Bud better controlled symptoms, and increasing the dose of the Bud better prevented exacerbations. The Gaining Optimal Asthma Control trial supported the Formoterol and Corticosteroids Establishing Therapy trial and reported that the addition of Sal to fluticasone (Flu) was superior to Flu alone in establishing asthma control, especially in patients with more severe disease.

The Best Add-on Therapy Giving Effective Responses trial showed similar findings in children (aged 6–17 years). Subgroups of the 182 patients who were not controlled on Flu at 100 μg b.i.d. had improved control with increasing the Flu to 250 μg b.i.d., adding montelukast at 5–10 mg or adding Sal at 50 μg BID, but Sal was the step-up therapy most likely to improve control. A meta-analysis by Bateman et al. in 2008 of 66 GlaxoSmithKline sponsored trials involving 20,966 patients showed no increased risk of hospitalization when Sal was combined with an ICS. The event rate for intubation or death (n = 2) was too low to draw firm conclusions, but no increased risk was identified in the ICS + Sal group. Taken together, these data show that LABAs are excellent at controlling symptoms, are the best first add-on therapy to ICS, and should never be used as a single controller therapy. However, the risks and benefits of LABA therapy must be contemplated for patients on an individual basis.
**Leukotriene Modifiers.** Leukotriene modifiers are effective in the treatment of asthma and exercise-induced and aspirin-induced bronchospasm but, in general, are less efficacious than ICSs when used as monotherapy to control asthma symptoms. Altman et al. evaluated montelukast in 343 adult patients with chronic asthma and found 10% improvement in FEV₁, 1 inhalation less use of a SABA per day, and improved QOL. However, when compared with ICSs, Malmstrom et al. reported superiority of beclomethasone dipropionate at 200 µg b.i.d. compared with montelukast at 10 mg q.d. in improving FEV₁ (13.1% versus 7.4%), daytime symptom score, nocturnal awakenings, asthma control, and in reducing asthma exacerbations.

**Monoclonal Antibodies: Anti-IgE.** Omalizumab is a recombinant humanized monoclonal antibody against IgE and is effective adjunctive therapy for moderate-to-severe asthma. Milgrom et al. evaluated omalizumab in 317 patients aged 11–50 years who were sensitized to a perennial allergen and required frequent SABA rescue therapy despite receiving >400 µg/day of an ICS. Compared with placebo, omalizumab provided greater reduction in corticosteroids, improved symptoms, and decreased exacerbations. The benefit of omalizumab for patients already requiring high doses of ICS and LABA is described. Omalizumab carries a small risk of anaphylaxis and requires subcutaneous administration at a doctor’s office.

**Allergen and Irritant Avoidance.** Allergen and tobacco avoidance are tenets to the practice of allergy–immunology and beneficial in the treatment of asthma. Failure to avoid animal dander or fungi to which a patient with asthma is allergic is a risk factor for a fatal attack. Morgan et al. reported that tailored intervention based on allergen skin testing and history aiming at removing or dramatically reducing exposure to allergens and tobacco smoke from the environments of children with asthma improved asthma control compared with sham intervention. Environmental intervention reduced sick days, missed school days, and unscheduled office visits for asthma.

### Evidence Regarding the Acute Exacerbation of Asthma

SABAs and early administration of systemic corticosteroids are critical for the management of acute exacerbations of asthma. Four to 12 inhalations of an SABA metered-dose inhaler with a spacer are equivalent to one 2.5-mg nebulized dose of Albuterol. In the emergency setting these treatments usually are administered every 20 minutes for the 1st hour (or there is continuous nebulization over an hour). Systemic corticosteroids in acute exacerbations have been noted in meta-analyses to decrease the relapse rate in the weeks after the exacerbation, decrease asthma mortality, and shorten the time to recovery.

The role of ICSs in acute asthma exacerbations is limited. Two double-blind randomized controlled trials showed no benefit of doubling the dose of an ICS in an acute exacerbation. Oborne et al. randomized patients (n = 403) in a blinded, placebo-controlled trial to quadruple the dose of the ICS in an exacerbation and found a nonsignificant trend toward less oral corticosteroid use in treatment population (9% versus 14%). In the subset of patients (n = 94) who experienced an exacerbation, there was significant decrease in oral corticosteroid use in the treatment group (21% versus 50%). Rowe et al. evaluated high-dose Bud after emergency room discharge and stabilization of asthma with systemic corticosteroids. At 3 weeks follow-up, Bud decreased the exacerbation relapse rate 48% compared with placebo.

### Evidence for Therapies to Alter the Development of Asthma

Current evidence shows that pharmacotherapy does not prevent the progression of asthma in children. In the Prevention of Early Asthma in Kids trial, children aged 2–3 years with a positive asthma predictive index were randomized to Flu at 88 µg b.i.d. or placebo for 2 years of treatment and 1 year of follow-up. Flu improved symptoms during the first 2 years of therapy, but by year 3, there was no difference between the groups suggesting that Flu did not alter the natural history of the disease.

Specific allergen immunotherapy (SIT) may reduce the development of asthma in children with allergic rhinoconjunctivitis. In the PAT study, 205 children (aged 6–14 years) with rhinoconjunctivitis were randomized to SIT or an open control group and monitored over 3 years for the development of asthma. After excluding patients who had asthma at the outset of the trial, significantly fewer patients developed asthma in the treatment group (19 of 79) compared with control (32 of 72). On 10-year follow-up, a statistically significant difference persisted with fewer new asthma cases in the treatment group.

### CLINICAL PEARLS

- Evidence-based medicine informs clinical decision making, but limitations of studies should be recognized, including generalizability, and management should be individualized for each patient.
- The preponderance of clinical data suggests ICS to be the preferred therapy for the long-term management of asthma, whereas oral corticosteroids and SABAs remain the mainstay treatment of acute exacerbations.
The Expert Panel Report 3 guidelines advise to consider SIT in patients with persistent asthma and a clear allergic trigger. The evidence is strongest for subcutaneous immunotherapy in monosensitized patients.\(^\text{10}\)

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Chapter 16

Asthma in pregnancy

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ABSTRACT

The course of asthma during pregnancy may be affected by maternal physiological changes and triggers of asthma such as viral infections, exposure to allergens, and nonadherence with therapy. If asthma is uncontrolled, there are recognized harmful effects not only to the mother but also to the fetus. However, with effective asthma control, most women have outcomes, at or near that of the general population. Many medications are considered appropriate for use in pregnancy including inhaled corticosteroids (ICSs) such as budesonide, beclomethasone dipropionate, and fluticasone and the leukotriene receptor antagonists montelukast and zafirlukast. When ICSs or ICS/long-acting beta₂-adrenergic agonist combinations are not effective during exacerbations of asthma, short courses of oral corticosteroids should be administered earlier rather than later. Spirometry and flow volume loop tracings are useful measures of pulmonary function for gravidas. Results may be compared with nonpregnant reference values. Vocal cord dysfunction may be suspected when the inspiratory loop is truncated. The gravida does not reject the fetus because of lack of vascular continuity, a trophoblast layer causing separation, and suppressive mechanisms at the placental interface. The secretion of IL-10 increases in pregnancy and is lower in women with recurrent spontaneous abortions. Only immunoglobulin G (IgG) subclasses are transported across the placenta, especially IgG1, IgG3, and IgG4. Fetal B cells can produce endogenous IgE by 20 weeks of gestation.


Asthma is the most common obstructive pulmonary disease affecting pregnant women and is one of the most common potentially serious medical conditions in pregnant patients. According to a national survey, the prevalence of asthma in pregnant women has increased to 8.4–8.8% as of 2006.1 This elevation may be attributable to the increasing prevalence of asthma, especially among the younger age groups. Physiological changes during pregnancy, asthma triggers such as viral infections and exposure to allergens, and adherence/nonadherence with therapy often affect the course of asthma. If asthma is uncontrolled, it can cause detrimental effects not only to the mother but also to the fetus. However, with effective asthma control, most women have outcomes, at or near that of the general population. Therefore, it is important to monitor and treat the pregnant patient with asthma.2

The literature reports varying degrees of improvement, worsening, or no change in asthma during pregnancy. It can be averaged that asthma improves in one-third, worsens in one-third, and remains unchanged in one-third of gravidas. Generally, the more severe the asthma prepregnancy, the more likely she is to have an exacerbation or worsen during pregnancy.3 It also has been reported that asthma is similar in severity to the year preceding pregnancy, provided medications are continued. If medications are stopped, asthma of any severity may worsen.4 The course of asthma tends to be similar in successive gestations.3 Regardless of the severity of asthma prepregnancy, the gravida should be monitored closely to ensure the health of the mother and fetus.

Normal physiological changes during pregnancy affect the respiratory system. Before significant enlargement of the uterus, tidal volume and minute ventilation increase. Minute ventilation can rise initially by 19% and up to 50% by late pregnancy. This ventilation increase is attributable to high levels of progesterone and carotid body sensitivity to hypocarbia, causing a compensated respiratory alkalosis.5 Physiological dyspnea of pregnancy is experienced by 75% of pregnant women. It is defined as shortness of breath at rest or with mild exertion thought to be caused by increased drive to breath and increased respiratory load.5 Total lung capacity remains unchanged or can be decreased by 4–6%. The residual volume may be decreased slightly, causing the vital capacity to remain stable or
slightly increase. As the uterus enlarges, functional residual capacity decreases by 10–25%, decreasing further in the supine position. Chest wall compliance also decreases by 35–40% because of the uterus causing an increase in abdominal pressure. The diaphragm elevates ~4 cm, and the circumference of the lower rib cage increases ~5 cm. Despite these respiratory and anatomic changes, pregnancy has no significant effect on forced expiratory volume in 1 second (FEV₁) or FEV₁/forced vital capacity. Peak expiratory flow rates remain unchanged throughout the majority of pregnancy; however, it can be slightly decreased, if measured supine in the advanced gravida.²,⁵ Of course, peak flows, FEV₁, and FEV₁/forced vital capacity will be decreased with acute exacerbations of asthma.

Severe and uncontrolled asthma may lead to adverse outcomes in pregnancy. Some complications may include preterm delivery, which is delivery before 37 weeks’ gestation; newborns small for gestational age, which is birth weight of <10th percentile for gestational age and gender; low birth weight, which is <2500 g; or fetal demise. These outcomes are attributed to fetal hypoxia. Maternal complications from uncontrolled asthma may include anepartum or postpartum hemorrhage, gestational hypertension, preeclampsia, oligohydramnios, hyperemesis gravidarum, increased need for cesarean delivery, or maternal death. Poor outcomes were observed in pregnant women whose asthma was more severe or who had more frequent exacerbations.²,⁶ It has been reported that gravidas with moderate-to-severe asthma are at a higher risk of having newborns that are small for gestational age.⁷ Prevention and appropriate treatment of acute and severe asthma leads to a decreased risk of adverse events and outcomes similar to healthy gravidas. Therefore, it is important that gravidas with asthma be treated appropriately to maintain good asthma control.²,⁶

The evaluation and treatment of gravidas with asthma should start with avoidance measures to sensitized allergens. If skin testing has not previously been completed, it may be done to evaluate allergens contributing to symptoms. Main avoidance measures include pets, dust, indoor molds, and cockroaches. Also, it is prudent to counsel regarding the avoidance of irritants such as tobacco or illicit drug use.²

It is advisable to monitor lung function and explore the level of control of asthma during pregnancy. Spirometry is a useful measure of asthma control and should be completed monthly according to the National Asthma Education and Prevention Program.⁸ If this is not possible, peak flow measurements are found to be sufficient.⁸ It is acceptable to use nonpregnant reference values to evaluate lung function in the pregnant patient.⁵

Medication remains an integral part of treating the gravida with asthma to prevent potential complications of pregnancy because of fetal oxygen impairment; however, many pregnant patients are fearful of taking medications because of potential harm to their fetus. Education is vital to ensure an understanding of the disease process, potential complications of uncontrolled asthma, and safety of medications. A stepwise approach to treatment is recommended according to asthma severity. The effectiveness of medications is assumed to be similar in pregnant patients compared with nonpregnant women. Budesonide is the most studied inhaled corticosteroid (ICS) and therefore is first-line therapy for the gravid with persistent asthma. Leukotriene receptor antagonists are considered appropriate in pregnancy, but data on effectiveness during pregnancy are minimal. Limited data are available regarding safety and efficacy of using combination ICS with long-acting β-agonist (LABA) in the pregnant patient.² However, there is justification to expect LABA’s safety to be similar to short-acting β-agonists.²,⁸ It is the recommendation of the American Congress of Obstetricians and Gynecologists Practice Bulletin on asthma in pregnancy to add an LABA to ICS if asthma is uncontrolled on medium-dose ICS.⁴ For patients whose asthma continues to be uncontrolled on high-dose combination therapy, treatment may require the addition of regular oral corticosteroids.²,⁶,⁸ Acute asthma exacerbations can lead to severe consequences for the fetus; therefore, it is imperative to treat quickly and aggressively often with systemic steroids, because doubling the ICS often is not adequate. Comorbid conditions, such as allergic rhinitis, gastroesophageal reflux disease, and rhinosinusitis should be treated to ensure adequate control of asthma.²

Finally, special considerations are given to the pregnant patient with asthma. Allergen immunotherapy may be continued or even initiated during pregnancy.² It has been shown in clinical practice to be safe as long as the patient does not experience severe systemic reactions. During labor and delivery, the goal is that the gravida should have no limitations to vaginal delivery. When the gravida has used moderate- to high-dose ICSs or systemic corticosteroids during gestation, it is advised to initiate hydrocortisone at 100 mg i.v. every 8 hours until postpartum and give prednisone preemptively if cesarean section is planned.²

In summary, the course of asthma in the pregnant patient should be monitored closely to avoid complications in pregnancy. Treatment should not be limited because of fear of harming the fetus (Table 1). It has been shown that appropriate management can ensure a pregnancy similar to the normal population for nearly all gravidas.

**IMMUNOLOGY**

- The mother does not reject the fetus because of lack of vascular continuity, a trophoblast layer causing separation, and suppressive mechanisms at the placental interface.³ The secretion of IL-10 increases in pregnancy and is lower in women with recurrent spontaneous abortions.
• Only immunoglobulin G (IgG) subclasses are transported across the placenta, especially IgG1, IgG3, and IgG4.
• Fetal B cells can produce endogenous IgE by 20 weeks of gestation.
• Prostaglandin D₂ and F₂α cause bronchoconstriction, whereas prostaglandin E mediates bronchodilation.
• Adaptive immunity remains stable during pregnancy. Influenza immunization is reliable during pregnancy.³

Pregnancy does not affect the quantity of CD4 and CD8 cells; however, in late pregnancy, there can be a decrease in the circulation of Th1 cells and increase in Th2 cells.³
• Antibody-dependent cell-mediated cytotoxicity is reported to be normal to decreased.³ The clinical implication is not clear.

CLINICAL PEARLS
• The course of asthma may improve, remain the same, or worsen during pregnancy. In gravidas with moderate and severe persistent asthma, frequent monitoring with examinations and pulmonary function should be performed.
• Asthma should be treated aggressively to prevent complications of pregnancy.
• If asthma is well controlled during pregnancy, outcomes can be similar to the general population.
• When ICSs or ICS/long-acting β₂-agonist combination are inadequate during exacerbations of asthma, short courses of oral corticosteroids should be administered early rather than later.
• Spirometry and flow volume loop tracings are useful measures of pulmonary function for gravidas. Results may be compared with nonpregnant reference values. Vocal cord dysfunction may be suspected when the inspiratory loop is truncated.

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Occupational immunologic lung disease

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ABSTRACT

Occupational immunologic lung disease is characterized by an immunologic response in the lung to an airborne agent inhaled in the work environment and can be subdivided into immunologically mediated occupational asthma (OA) and hypersensitivity pneumonitis (HP). Irritant-induced OA, a separate nonimmunologic entity, can be caused by chronic exposure to inhaled irritants or reactive airways dysfunction syndrome, defined as an asthma-like syndrome that persists for >3 months and occurs abruptly after a single exposure to a high concentration of an irritating industrial agent. High-risk fields for OA include farmers, printers, woodworkers, painters, plastic workers, cleaners, spray painters, electrical workers, and health care workers. OA can be triggered by high molecular weight (HMW) proteins that act as complete allergens or low molecular weight (LMW) sensitizers that act as haptens. HMW proteins (>10 kDa) are generally derived from microorganisms (such as molds and bacteria, including thermophilic actinomycetes), plants (such as latex antigens and flour proteins), or animals (such as animal dander, avian proteins, and insect scales) and are not specifically regulated by the Occupational Safety and Health Administration (OSHA). LMW haptens that bind to proteins in the respiratory mucosa include some OSHA-regulated substances such as isocyanates, anhydrides, and platinum. HP can present in an acute, a chronic, or a subacute form. The acute, subacute, and early chronic form is characterized by a CD4⁺ T_H1 and CD8⁺ lymphocyte alveolitis. Classically, the bronchoalveolar lavage will show a CD4/CD8 ratio of <1.


Occupational immunologic lung disease (OILD) is characterized by an immunologic response in the lung to an airborne agent inhaled in the work environment and can be subdivided into immunologically mediated occupational asthma (OA) and hypersensitivity pneumonitis (HP). Irritant-induced OA, a separate nonimmunologic entity, can be caused by chronic exposure to inhaled irritants or reactive airways dysfunction syndrome, defined as an asthma-like syndrome that persists for >3 months and occurs abruptly after a single exposure to a high concentration of an irritating industrial agent. Diagnostic criteria for reactive airways dysfunction syndrome have been published elsewhere. OILD must also be differentiated from “work-exacerbated asthma” in which preexisting or concurrent asthma is worsened by workplace conditions such as cold air or dust exposure rather than caused by an immune response to a workplace sensitizer.

The incidence and prevalence of OILD has remained difficult to estimate. Affected workers may avoid or leave a profession before coming for medical attention (the healthy worker effect). Two percent of all asthma cases in industrialized nations and 9–15% of all U.S. adult asthma cases have been estimated to be occupational in origin. High-risk fields for OA include farmers, printers, woodworkers, painters, plastic workers, cleaners, spray painters, electrical workers, and health care workers. Tables detailing professions and the specific associated sensitizer have been described elsewhere. Over 250 substances have been implicated in OA with the most common being isocyanates, flour and grain dust, airborne particles from food including fish, colophony, latex, animal dander, aldehydes, and wood dust. The incidence of OA varies by the level, duration of exposure, and the specific agent implicated. Genetic risk has also been identified through positive associations with various HLA alleles and glutathione S-transferase polymorphisms, but this has not been shown to be helpful in diagnosis.

OA can be triggered by high molecular weight (HMW) proteins that act as complete allergens or low molecular weight (LMW) sensitizers that act as haptens. HMW proteins (>10 kDa) are generally derived from microorganisms (such as molds and bacteria, including thermophilic actinomycetes), plants (such as latex antigens and flour proteins), or animals (such as animal dander, avian proteins, and insect scales) and are not specifically regulated by the Occupational Safety and Health Administration (OSHA). LMW haptens that bind to proteins in the respiratory mucosa include some OSHA-regulated substances such as isocyanates, anhydrides, and platinum.
from microorganisms (such as molds and bacteria, including thermophilic actinomycetes), plants (such as latex antigens and flour proteins), or animals (such as animal dander, avian proteins, and insect scales) and are not specifically regulated by the Occupational Safety and Health Administration (OSHA). LMW hapten that bind to proteins in the respiratory mucosa include some OSHA-regulated substances such as isocyanates, anhydrides, and platinum.\(^\text{6}\) HMW sensitizers and some LMW sensitizers, such as trimeric anhydride, phthalic anhydride, platinum, chromium, nickel, epoxy amines, and penicillin, act through an IgE-mediated mechanism.\(^\text{3}\) In type I hypersensitivity reactions,\(^\text{7}\) allergen crosslinks IgE on sensitized mast cells or basophils in the airway mucosa leading to the release mediators including histamine and leukotrienes, as well as cytokines, such as IL-3, IL-4, and IL-5, and chemokines. The bioactive mediators contribute to immediate-type asthma via the development of allergic inflammation involving the large airways. Wheezing is the predominant symptom during the acute stage. The late asthmatic response occurs several hours later and may result from a type IV\(_{a2}\) hypersensitivity reaction in which Th2 cells are involved.\(^\text{7}\) The late response presents as a small airway obstruction and lasts several hours. Patients frequently complain of a cough and dyspnea, but less commonly of wheezing. Other responses have been described, including the repetitive asthmatic responses in which patients have recurrent bronchospastic events over several days after a single inhalation challenge. This may be mediated by a type IV\(_{b}\) hypersensitivity reaction involving CD8\(^+\) T cells.\(^\text{7}\) A latent period of asymptomatic inhalation exposure of months to years usually occurs before the onset of any respiratory symptoms. Occupational rhinitis or conjunctivitis often predate the development of OA.\(^\text{8}\) Once symptoms have started, removal of the worker from the offending environment typically results in improvement or termination of symptoms.\(^\text{4}\)

Occupational HP results from occupational dusts derived from fungal spores or bacteria, such as moldy hay and avian dust, or from chemicals, such as isocyanates. HP can present in an acute, chronic, or subacute form. The acute, subacute, and early chronic form is characterized by a CD4\(^+\) T\(_{h1}\) and CD8\(^+\) lymphocyte alveolitis. Classically, the bronchoalveolar lavage will show a CD4/CD8 ratio of <1. Later in the course of the disease there may be a skewing toward T\(_{h2}\) lymphocytes and IL-4 production.\(^\text{9}\) The acute form results from short-term, high-level exposure to a workplace antigen. Symptoms occur 4–8 hours after inhalation exposure and include fever, chills, nonproductive cough, dyspnea, and myalgias. The chronic form results from persistent low-level exposure to an antigen. Patients present with cough, dyspnea, weight loss, and fatigue. In the subacute form, patients usually have an insidious onset of symptoms after several days to weeks of exposure. Symptoms in the subacute form include exertional dyspnea, productive cough, and malaise. All three forms can progress to irreversible lung disease with severe pulmonary fibrosis. Early recognition of HP and avoidance of further exposure to the causative antigen are instrumental in preventing the progression to irreversible disease.\(^\text{4}\)

Tools for the diagnosis of OILD include the medical history and examination, immunologic testing, pulmonary function studies, and bronchial provocation challenge. The history should include the clinical features of airway disease, temporal relationships between symptoms and workplace exposure, a detailed job history, a review of work processes, and the presence of concomitant rhinitis and conjunctivitis. Review of the material safety data sheets may be helpful for workplace exposure but they may be incomplete, lacking information about potential for respiratory sensitization.\(^\text{3}\) Validated skin tests\(^\text{10}\) for HMW antigens have a high negative predictive value and thus can rule out a specific antigen as the culprit. Conjugated extracts for LMW antigens are not commercially available, and \textit{in vitro} IgE assays\(^\text{11}\) are of low sensitivity.\(^\text{3}\) Double gel immunodiffusion techniques can detect the presence of precipitating antibodies against antigens present in the workplace and suggest a causal relationship in HP.\(^\text{5}\) Serial measurements of forced expiratory volume in 1 second or peak expiratory flow every 4 hours during a 1-week period of work absenteeism followed by a 3- to 4-week period of work attendance can establish a relationship to a workplace antigen. Generally, patients show a trans-shift decrement in expiratory flow that either worsens or stabilizes during the workweek and improves on the weekend. Specific allergen inhalation challenges are regarded as the gold standard for the diagnosis of OILD; however, these studies require specialized equipment and are only performed in select centers. Natural challenges can be performed by exposure of the patient to the work environment with measurement of pulmonary functions before and after exposure. Non-specific bronchoprovocation with methacholine is highly sensitive but not specific for OA. A threefold improvement in PC\(_{20}\) after 10–14 days of absenteeism compared with the end of a workweek suggests OA.\(^\text{3}\)

The prognosis of OILD appears to be good if the disease is detected early and additional exposure is avoided. However, patients diagnosed with late-stage disease usually do not recover completely. Poor prognosis of OA is associated with duration of symptoms of >1–2 years, abnormal pulmonary function test results, persistently elevated specific IgE levels, and a high degree of bronchial hyperreactivity.\(^\text{4}\)

The first step in the management of OILD involves preventing further exposure to the causative antigen. Complete avoidance of the antigen is ideal; however,
environmental measures can be instituted at the workplace to control the worker’s exposure. These measures include transferring the worker to another department, respiratory protection devices, or improving the ventilation of the workplace. Inhaled bronchodilators, cromolyn, and corticosteroids are useful in the treatment of OA but are not efficacious in the setting of ongoing exposure and should not be used as a substitute for complete avoidance. A short course of oral corticosteroids may be useful in acute HP. Immunotherapy12 with allergens causing OA have been used in oyster gatherers, bakers, and laboratory animal workers with some success. However, prevention of OILD through education, improved workplace ventilation, and adherence to established limits of exposure is the ultimate goal.4 A good example of this is the near resolution of farmer’s lung with the elimination of animal feed (hay, grain, etc.) storage in silos on dairy farms.5

IMMUNOLOGY
• HMW sensitizers are complete allergens whereas LMW sensitizers behave as haptens.
• The immediate immunologic response occurs in the large airways through classic IgE crosslinking and release of histamine; leukotrienes; cytokines such as IL-3, IL-4, and IL-5; and chemokines.
• The late asthmatic response in OA occurs in the small airways and may result from a type IVa2 hypersensitivity reaction in which TH2 cells are involved.
• The bronchoalveolar lavage in HP shows a CD4/CD8 ratio of <1.

CLINICAL PEARLS
• The earlier OILD is diagnosed and the sooner the worker is removed from the environment, the better the prognosis.
• The most common sensitizers include isocyanates, flour and grain dust, airborne particles from food including fish, colophony, latex, animal dander, aldehydes, and wood dust.
• Occupational rhinitis or conjunctivitis often precedes asthma and may provide a warning for at risk workers.
• The primary goal should lie in prevention of the disease, rather than management.
• Pharmacologic treatment of occupational lung disease should not be used as a substitute for complete avoidance of the causative agent.

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Allergic bronchopulmonary aspergillosis

Paul A. Greenberger, M.D.

ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with asthma or cystic fibrosis resulting in pulmonary infiltrates, tenacious mucus plugs that harbor hyphae of Aspergillus fumigatus, elevations of total serum IgE concentration and peripheral blood, and sputum eosinophilia. Bronchiectasis is an irreversible complication of ABPA. The key to early diagnosis is considering ABPA in anyone with asthma or cystic fibrosis and a positive skin test to Aspergillus and/or recurrent infiltrates on radiographs. The differential diagnosis for ABPA in patients with asthma includes diseases in which there is an overlap of asthma, peripheral blood eosinophilia, and radiographic infiltrates. Examples include chronic eosinophilic pneumonia, Churg-Strauss syndrome, drug-induced pulmonary infiltrates, infection with a parasite, asthma with atelectasis, and lymphoma. Mucus plugging causing a “tree in bud” pattern on CT examination of the lungs may be from ABPA or other conditions such as nontuberculous (atypical) mycobacteria (Mycobacteria avium–intracellulare complex). Prednisone is indicated to clear pulmonary infiltrates, and a usual course is for 3 months. Itraconazole and voriconazole are adjunctive and drug–drug interactions must be considered as azoles decrease elimination of various medications. Although not familial in most patients, presentation of Asp f1 antigen is restricted to specific major histocompatibility complex class II molecules, HLA-DR2 and HLA-DR5. There is an increased number of CD4+ Th2 lymphocytes in bronchoalveolar lavage, and Aspergillus fumigatus can serve as a growth factor of eosinophils potentiating the effects of IL-3, IL-5, and granulocyte colony-stimulating factor.


Allergic bronchopulmonary aspergillosis (ABPA) is a disease that occurs when the pulmonary immune system reacts to antigens of Aspergillus fumigatus, a ubiquitous thermophilic fungus that colonizes bronchial mucosa. It is thought that Aspergillus spores within the bronchial tree activate the immune system to cause tissue damage including proximal bronchiectasis and bronchiolitis obliterans distally. Patients at risk for ABPA typically are those with asthma or cystic fibrosis.

This disease occurs in 1–2% of patients with persistent asthma and 2–15% of patients with cystic fibrosis.1 ABPA should be suspected in any patient with asthma and a positive skin test to A. fumigatus, worsening asthma, recurrent infiltrates, expectoration of golden brown mucous plugs, or in cystic fibrosis patients who begin to wheeze regularly or have an elevated IgE concentration of >500 kU/L. Patients with ABPA have lung disease that ranges from mild intermittent asthma to corticosteroid-dependent asthma. ABPA exacerbations correlate with increased fungal spore counts; therefore, in Chicago, exacerbations predominantly occur from June to November, and in Great Britain, they occur during the months of October through February.

The differential diagnosis for ABPA includes diseases in which there is an overlap of asthma, peripheral blood eosinophilia, and radiographic infiltrates and in patients with asthma and sensitization to fungal antigens. The former may include chronic eosinophilic pneumonia, Churg-Strauss syndrome, drug-induced pulmonary infiltrates, infection with a parasite, asthma with atelectasis, and lymphoma. Mucus plugging causing a “tree in bud” pattern on CT examination of the lungs may be from ABPA or other conditions such as nontuberculous (atypical) mycobacteria (Mycobacteria avium–intracellulare complex) and may occur in patients with asthma, especially during exacerbations. The latter refers to one of two populations, either the 25% or more of patients with persistent asthma who have immediate skin test reactivity to Aspergillus species or other fungal antigens or patients with severe asthma with fungal sensitization.2 Patients with severe asthma with fungal sensitization should
not meet criteria for ABPA but should have a total serum IgE of <1000 kU/L and immediate skin test reactivity or in vitro IgE antibodies to at least one fungal antigen.

One approach to diagnose ABPA, however, is by fulfilling the following minimal essential diagnostic criteria:

1. Asthma.
2. Immediate cutaneous reactivity on skin-prick testing (1:10 wt/vol of A. fumigatus); nearly all patients have reactivity on prick (epicutaneous) testing.
3. Elevated total serum IgE (>417 kU/L).
4. Elevated serum IgE and IgG to A. fumigatus (2× asthma controls).
5. Proximal (central) bronchiectasis on radiograph (inner 2/3 of lung on CT scan).

Patients with criteria 1 through 4 are labeled ABPA-S (seropositive), and if 5 is present, they are labeled ABPA-CB (central bronchiectasis). Patients with classic ABPA may also have radiographic infiltrates, peripheral blood eosinophilia if not treated with prednisone, precipitating antibodies, and mucous plugs with A. fumigatus.

Radiographs of patients with ABPA can show transient or permanent infiltrates, and when advanced, can show pulmonary fibrosis, cavitation, contracted upper lobes, and lobar collapse.

ABPA is classified into five stages. Stage I (acute) is diagnosed when a patient first appears with the essential criteria of ABPA including elevated serologies of total IgE concentration, IgE–A. fumigatus, IgG–A. fumigatus, and a pulmonary infiltrate. The chest radiograph or CT (high resolution) examination may or may not have bronchiectasis. Stage II (remission) occurs when the total IgE concentration has fallen to 50–75% of the peak IgE; it may not normalize. Stage III (exacerbation) occurs when there are new radiographic infiltrates by chest radiograph, CT examination and in most patients, the total serum IgE doubles. Stage IV (corticosteroid-dependent asthma) occurs when a patient’s oral prednisone can not be tapered without causing an increase in the IgE level or worsening of the asthma or recurrent pulmonary infiltrates. Stage V (fibrotic) is the most severe stage of the disease. In this stage, the lungs are fibrotic, cavitory, or both. Radiographic images will show fibrosis, and pulmonary function tests will show restrictive physiology with irreversible obstruction. Lung transplant has been attempted in a few patients and in one patient has been associated with recurrence of ABPA within a year. It should be noted that patients in stage V are never classified as ABPA-S, and if patients are diagnosed and treated early and aggressively, few if any will progress to stage V.

ABPA is treated with avoidance measures (remediation of fungal sources in the home or workplace), management of asthma (and comorbidities such as rhinitis or rhinosinusitis), and prednisone. Initially, 0.5 mg/kg of prednisone is administered every day for 2 weeks. This dose is converted to every other day for 6–8 weeks and then discontinued. The total serum IgE concentration is measured at the time of diagnosis and repeated at 4 and 8 weeks and then every 8 weeks for 1 year. If the IgE concentration has decreased by one-third and radiographs are clear of infiltrates at 8 weeks, the prednisone is tapered by 5 mg every 2 weeks. However, if the total serum IgE concentration doubles, this change may be indicative of an indolent exacerbation, and the prednisone is increased. Also, if after 2 months of treatment the radiographic infiltrates do not clear or the IgE does not decrease, one must also consider medication nonadherence, a continuing ABPA exacerbation, or the incorrect diagnosis. A repeat high-resolution CT scan of the lung could be helpful in the establishing a diagnosis.

Patients with ABPA need to have spirometry measured yearly and treated for current comorbidities like allergic rhinitis, gastroesophageal reflux, and rhinosinusitis. They should also avoid places that are harbingers for mold including leaky basements and mulch because this exposure can exacerbate their condition.

The use of itraconazole and voriconazole in the management of ABPA is adjunctive. Short-term studies with itraconazole have reported significant reductions in symptoms but not prevention of infiltrates or preservation of lung function. Also, itraconazole and voriconazole have adverse effects including inhibition of hepatic metabolism of medications via effects on CYP3A4. Voriconazole can cause reversible photosensitivity or unpleasant alterations in perception of colors and can reduce metabolism of prednisolone.

Omalizumab has not been found to be harmful, and occasional patients are described who have improved, at least in terms of management of persistent asthma. Formal studies are lacking.

**IMMUNOLOGY**

- Presentation of Asp f1 antigen is restricted to specific major histocompatibility complex class II molecules, HLA-DR2 and HLA-DR5.
- In ABPA, there is an increased number of CD4 (Th2 phenotype) T cells in the bronchoalveolar lavage.
- There is gain of function of IL-4 causing activation of CD20 B cells and up-regulation of CD23 (the low-affinity IgE receptor, FcεRII).
- A. fumigatus can serve as a growth factor of eosinophils potentiating the effects of IL-3, IL-5, and granulocyte colony-stimulating factor.
CLINICAL PEARLS

- Early treatment of ABPA prevents the progression of disease to fibrotic lung disease.
- The key to early diagnosis is considering this disease in anyone with asthma and a positive skin test to *Aspergillus* and/or recurrent infiltrates on radiographs.
- Prednisone is indicated to clear pulmonary infiltrates, and a usual course is for 3 months, not indefinitely because the total serum IgE concentration remains >417 kU/L after 3 months of treatment with prednisone. Avoid prednisone for ABPA when there are no pulmonary infiltrates (consolidations and significant mucus plugging) or corticosteroid-dependent asthma or end-stage fibrocavitary ABPA.
- Peripheral blood eosinophilia (in the absence of systemic corticosteroids) often is from 10 to 25% (in contrast to 40–90% that occurs with parasitism).

REFERENCES

Hypersensitivity pneumonitis

Karen Hsu Blatman, M.D., and Leslie C. Grammer, M.D.

ABSTRACT

Hypersensitivity pneumonitis (HP), also referred to as extrinsic allergic alveolitis, is characterized by non-IgE–mediated inflammation of the parenchyma, alveoli, and terminal airways of the lung initiated by inhaled antigens in a susceptible host. Etiologic agents of HP are either organic high molecular weight compounds such as bacteria, fungi, amoebae, plant, and animal proteins or inorganic low molecular weight haptens such as isocyanate and drugs including amiodarone, nitrofurantoin, and minocycline. Six significant predictors have been identified that provide ~95% diagnostic accuracy. These six predictors are (1) exposure to a known offending allergen, (2) positive precipitating antibodies to the offending antigen, (3) recurrent episodes of symptoms, (4) inspiratory crackles on lung auscultation, (5) symptoms occurring 4–8 hours after exposure, and (6) weight loss. HP is staged into acute, subacute, and chronic. In the acute stage after direct exposure to the antigen, there is fever, chills, nonproductive cough, dyspnea, malaise, and myalgias, all resembling influenza. However, if obtained, a chest radiograph shows nodular infiltrates, and pulmonary function testing is restrictive (unless the cause is avian in which obstruction or obstruction with restriction is present). In the chronic stage, fever and chills are absent, but weight loss can occur. The immunologic response includes activated macrophages and CD8+ cytotoxic lymphocytes, and bronchoalveolar lavage fluid reveals marked lymphocytosis with a ratio of CD4+ cells to CD8+ cells <1. Activated macrophages have increased expression of CD80/CD86, and T cells have increased expression of its counter-ligand CD28, evidence for heightened antigen presentation.

agents continue to emerge. In recent literature, biologics have been linked to HP. Several case reports have identified new cases of HP induced by rituximab.4

HP presents in an acute, subacute, or chronic form depending on the amount and duration of exposure and the level of host reactivity. The acute form typically occurs within 6–12 hours of an intense exposure with symptoms of fever, dyspnea, and nonproductive cough. The chronic form is associated with continuous low-level exposure and presents with insidious onset of shortness of breath that particularly occurs with exertion, productive cough, and weight loss. Fever is not typical for the chronic HP. The subacute form has features of both the acute and the chronic forms. Table 2 has additional information distinguishing the three forms of HP.2

A high index of suspicion is required to make a diagnosis of HP. There is no single confirmatory test

Table 1 Some Antigens of hypersensitivity pneumonitis

<table>
<thead>
<tr>
<th>Disease or Condition</th>
<th>Source of Antigens</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer’s lung</td>
<td>Moldy hay</td>
<td>Thermophilic actinomycetes</td>
</tr>
<tr>
<td>Bird fancier’s disease, pigeon breeder’s disease, and budgerigar disease</td>
<td>Droppings and feather bloom</td>
<td>Avian proteins</td>
</tr>
<tr>
<td>Summer-type hypersensitivity pneumonitis</td>
<td>Moldy homes in Japan</td>
<td>Trichosporon cutaneum</td>
</tr>
<tr>
<td>Humidifier lung</td>
<td>Air conditioner and humidifier</td>
<td>Bacillus, Klebsiella, and Cytophaga</td>
</tr>
<tr>
<td>Chemical worker’s lung</td>
<td>Paint/chemical catalyst, varnish, and lacquer</td>
<td>Isocyanates</td>
</tr>
<tr>
<td>Yacht-maker’s lung</td>
<td>Chemicals used in making yachts</td>
<td>Dimethyl phthalate or styrene</td>
</tr>
<tr>
<td>Saxophonist’s lung</td>
<td>Moldy reed</td>
<td>Candida</td>
</tr>
<tr>
<td>Lab worker’s lung</td>
<td>Rats and other mammals</td>
<td>Urine antigens</td>
</tr>
<tr>
<td>Cheese worker’s lung</td>
<td>Moldy cheese</td>
<td>Penicillium</td>
</tr>
<tr>
<td>Hot tub lung</td>
<td>Hot tub</td>
<td>Mycobacterium</td>
</tr>
<tr>
<td>Drug-induced hypersensitivity pneumonitis</td>
<td></td>
<td>Drugs such as amiodarone, gold, sulfonamide, nitrofurantoin, minocycline, leflunomide, methotrexate, fluoxetine, sirolimus, and HMG-CoA reductase inhibitor</td>
</tr>
</tbody>
</table>

Table 2 Clinical presentations of hypersensitivity pneumonitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute</th>
<th>Subacute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever and chills</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cough</td>
<td>Non-productive</td>
<td>Productive</td>
<td>Productive</td>
</tr>
<tr>
<td>Malaise and myalgia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rales</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chest film</td>
<td>Nodular infiltrates</td>
<td>Nodular infiltrates</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>PFTs</td>
<td>Restrictive</td>
<td>Mixed</td>
<td>Mixed</td>
</tr>
<tr>
<td>DLCO</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>High-resolution chest CT</td>
<td>May have normal chest CT</td>
<td>Ground glass opacities with centrilobular micronodular pattern (&lt;5 mm) and mosaic pattern</td>
<td>Parenchymal fibrosis, including honeycombing and traction bronchiectasis</td>
</tr>
</tbody>
</table>

Source: Adapted with permission from Ref. 2.
PFTs = pulmonary function tests; DLCO = diffusion capacity of the lung for carbon monoxide.
for HP. Physicians must identify exposure to an agent capable of causing HP with an appropriate temporal relation to symptoms. Diagnostic tests are used to support the diagnosis. Six significant predictors have been identified that provide ~95% diagnostic accuracy. These six predictors include (1) exposure to a known offending allergen, (2) positive precipitating antibodies to the offending antigen, (3) recurrent episodes of symptoms, (4) inspiratory crackles on lung auscultation, (5) symptoms occurring 4–8 hours after exposure, and (6) weight loss. For the acute form of HP, an inhalation challenge can clearly establish exposure and an appropriate temporal relation to symptoms, but it is rarely done because severe respiratory reactions may occur.

Skin testing is not useful because HP is not an IgE-mediated disease. The presence of serum-precipitating IgG antibodies to the offending antigen are found in HP but are not diagnostic because many individuals with exposure, but no disease, may have precipitating antibodies. In addition, the absence of precipitating antibodies does not exclude the diagnosis. The results of physical examination, chest x-ray, and pulmonary function tests differ depending on the form of HP. Details of the differences are shown in Table 2. Lung biopsy is not diagnostic but is often characterized by poorly formed granulomas, alveolar wall infiltration with lymphocytes, plasma cells and neutrophils, and, in the chronic form of HP, fibrosis. Usual interstitial pneumonia patterns may be seen.

The cornerstone of management in HP is early diagnosis and avoidance of the offending agent. Avoidance often requires a change in occupation or parting with a beloved pet bird. Therefore, there are frequently emotional, psychological, social, and economic factors that lead to noncompliance. Prednisone at a dose of 0.5 mg/kg per day can decrease symptoms in the acute and subacute phases but has no benefit in terms of disease progression. It is recommended not to treat a patient with more than a brief course of oral steroids in the setting of continued antigen exposure.

The majority of patients with HP enjoy a complete recovery once the offending agent is identified and avoided. However, deaths have been reported if exposure continues.

IMMUNOLOGY

- The inflammation in HP is not IgE mediated.
- Activated macrophages and CD8⁺ cytotoxic lymphocytes are key mediators of inflammation in HP.
- Bronchoalveolar lavage fluid typically reveals a lymphocytosis with a ratio of CD4⁺ cells to CD8⁺ cells <1.
- Activated macrophages have increased expression of CD80/CD86 and T cells have increased expression of its counter-ligand CD28.
- Although HP is classically thought of as a Th1 disease, a Th2 profile may be involved in those with chronic HP.
- Levels of Th1 cytokines are increased, including IL-12, IL-18, and TNF-α.
- IL-17, a proinflammatory cytokine that increases the number and activation of neutrophils, may also be an important participant in HP.

REFERENCES

Atopic dermatitis

Bradley R. Sabin, M.D., Neill Peters, M.D., and Anju T. Peters, M.D.

ABSTRACT

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing inflammatory dermatosis characterized by pruritus, xerosis, and a close association with IgE-mediated sensitization to aeroallergens and foods. More than 60% of children with AD are at risk to develop allergic rhinitis or asthma (the atopic march). The distribution of lesions varies by age. Infants tend to have lesions on the cheeks and scalp, and very young children typically have involvement over the extremities, cheeks, forehead, and neck. Rash in the diaper area of infants is rarely AD. Lesions in older children and adults are usually located in flexural areas, such as the antecubital and popliteal fossae, along with the head and neck. Acute lesions of AD begin as erythematous papules and serous exudates. Secondary lesions include excoriations and crusted erosions due to scratching. Subacute lesions appear as erythematous scaling papules and plaques. If the itch and rash progress uncontrolled, chronic lichenified AD develops featuring accentuated skin markings with hyperpigmentation. Trigger avoidance, skin hydration, and topical steroids are the first steps for improvement. In acute lesions of AD, the Th2 cells produce IL-4, IL-13, and IL-31, which may potentiate barrier dysfunction and contribute to pruritus. In chronic lesions, the Th1 cells predominate and secrete interferon gamma and IL-12. Barrier dysfunction from filaggrin predisposes patients to AD. Skin superinfection, particularly with Staphylococcus aureus, is common, and cultures of affected lesions help guide therapy. Eczema herpeticum from herpes simplex virus can be life-threatening in AD patients.

are severe. Seventy percent of patients outgrow AD by puberty. Persistent AD usually occurs in patients with moderate-to-severe disease. A minority of AD patients have disease onset in adulthood, and they tend to be nonatopic. New onset of lesions in adulthood should raise suspicion of another disorder. Diagnostic criteria with good sensitivity and specificity were described by the United Kingdom’s Working Party in 1994. These guidelines include pruritus, the pattern of skin involvement, personal or family history of atopic disease, and young age of onset. Laboratory evaluation of patients with AD may reveal elevated serum IgE concentrations and total eosinophil counts, especially in children with asthma. Skin-prick and in vitro IgE tests for suspected foods or common food allergens may be performed, but the positive predictive value of these tests is only 50%. However, especially in young children with severe eczema, these results may direct a trial elimination diet while monitoring for clinical improvement. Gradual reintroduction of suspected foods as oral challenges should be performed under the supervision of a physician aware of anaphylaxis risks.

The pathogenesis of AD includes skin barrier dysfunction and altered innate and adaptive immune responses. Some patients harbor null mutations in the filaggrin gene, which lead to altered barrier function and persistent severe eczema. Keratinocytes of AD patients show diminished up-regulation of innate antimicrobial peptides such as defensins and cathelicidins, which contribute to defective killing of Staphylococcus aureus and subsequent colonization in 90% of patients. S. aureus exotoxin augments skin inflammation by serving as a superantigen to initiate antigen-independent proliferation of T cells, increase cutaneous lymphocyte homing, and provoke the production of S. aureus exotoxin-specific IgE. An elevation of total IgE in AD is correlated with bacterial superinfection. Acute AD lesions show a Th2 phenotype with increased IL-4, IL-13, and IL-31 (which is pruritogenic) perhaps secondary to accentuated thymic stromal lymphopoietin production by keratinocytes. Th2 inflammation decreases filaggrin gene expression and contributes to barrier dysfunction. Chronic AD lesions deviate toward Th1 inflammation with predominant IL-12, IL-18, and interferon (IFN) γ.

The differential diagnosis of AD is broad and has been outlined in other sources. Common mimickers include seborrheic dermatitis, contact dermatitis, psoriasis, keratosis pilaris, and pityriasis rosea, along with infections such as scabies, candidiasis, and human immunodeficiency virus–associated eczema, and neoplastic conditions, such as cutaneous T-cell lymphoma. In children, AD is a component of various immunodeficiencies such as hyper-IgE syndrome, Wiskott-Aldrich syndrome, and severe combined immunodeficiency disease.

The severity of the signs and symptoms of AD may be assessed by validated scoring systems including the Eczema Area and Severity Index or scoring atopic dermatitis (SCORAD). Eczema Area and Severity Index evaluates total body surface involved with AD and focuses on signs of inflammation such as erythema, induration, excoriation, and lichenification, whereas SCORAD also accounts for subjective symptoms such as pruritus. These measures help quantify disease burden, tailor treatment intensity, and gauge response to therapy and are used primarily in clinical trials of AD.

Initial management of AD includes education, trigger avoidance, restoration of the epidermal barrier with emollients, itch control, and topical corticosteroids. Patient education to maximize compliance is essential. Avoidance of irritants and identified allergens that worsen eczema should be assessed during medical evaluations. Clothes with harsh fabrics, such as wool, should be avoided. Cleansers that are syndets (Dove, Cetaphil, etc.) are better tolerated than surfactants (Ivory, etc.) because they do not remove ceramides as readily from skin and thus reduce transepidermal water loss. Exposure to secondhand smoke, temperature extremes, and excessive sunlight should be avoided. In dust-mite allergic patients, preliminary evidence suggests some efficacy of immunotherapy in the treatment of AD, but, currently, immunotherapy is reserved for AD patients with concomitant respiratory allergies. Skin hydration is facilitated by short, lukewarm baths once a day, followed by immediate application of a topical emollient. Although ointments are more occlusive and keep evaporation to a minimum, moisturizing creams may be preferred in hot, humid conditions to prevent sweat from irritating AD lesions.

Topical corticosteroids are the first-line therapy to control inflammation in AD flares. These are applied once to twice a day, preferably immediately after a bath and before an emollient is applied. They are classified into seven potency ratings with the highest potency products having the lowest Roman numeral. Mild AD and moderate-to-severe AD usually requires low-potency topical corticosteroids (groups VI and VII), and midpotency topical corticosteroids (groups IV and V), respectively. Steroid potency may be increased to control inflammation. Wet wraps with topical corticosteroids increase skin penetration and can be used for severe AD by experienced physicians. Local adverse effects of topical steroids may include skin atrophy, striae, and telangiectasias. The risk of significant systemic absorption and hypothalamic–pituitary–adrenal axis suppression increases with potency and duration of topical steroid use. Local and systemic adverse effects are limited by using weaker strengths and nonfluorinated preparations on the face and inter-
trigeminal areas and by using stronger preparations on other areas for short courses. Topical calcineurin inhibitors, tacrolimus, and pimecrolimus have been approved in AD management but carry a Food and Drug Administration “black box” warning for possible development of malignancies with long-term use. They are commonly used twice daily in atrophy-prone areas such as the face, groin, and axillae. Other medical therapies may assist with AD management. In children with bacterial skin infection, the combination of bleach baths twice weekly and intranasal mupirocin twice daily for 5 consecutive days each month after a 14-day course of cephalaxin has been shown to decrease severity of AD on water-exposed skin and not on the face. For bleach baths, it is suggested that a ¼ cup of bleach be added to a ¾ filled tub and the patient should soak for 5–10 minutes. Immunosuppressants such as oral corticosteroids used on alternate days, cyclosporine A, azathioprine, methotrexate, or mycophenolate mofetil may be of benefit. Phototherapy may be helpful in severe refractory cases under the supervision of a specialist.

Skin superinfection in AD, particularly with S. aureus, is quite common, and cultures of affected lesions help guide therapy. Eczema herpeticum due to herpes simplex virus can be life-threatening in AD patients. Systemic acyclovir should be administered promptly. Eczema vaccinatum is a life-threatening reaction from the vaccinia virus in the small pox vaccine. Small pox vaccination should be avoided both in patients with history of AD and in their household contacts. Ocular complications of AD include keratoconjunctivitis, atopic keratoconjunctivitis, and recurrent conjunctivitis. AD patients may suffer psychological and emotional complications by dealing with a chronically uncomfortable condition. The itch of AD profoundly affects sleep. This is not histamine related, and first-generation antihistamines are efficacious because of their sedative effect. Additional studies on methods to decrease a patient’s risk of AD are needed; however, in 2008 the American Academy of Pediatrics recommended exclusive breastfeeding for at least 4 months in high-risk infants to decrease their risk of AD.

IMMUNOLOGY

- Barrier dysfunction related to filaggrin may predispose patients to AD.
- In acute lesions of AD, the Th2 cell produce IL-4, IL-13, and IL-31, which may potentiate barrier dysfunction and contribute to pruritus.
- In chronic lesions, the Th1 cell predominates and secretes IFN-γ and IL-12.
- Keratinocytes produce insufficient antimicrobial peptides in AD, which contribute to S. aureus colonization. S. aureus endotoxin potentiates inflammation within the lesion.
- Polymorphisms in Toll-like receptor 2 may contribute to recurrent bacterial infections in AD.
- The interaction of the IgE receptor FcεRI and Toll-like receptor 9 on plasmacytoid dendritic cells diminishes IFN-α and IFN-β production and may contribute to viral infection.

CLINICAL PEARLS

- AD is characterized by chronic, relapsing periods of intense itching with typical lesions induced by scratching. The pattern of disease varies by age.
- AD has a strong association with a personal or family history of asthma or allergic rhinitis.
- Trigger avoidance, skin hydration, and topical steroids should be the first steps for improvement.
- Use of topical corticosteroids requires knowledge of differences in preparations, appropriate duration of application, and risks of long-term use.
- There is evidence that exclusive breastfeeding for 4 months in high-risk infants decreases risk for development of AD.

REFERENCES

Urticaria and angioedema

Tara F. Carr, M.D., and Carol A. Saltoun, M.D.

ABSTRACT

Urticaria, also known as hives, may affect up to 20% of the population at some time in their lives. Urticaria is characterized by extreme pruritus and described as erythematous, raised, circumscribed lesions with central pallor that blanch with pressure. The pathogenesis of urticaria involves mast cell activation, with subsequent release of histamine and other vasoactive mediators, leading to increased vascular permeability of postcapillary venules and development of edema, erythema, and pruritus. Urticarial lesions often are generalized with multiple lesions in no specific distribution; angioedema tends to be localized, commonly affecting the face (periorbital and perioral regions), tongue, uvula, soft palate or larynx, extremities, and genitalia. Urticaria is subdivided into acute and chronic urticaria based on duration of symptoms. Acute urticaria lasts <6 weeks and an identifiable cause may be discovered such as food products, medications (aspirin, nonsteroidal anti-inflammatory drugs, and antibiotics), or insect stings. Urticaria lasting >6 weeks is designated as chronic urticaria, and an etiology is seldom identified and thus considered idiopathic. Chronic urticaria may have an autoimmune basis. There is a well-documented association between autoimmune hypothyroidism (Hashimoto’s disease) and urticaria and angioedema with higher incidence of antithyroid (antithyroglobulin and antiperoxidase) antibodies in these usually euthyroid patients. Furthermore, studies have revealed a circulating IgG antibody directed against the IgE receptor (F_{c,R1a}) or IgE in 40–60% of patients with chronic urticaria. Histamine 1–receptor antagonists (antihistamines) are initial therapy.


Urticaria, also known as hives, may affect 20% of the population at some time in their lives.1 Urticaria is characterized by extreme pruritus and described as erythematous, raised, circumscribed lesions with central pallor that blanch with pressure. An individual lesion may enlarge, coalesce with other lesions, and typically disappears within 24 hours. The pathogenesis of urticaria involves mast cell activation, with subsequent release of histamine and other vasoactive mediators, leading to increased vascular permeability of postcapillary venules and development of edema, erythema, and pruritus. Urticaria is closely associated with angioedema in 40% of individuals; ~10% of patients experience angioedema without urticaria. Although urticaria involves the superficial dermis, angioedema is a similar pathophysiological process that occurs in the deep dermis and subcutaneous tissues, resulting in ill-defined, nonpitting swelling. Because there are fewer mast cells and sensory nerve endings in the deeper skin layers, patients with angioedema experience minimal or no pruritus but may report a burning or swollen sensation instead. Urticarial lesions often are generalized with multiple lesions in no specific distribution; angioedema tends to be localized, commonly affecting the face (periorbital and perioral regions), extremities, and genitalia.

Urticaria is subdivided into acute and chronic urticaria based on duration of symptoms. Acute urticaria typically lasts <6 weeks and an identifiable cause is frequently discovered such as food products, medications, or insect stings. Urticaria lasting >6 weeks is designated as chronic urticaria, and an etiology is seldom identified and thus considered idiopathic. Some idiopathic cases of chronic urticaria may have an autoimmune basis. There is a well-documented association between autoimmune hypothyroidism (Hashimoto’s disease) and urticaria and angioedema,1,2 with higher incidence of antithyroid antibodies in these patients. Furthermore, studies have revealed a circulating IgG antibody directed against the IgE receptor (F_{c,R1a}) or IgE in 40–60% of patients with chronic urticaria.2,3 There are various causes of urticaria and angioedema, many of which are listed in Table 1. Foods such
as nuts, shellfish, milk, and eggs are frequent culprits with IgE-mediated reactions often accompanied by gastrointestinal symptoms. Medications including NSAIDs, aspirin, opiates, and radiocontrast media.

Table 1 Causes of urticaria and angioedema

| Food products | Most commonly shellfish, nuts, legumes, milk, and eggs |
| Medications/therapeutic agents | IgE mediated: penicillins, cephalosporins, and sulfonamides |
| | Immune complex and complement mediated: transfusion products |
| | Bradykinin mediated: angiotensin-converting enzyme inhibitors |
| | Other: nonselective NSAIDs, aspirin, opiates, and radiocontrast media |
| Insect stings | Physical |
| | Cold, cholinergic, solar, delayed pressure, dermatographism, vibratory, and aquagenic |
| Infection | Viral, fungal, bacterial, and helminthic |
| Underlying medical disease | Urticaria pigmentosa (systemic mastocytosis), cutaneous vasculitis associated with connective tissue disorder, serum sickness, malignancy, and acquired angioedema |
| Hereditary | Hereditary angioedema, hereditary vibratory angioedema, and familial cold urticaria, C3b inactivator deficiency |
| | Muckle-Wells syndrome (amyloidosis, nerve deafness, and urticaria) |
| Idiopathic | Note: an autoimmune etiology has been identified in some of these cases and activation by thrombin in others |

NSAIDs = nonsteroidal anti-inflammatory drugs.

matographism, which literally means “write on skin,” is characterized by a “wheal and flare” reaction after stroking the skin and may occur alone or coexist with chronic urticaria. Some patients have multiple different types of urticaria, one example being chronic idiopathic urticaria with cholinergic urticaria and dermatographism.

Urticaria and angioedema may be associated with underlying disorders, such as during the prodrome to some infections, especially viral (hepatitis A and B and Epstein-Barr virus), or during infection with Helicobacter pylori and parasitic diseases. Malignancy, although very rare in patients with chronic urticaria, should be considered in patients who are older or complain of systemic symptoms. Persistent, red–brown maculopapular lesions that urticate with stroking, known as Darier’s sign, characterize urticaria pigmentosa. A proportion of patients with urticaria pigmentosa are diagnosed eventually with indolent systemic mastocytosis. Urticarial vasculitis, with or without an associated connective tissue disorder, should be suspected if the lesions last >24 hours or residual ecchymoses remain after the urticaria subsides.

A focused clinical history is necessary to differentiate the many possible triggers of urticaria and angioedema. Establishing a temporal course of exposure and reaction is important, because exposure to an offending food or medication generally causes symptoms within 2–3 hours, and often within 30 minutes of ingestion. In addition, the duration of individual urticarial lesions and each episode or attack is helpful. A general review of systems may be useful for eliminating or raising suspicion of infectious processes, malignancy, and connective tissue disorders.

On physical exam, urticarial lesions are typically erythematous, raised, circumscribed lesions that blanch with pressure. The extent and distribution of urticaria and angioedema should be noted. Examine the skin for evidence of bruising or urticaria pigmentosa. Check for dermatographism by stroking the skin with a tongue depressor three times in the same location and observe in 15 minutes. Finally, evaluate the patient for any signs or symptoms of underlying systemic disorders (i.e., thyroid disorders, lymphoproliferative neoplasms, and connective tissue disorders).

For acute urticaria, a trigger may be identified, and further workup is unnecessary. If urticaria is chronic and there is suspicion for a systemic disorder, additional screening tests may be warranted. Blood tests that are considered include CBC (with platelets and differential), chemistry panel, liver function tests, TSH, ESR, and ANA. Complement levels (specifically C4 for screening) are considered for angioedema. It is not recommended that laboratory work be obtained on all individuals, but ordered based on clinical suspicion. A skin biopsy may be necessary to identify neutrophil-
rich urticaria or to distinguish chronic urticaria from more serious conditions such as urticarial vasculitis or indolent systemic mastocytosis. Skin testing or in vitro testing for anti-aeroallergen IgE antibody is not recommended.

Treatment begins with avoidance if a trigger is identified. Aspirin and nonselective nonsteroidal anti-inflammatory drugs are frequent causes, as well as known aggravators of urticaria/angioedema, and thus should be avoided. H1-receptor antagonists are the mainstay of therapy for urticaria and angioedema. Older, first-generation H1-receptor antagonists such as diphenhydramine and hydroxyzine are effective and are frequently prescribed; however, their use may be limited by sedation. One or more of the second-generation H1-receptor antagonists often is preferred by the patient because these medications are either nonsedating or less sedating. At times, using two to four times the Food and Drug Administration–approved dose of these medications may be required to control symptoms. However, some cases of chronic urticarial may be resistant to antihistamine treatment. Furthermore, other medications may be used individually or in conjunction with antihistamines. Doxepin, in a dose of 10–30 mg, is both an H1- and H2-receptor antagonist and is effective. Montelukast, a leukotriene inhibitor, is helpful in a few cases within 1 month of administration. Ketotifen (2 mg t.i.d.), a mast cell stabilizer not available in the United States, can be prescribed as adjunctive therapy. Refractory or severe cases may require short-term or chronic use of corticosteroids. Alternate-day dosing, if it can be achieved, is preferable. Other medications that may be effective include zileuton, colchicine, dapsone, azathioprine, tacrolimus, cyclosporine, and cyclosporine. Omalizumab may be effective in some patients with recalcitrant chronic idiopathic urticarial, but use is not Food and Drug Administration approved. If there is development of life-threatening symptoms (upper airway obstruction, acute wheezing dyspnea, lightheadedness with a 30-mmHg drop in blood pressure) in a patient with chronic idiopathic urticaria, the patient has subsequently developed anaphylaxis, and epinephrine should be administered immediately followed by medical evaluation.

IMMUNOLOGY

Biopsy patterns of urticarial and angioedema lesions are as follows:

- Acute urticaria/angioedema—dilation of small venules and capillaries in superficial dermis (urticaria) or subcutaneous tissue (angioedema), flattening of rete pegs, edematous collagen fibrils.
- Chronic idiopathic urticaria—nonnecrotizing perivascular mononuclear cell infiltrate consisting of activated T lymphocytes (predominantly CD4+), monocytes, and granulocytes (neutrophils, eosinophils, and basophils).
- Urticarial vasculitis—neutrophil infiltration with vessel wall necrosis and occasional deposition of immunoglobulin and complement.

CLINICAL PEARLS

- Urticaria is characterized by extremely pruritic, erythematous, raised migratory lesions that typically last <24 hours.
- Angioedema is a similar pathological process characterized by deeper swelling and is associated with urticaria in 40% of cases.
- Laboratory workup is based on clinical suspicion and includes some or all of the following: CBC with platelet and differential, chemistry, liver function panel, ESR, ANA, TSH, and complement studies.
- If individual urticarial lesions last >24 hours or leave residual ecchymoses or pigmentation, consider a skin biopsy to exclude urticarial vasculitis. Also consider skin biopsies in severe refractory cases or multiple systemic complaints.
- Treatment of severe chronic idiopathic urticaria usually requires a combination of or higher doses of second-generation (cetirizine, fexofenadine, and loratadine) H1-receptor antagonists and in severe refractory cases, oral steroids.

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Hereditary and acquired angioedema

Mary S. Georgy, M.D., and Jacqueline A. Pongracic, M.D.

ABSTRACT

Hereditary angioedema (HAE) is an autosomal dominant disorder defined by a deficiency of functional C1 esterase inhibitor (C1-INH). Acquired angioedema (AAE) is caused by either consumption (type 1) or inactivation (type 2) of C1-INH. Both HAE and AAE can be life-threatening. The screening test for both conditions is complement component C4, which is low to absent at times of angioedema or during quiescent periods. A useful test to differentiate HAE from AAE is C1q protein, which is normal in HAE and low in AAE. There are three types of HAE: type 1 HAE is most common, occurring in ~85% of patients and characterized by decreased production of C1-INH, resulting in reduced functional activity to 5–30% of normal. In type 2, which occurs in 15% of cases, C1-INH is detectable in normal or elevated quantities but is dysfunctional. Finally, type 3, which is rare and almost exclusively occurs in women, is estrogen dependent and associated with normal CI-INH and C4 levels. One-third of these patients have a gain-of-function mutation in clotting factor XII leading to kallikrein-driven bradykinin production. Although the anabolic steroid, danazol, is useful in increasing the concentration of C4 and reducing the episodes of angioedema in HAE and AAE, it has expected adverse effects. Fortunately, disease-specific therapies are available and include C1-INH enzyme for i.v. infusion either acutely or empirically, ecallantide, an inhibitor of kallikrein, and icatibant, a bradykinin B2-receptor antagonist, both approved for acute angioedema and administered, subcutaneously.

detectable as “normal” C1-INH. Hence, as in type 2 HAE, quantitative measurement of C1-INH may be normal but functional analysis reveals its inactivity.

C1-INH belongs to the serine protease inhibitor family and is synthesized primarily by hepatocytes. The major functions of C1-INH include inhibition of activated C1r and C1s, activated Hageman factor (XIIa), Hageman factor fragment (XIIif), activated factor XI, tissue plasminogen activator, and activated kallikrein.1 A brief discussion of these pathways follows.

The classic pathway of the complement cascade is initiated by an antibody–antigen complex, activating C1, which is a trimolecular complex composed of C1q, C1r, and C1s. C1q initially binds to the antibody (IgM or IgG), recruiting C1r first and later C1s, which becomes activated. Activated C1qrs cleaves C4, the product of which cleaves C2, which leads to the classic complement cascade, activating C3, which eventually generates the membrane attack complex (C5–C9) responsible for cell lysis. C1-INH inhibits C1r and C1s, keeping the classic complement pathway quiescent. Because C1-INH is consumed when acting as an inhibitor, the product of two active genes is required for effective inhibition.

C1-INH also inactivates plasma kallikrein and factor XIIa in the bradykinin-producing contact system. The primary mediator of HAE is bradykinin, generated through the contact system, and plasma bradykinin concentrations are elevated in acute HAE and AAE.14,5,7 However, the specific trigger that initiates angioedema via this pathway is unknown.

Clinical manifestations of HAE consist of localized subcutaneous or submucosal edema that may be spontaneous or triggered by trauma, medical or dental procedures, emotional stress, menstruation, infections, oral contraceptive use, or use of other medications. Patients may have a prodrome of tightness or tingling in the affected area several hours before the onset of angioedema.1 In addition, some attacks are preceded by erythema marginatum, a flat, nonpruritic rash.1 Typically, the angioedema worsens over ~1.5 days and lasts for 2–5 days before resolving spontaneously. The edema is nonpitting, tensely swollen, and often painful but not erythematosus, warm, or pruritic. HAE is not associated with urticaria.8 Areas most commonly affected include the face (lips, eyelids, and tongue), extremities, and genitals. Cutaneous angioedema of an extremity is the first presenting symptom in 75% of patients with HAE.5 Symptoms begin in childhood and become more severe during adolescence. However, onset of symptoms in infants and in the elderly has been reported. The frequency of attacks is variable; some patients may have weekly episodes, whereas years may lapse between episodes in others.1

The gastrointestinal system also is affected because of visceral edema resulting in intestinal obstruction, anorexia, vomiting, and severe abdominal pain. Diarrhea can occur on resolution of visceral edema. The abdomen is typically tender to palpation but without guarding. When cutaneous symptoms are absent, this picture mimics an acute abdomen, which may lead to unnecessary surgical exploration. Some fatalities have occurred when surgery was performed for an “acute abdomen” in undiagnosed patients with HAE.

The most ominous symptoms of HAE relate to the airway with edema of the oropharynx and larynx, resulting in airway obstruction. More than 50% of patients with HAE will have laryngeal involvement at some point in their disease course. Early symptoms include buccal or lingual edema, throat tightness, or voice changes. These symptoms may progress to difficulty swallowing and frank stridor within 20–30 minutes. Mortality can be as high as 15–33%.9 Asphyxiation can occur at any age.

The diagnosis of HAE is dependent on the laboratory hallmarks of a low (<30% normal) functional C1-INH titer and profoundly depressed C4 level.10,11 Antigenic (or quantitative) levels of C1-INH are low in type 1
HAE patients. The absolute concentrations of C4 or C1-INH function do not change with acute symptoms. Hence, it is not necessary to await an attack of angioedema to obtain a diagnostic specimen; the C4 concentration will be <10 mg/dL even during quiescent periods. In type 2 HAE, quantitative measurement of C1-INH is normal, but functional analysis reveals reduced activity. Patients with type 3 HAE have normal C4 concentrations; CI-INH levels and function are also normal (Table 1). In addition to low C4 concentrations, patients with AAE have low Clq concentrations.6

C1-INH is available for both prophylaxis and treatment of acute attacks.12,13 The products available in the United States for the treatment of acute attacks are plasma C1-INH (Berinert; CSL Behring, King of Prussia, PA), a kallikrein inhibitor, ecallantide (Kalbitor; Dyax, Cambridge, MA), and a bradykinin receptor B2-antagonist, icatibant (FIRAZYR; Shire Orphan Therapies, Inc, Lexington, MA).14 Anabolic steroids, such as danazol (200 mg q.i.d.) or stanozolol (4 mg q.i.d.), have slower onset of action for treatment of acute attacks. Intubation may be indicated and a tracheostomy can be potentially lifesaving because the swelling does not extend below the larynx.15 H1-receptor antagonists, glucocorticoids, and epinephrine have not been proven to be efficacious. Intravenous administration of fresh frozen plasma (FFP), which contains C1-INH, is controversial because it also contains kininogen and therefore may lead to increased bradykinin production. Therefore, FFP is not routinely used to treat acute exacerbations.

Chronic prophylactic therapy may be indicated in the following scenarios: diminished quality of life, more than one attack per month, previous intubation or intensive care unit stay, previous laryngeal swelling, >10 days lost from school or work per year, narcotic dependence, limited access to health care, and/or rapid onset of attacks.9,12 Purified C1-INH (Cinryze; Viropharma, Inc., Exton, PA) is approved in the United States for prophylaxis of HAE; it is administered i.v. every 3–4 days.6,12 Attenuated androgens (17-α alkylated androgens), such as danazol or stanozolol (if available), are commonly used for prophylaxis. These agents are thought to stimulate synthesis of C1-INH directed by the one normal gene. Side effects may include weight gain, altered libido, hirsutism, liver enzyme abnormalities, hypercholesterolemia, and microscopic hematuria. These medications are absolutely contraindicated in pregnancy because of concerns of potential virilization to the fetus, during lactation, and in children who have not attained sexual maturity or full growth potential (because of premature closure of bony epiphyses). Use of these medications is a relative contraindication in men undergoing treatment for prostate cancer. Dosing ranges for danazol and stanozolol (not available in the United States) are 200–800 mg/day and 2–12 mg/day, respectively. The lowest effective dose should be used for maintenance. Short-term prophylaxis for surgical and dental procedures may also be achieved with 1 week of androgen therapy.

FFP, although not generally used for acute attacks, may be useful for short-term prophylaxis 12–24 hours before surgical and dental procedures. However, pretreatment for 4 days with anabolic attenuated androgens is preferable unless a patient receives C1-INH.

Antifibrinolytic agents (plasmin inhibitors), such as tranexamic acid and e-aminocaproic acid, may be used for prophylaxis in children as well as adults who have failed attenuated androgens. These agents result in the inhibition of kallikrein and bradykinin production.9 Side effects include myalgias, muscle weakness, hypotension, fatigue, and elevation of serum creatine kinase. Thus, the indication for these medications has decreased unless the more expensive alternatives are not available.

Management of AAE differs from HAE. With regard to type 1 AAE, treatment of the underlying disorder may result in resolution of abnormalities. Therapy with attenuated androgens may be of little benefit in type 2 AAE and labeled indications of C1-INH and ecallantide do not include AAE. Infusion of C1-INH, although seemingly logical, is not as effective because the antibodies also inactivate the concentrate. Products on the horizon include a recombinant C1-INH.10

IMMUNOLOGY

- Most cases of HAE are autosomal dominant disorders resulting in a deficiency of functional C1-INH.
- AAE occurs due to increased consumption or inactivation of C1-INH.
- Bradykinin is the primary mediator of HAE.

CLINICAL PEARLS

- HAE and AAE are uncommon but very important causes of angioedema.
- HAE tends to present earlier in life than AAE.
- Clq concentrations distinguish AAE from HAE; they are low in AAE but normal in HAE.
- C4 is low during both acute episodes and quiescent periods. Normal C4 concentrations virtually exclude the diagnosis of HAE (as well as AAE; except for type 3 HAE).
- C1-INH is available for i.v. administration for both the treatment of acute attacks and the prophylaxis of HAE.
- Ecallantide, a kallikrein inhibitor, is available for subcutaneous administration for acute attacks of HAE.
• Icatibant, a bradykinin B2-receptor antagonist, is available for subcutaneous administration for acute attacks of HAE.

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Food allergy

Rachel G. Robison, M.D., and Jacqueline A. Pongracic, M.D.

ABSTRACT

The onset of IgE-mediated food allergy is usually within minutes to 2 hours of food ingestion. Risk factors for fatal food-induced anaphylaxis include presence of asthma (which is a risk factor for anaphylaxis in general), failure to use epinephrine autoinjectors promptly, history of prior severe reactions, known food allergy, denial of symptoms, and adolescent/young adult age. The most commonly implicated foods are cow’s milk, eggs, peanuts, soy, tree nuts, fish, shellfish, and wheat. Allergies to peanut, tree nuts, and seafood are the most common food allergens in adults. The major food allergens are glycoproteins that are generally water soluble and stable to the effects of heat, proteases, and acids. Food proteins that escape proteolysis are taken up by intestinal epithelial cells and presented to primed T cells. This process leads to the generation of T-helper type 2 (Th2) cells that produce IL-4, IL-5, and IL-13. Recent studies have found that tolerance can be acquired with >70% of children becoming tolerant to cow’s milk and eggs by age 16 years. Allergies to peanuts, tree nuts, and seafood are frequently lifelong. Food-allergic patients or their care givers should be taught when and how to administer injectable epinephrine. In terms of prevention, the American Academy of Pediatrics concluded that there is no convincing evidence that delaying the introduction of solid foods, including common allergens, beyond 4–6 months of age has a protective effect on the development of atopic disease.

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infrequent and more commonly occur as part of a generalized anaphylactic reaction. Symptoms such as sneezing, rhinorrhea, and nasal pruritus may occur in conjunction with the other symptoms noted previously but are not suggestive of food allergy when occurring in isolation.

Food allergy is the most common cause of generalized anaphylaxis seen in hospital emergency departments.\(^6\) Anaphylaxis is discussed in greater detail in another article of this journal.\(^7\) Peanut and tree nut ingestions account for >85% of food-induced anaphylaxis fatalities in the United States.\(^8\) The onset of symptoms is usually within minutes of food ingestion but may occur up to 2 hours after ingestion. Even after initial treatment, symptoms of anaphylaxis may recur again several hours after the initial reaction. These biphasic or late-phase reactions can occur up to one-third of the time and may be just as severe as the initial reaction.\(^5\) It is important to note that food-induced anaphylaxis may be fatal. Risk factors for fatal food-induced anaphylaxis include presence of asthma, failure to use epinephrine autoinjectors promptly, history of prior severe reactions, known food allergy, denial of use to use epinephrine autoinjectors promptly, history induced anaphylaxis include presence of asthma, fail-

Anaphylaxis is discussed in greater detail in another article of this journal.\(^7\) Peanut and tree nut ingestions account for >85% of food-induced anaphylaxis fatalities in the United States.\(^8\) The onset of symptoms is usually within minutes of food ingestion but may occur up to 2 hours after ingestion. Even after initial treatment, symptoms of anaphylaxis may recur again several hours after the initial reaction. These biphasic or late-phase reactions can occur up to one-third of the time and may be just as severe as the initial reaction.\(^5\) It is important to note that food-induced anaphylaxis may be fatal. Risk factors for fatal food-induced anaphylaxis include presence of asthma, failure to use epinephrine autoinjectors promptly, history of prior severe reactions, known food allergy, denial of use to use epinephrine autoinjectors promptly, history induced anaphylaxis include presence of asthma, fail-

As emphasized in food allergy guidelines, a thorough history is essential for proper assessment of IgE-mediated food allergy.\(^9\) The temporal association (best within 2 hours of ingestion), reproducibility (symptoms occur on every exposure), and clinical features are important to ascertain. Diet history and ingredient labels should be reviewed carefully, although occult ingredients may be the cause. Confirmation of the diagnosis of an IgE-mediated food allergy can be provided by skin-prick tests (SPT) or in vitro tests to assess the presence of food-specific IgE as further discussed in the diagnostic testing practice parameter and other articles of this journal.\(^10-12\) The positive predictive value of food SPT is <50%, but the negative predictive accuracy is >95%. Thus, negative SPTs essentially rule out an IgE-mediated process. Intradermal tests should not be used in the assessment of food hypersensitivity because of a high false positive rate and a risk of systemic reaction, which could be fatal. In vitro tests, although more expensive, are more accessible to the general practitioner. These tests quantify the level of food-specific IgE present in the patient’s serum and are very sensitive but have a high false positive rate. Similar to SPT, food-specific IgE testing can be difficult to interpret, particularly when positive with only a vague history of reaction, and is more useful when yielding a negative result. Both SPT wheal diameter and food-specific IgE levels do not correlate with the severity of food reactions, but rather higher results are associated with a greater likelihood of a reaction occurring if the item is ingested.

Oral food challenges may be indicated for diagnosis when history and testing are inconclusive or when evaluating for the development of tolerance. Double-blind placebo-controlled food challenges are considered to be the gold standard for the diagnosis of food allergies because they are least susceptible to bias.\(^13\) However, open challenges often are used in the allergist’s office. Medications and supplies for emergency resuscitation must be immediately available to the supervising physician in such settings.

IgE-dependent food hypersensitivities are characterized as acute responses, but there are other subacute and chronic immunologic aberrancies that may affect the gastrointestinal tract or skin, particularly in children. Atopic dermatitis can be exacerbated by a food allergen; up to 35% of children with moderate-to-severe atopic dermatitis have been confirmed to have food allergy as a contributory factor.\(^4,14\) Pollen–food allergy occurs when plant proteins, especially those in raw fruit that are cross-reactive with aeroallergens, induce immediate symptoms on contact with the oral mucosa causing local mast cell activation.\(^15\) Eosinophilic gastroenteropathies are considered to be mixed IgE, non-IgE processes, and in some patients can be attributed to food allergens.\(^16\) Symptoms depend on the site of eosinophilic infiltration and can include dysphagia, gastroesophageal reflux, gastric outlet obstruction, postprandial emesis, weight loss, and failure to thrive. Several non–IgE-mediated food reactions are described as well. Food protein-induced enterocolitis syndrome has the most dramatic presentation of cell-mediated gastrointestinal food allergy in infants and is usually triggered by exposure to cow’s milk or soy. Patients present with delayed onset (>2 hours after ingestion) of profuse vomiting, abdominal cramps, and/or diarrhea, resulting in dehydration, metabolic acidosis, and possibly hypotension and shock. Some cases may have chronic diarrhea and poor growth, which resolve on elimination of the antigen. Dietary protein-induced proctitis or proctocolitis, in contrast, is a relatively benign disorder resulting in bloody, mucousy stools in infants caused by cow’s milk exposure and usually resolves by 1 year of age. Dietary protein enteropathy, also usually attributable to cow’s milk, is a malabsorptive disorder that presents with diarrhea and poor weight gain. This disorder is transient and does not require permanent elimination diets.

Available treatment options at this time for IgE-mediated food reactions include avoidance of food allergens and prompt treatment of reactions caused by accidental ingestions. Treatment of acute reactions is dependent on the severity of symptoms with isolated, nonprogressive cutaneous symptoms being treated with H1-receptor antagonists and severe or multisystem anaphylactic reactions requiring epinephrine. Autoinjectors containing epinephrine, such as EpiPen (Dey, Napa, CA) or Twinject
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Common food allergens in children include eggs, peanuts, cow’s milk, soy, tree nuts, fish, and shellfish.

Food-induced anaphylaxis may occur without skin manifestations, so health care providers need to have a high index of suspicion when treating patients with possible IgE-mediated food reactions.

Recent studies indicate that it is taking longer for children to outgrow allergies to foods such as cow’s milk and eggs and these allergies may not be outgrown until adolescence. Allergies to peanuts, tree nuts, fish, and shellfish often are present through adulthood.

It is advisable that any patient with a food allergy carry an epinephrine autoinjector at all times and family and friends must be instructed on its proper use.

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Anaphylaxis

Paul A. Greenberger, M.D., and Anne M. Ditto, M.D.

ABSTRACT

Anaphylaxis is a sudden-onset, immediate reaction that implies a risk of death. Think of a “rule of 2’s” for anaphylaxis implying that reactions usually begin within 2 minutes to 2 hours after injection, infusion, ingestion, contact, or inhalation. Fatalities can be from asphyxiation from laryngeal or oropharyngeal swelling, collapse from hypotensive shock, cardiac arrest, or acute severe bronchoconstriction causing respiratory failure and arrest. When there is activation of mast cells and basophils in anaphylaxis, chemical mediators are detectable. The preformed mediators from mast cells include histamine, tryptase, carboxypeptidase A, and proteoglycans (heparin and chondroitin sulfates). Newly synthesized mediators include prostaglandin D₂, leukotriene D₄, and platelet-activating factor. Crucial actions of the mediators include an abrupt increase in vascular permeability, vascular smooth muscle relaxation, and bronchial smooth muscle contraction. Anaphylaxis can be classified into immunologic, nonimmunologic, or idiopathic based on the associated mechanism. For example, immunologic causes of anaphylaxis are those mediated by IgE antibodies acting through the FcεRI (foods, insect venom, and beta-lactam antibiotics) whereas non-IgE immunologic anaphylaxis is mediated without presence of antiallergen IgE antibodies or via FcεRI activation (radiographic contrast material). Nonimmunologic anaphylaxis involves mast cell mediator release such as occurs with exercise, cold temperature exposure, or from medications such as opioids or vancomycin. Idiopathic anaphylaxis involves mast cell activation (acutely elevated urine histamine or serum tryptase) and activated lymphocytes. Because anaphylaxis is a medical emergency, the drug of choice is epinephrine, not H₁-receptor antagonists.


Anaphylaxis is a sudden-onset, immediate reaction that is potentially fatal.¹ Most patients do not succumb from anaphylaxis but when they do, in half the cases, death occurs within the 1st hour after onset of anaphylaxis.² From a pathophysiological basis, fatalities can be from asphyxiation from laryngeal or oropharyngeal swelling, collapse from hypotensive shock, cardiac arrest, or acute severe bronchoconstriction causing respiratory failure and arrest.² When any one of the following three criteria are present, the diagnosis of anaphylaxis is considered “highly likely”:³

1. Acute onset of an illness (over minutes to hours) involving skin (generalized hives), mucosal tissue (swollen lips–tongue–uvula) or both and at least one of the following: (a) respiratory compromise or (b) reduced blood pressure or associated symptoms of end organ dysfunction (collapse, syncope, or incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen (minutes to several hours): (a) involvement of the skin–mucosal tissue (generalized hives, swollen lips, tongue, or uvula), (b) respiratory compromise (acute dyspnea, wheezing, stridor, or hypoxemia), (c) reduced blood pressure or associated symptoms (collapse or syncope), (d) persistent gastrointestinal symptoms (abdominal cramping or vomiting).

3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours), for infants age-specific declines or >30% decrease; for adults, systolic blood pressure <90 mmHg or >30% decrease from a patient’s baseline.

Anaphylaxis can be classified into immunologic, nonimmunologic or idiopathic based on the associated mechanism.⁴ For example, immunologic causes of anaphylaxis are those mediated by IgE antibodies acting through the FcεRI whereas nonimmunologic anaphylaxis is mediated without presence of antiallergen IgE antibodies or via FcεRI activation.⁴ Idiopathic anaphylaxis involves mast cell activation (acutely elevated
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urine histamine or serum tryptase) and activated lymphocytes.\textsuperscript{5} The term “anaphylactoid” describing types of non—IgE-mediated anaphylaxis, such as with radiographic contrast materials, is not recommended currently. Such reactions are categorized as non-IgE immunologic anaphylaxis.\textsuperscript{4}

Type I immediate or IgE-mediated reactions are discussed in another article of this journal, which focuses on the classification of hypersensitivity disorders.\textsuperscript{6} Examples of IgE-mediated immunologic anaphylaxis include foods\textsuperscript{7,8}; stings, or bites from insects\textsuperscript{9}; medications (penicillins and cephalosporins)\textsuperscript{10}; latex; allergen immunotherapy injections\textsuperscript{11,12}; and some food additives such as spices, bee pollen, colorants (carmine),\textsuperscript{13} dust mites contaminating wheat used for baked goods (beignets), and nematode (\textit{Anisakis simplex}) contamination of mackerel. In children, the common foods are eggs, milk, peanuts, soy, shellfish, tree nuts, wheat, and fish. In adults, common food allergens are peanuts, tree nuts, shellfish, and fish.

Some examples of non-IgE immunologic anaphylaxis, besides radiographic contrast material, are attributable to dextran and oversulfated chondroitin sulfate (a contaminant in heparin) that caused activation of complement-derived anaphylatoxins, C3a and C5a, (a contaminant in heparin) that caused activation of mast cells.\textsuperscript{5} The term “anaphylactoid” describing types of non-IgE-mediated anaphylaxis.\textsuperscript{4}

Type I immediate or IgE-mediated reactions are discussed in another article of this journal, which focuses on the classification of hypersensitivity disorders.\textsuperscript{6} Examples of IgE-mediated immunologic anaphylaxis include foods\textsuperscript{7,8}; stings, or bites from insects\textsuperscript{9}; medications (penicillins and cephalosporins)\textsuperscript{10}; latex; allergen immunotherapy injections\textsuperscript{11,12}; and some food additives such as spices, bee pollen, colorants (carmine),\textsuperscript{13} dust mites contaminating wheat used for baked goods (beignets), and nematode (\textit{Anisakis simplex}) contamination of mackerel. In children, the common foods are eggs, milk, peanuts, soy, shellfish, tree nuts, wheat, and fish. In adults, common food allergens are peanuts, tree nuts, shellfish, and fish.

Exercise-induced anaphylaxis (EIA) is a unique subset of anaphylactic reactions of which there are three main types: (1) food specific, (2) postprandial, and (3) food independent. Patients with food-specific EIA have symptoms when exercising within 4–6 hours after ingestion of a particular food. These patients are nearly always skin-test or in vitro–test positive to the specific food. The mechanism of this type of reaction is poorly understood but is thought to be IgE mediated and fairly reproducible, meaning that ingestion of a particular food with exercise will always cause some degree of anaphylaxis; however, consumption of the food independent of exercise does not produce symptoms and neither does exercise alone. In postprandial and food-independent EIA, patients develop anaphylaxis after ingestion of food followed by exercise or after exercise alone. These reactions often are not reproducible, and varying degrees of exercise may precipitate a reaction. Treatment of patients with the food-specific or postprandial EIA entails avoidance of food within 6 hours of exercise. All patients with EIA should carry self-injectable epinephrine and exercise with a “buddy” who knows about the patient’s condition and can administer epinephrine, if needed.

When there is activation of mast cells and basophils in anaphylaxis, chemical mediators are detectable.\textsuperscript{14} The preformed mediators from mast cells include histamine, tryptase, carboxypeptidase A, and proteoglycans (heparin and chondroitin sulfates). Newly synthesized mediators include prostaglandin D\textsubscript{2}, leukotriene D\textsubscript{4}, and platelet-activating factor. Crucial actions of the mediators include an abrupt increase in vascular permeability, vascular smooth muscle relaxation, and bronchial smooth muscle contraction.

A focused history is needed to diagnose anaphylaxis. The temporal relation of anaphylaxis after the ingestion of foods or medications should be ascertained as the majority of these reactions occur within minutes to hours after exposure. Most reactions occur within 2 hours. Think of a “rule of 2’s” for anaphylaxis implying that reactions usually begin within 2 minutes to 2 hours after injection, infusion, ingestion, contact, or inhalation.

Laboratory tests can be considered according to the clinical status. In the acute setting, serum tryptase can be obtained in the first 6 hours but preferably from 15 minutes to 3 hours (a spot sample of urine might be obtained if there is access to an assay for histamine or a metabolite, \textit{N}-methylhistamine). In the office setting when the patient is stable, a serum tryptase can be obtained if it is necessary to exclude indolent systemic mastocytosis and skin (or potentially \textit{in vitro} tests for anti-food, anti-stinging insect venom or medication IgE antibodies.\textsuperscript{15} To exclude hereditary angioedema or acquired C1 inhibitor deficiency syndrome, the complement factor C4 is the critical screening test.\textsuperscript{16} A normal value excludes these two conditions. It remains uncertain how to diagnose type III hereditary angioedema because complement concentrations are normal and tests for activation of factor XII are not available widely.

The differential diagnosis of anaphylaxis includes syncope (such as a faint or vasodepressor syncope immediately after an injection of a potential allergen), acute severe asthma with facial erythema and swelling just before a patient has a respiratory arrest from asthma,\textsuperscript{17} cardiac arrhythmia or flash pulmonary edema after injection of radiographic contrast material, systemic capillary leak syndrome (extreme capillary permeability occurring over several hours with marked hypotension and hemoconcentration, often with monoclonal gammapathy), panic attack, neurological-based seizure in the setting of an infusion of an antibiotic or radiographic contrast material, indolent systemic mastocytosis, urticaria pigmentosa, vocal cord dysfunction, postprandial episode of poisoning from spoiled fish harboring histamine-generating bacteria,\textsuperscript{8} Munchausen syndrome (nonorganic production of loud or terrifying
sions that mimic stridor or frighten medical personnel who fear infectious epiglottitis or hereditary angioedema), and undifferentiated somatoform idiopathic anaphylaxis (upper airway obstruction, hypertensive collapse, wheezing dyspnea, generalized flushing, or limited urticaria that are not confirmed objectively but whose description by the patient appears completely consistent with anaphylaxis). Munchausen anaphylaxis is true anaphylaxis that has been produced deliberately either by the subject (ingestion of aspirin or a food in a subject known to be allergic to such) or by proxy (parent or caregiver to subject). The perpetrator–patient lies when queried about the ingestion of a known allergen.

Because anaphylaxis is a medical emergency, the drug of choice is epinephrine, not H1-receptor antagonists. Epinephrine (0.3 mL of a 1:1000 solution for adults and 0.01 mL/kg maximum of 0.3 mL in children) should be administered i.m. in any patient suspected of having anaphylaxis and repeated if necessary, as frequently as 5–15 minutes. In such a case, emergency assistance should be sought. A recent study suggests that in 17% of cases of food anaphylaxis, a second dose of epinephrine may be necessary. An H1-receptor antagonist and corticosteroid also should be administered because the former can relieve some symptoms and the latter may reduce or prevent a late reaction (no studies are available in this regard). Patients should be taught how and when to self-administer epinephrine such as in patients with peanut or tree nut anaphylaxis, EIA, idiopathic anaphylaxis, and patients with stinging or biting insect anaphylaxis. Self-injectable epinephrine devices contain autoinjectors with 0.15 or 0.30 mg or a device with an autoinjector and preloaded syringe as backup.

For idiopathic anaphylaxis or non-IgE immunologic anaphylaxis from radiographic contrast material, corticosteroid pretreatment has been found to be effective in reduction of either repeated episodes of idiopathic anaphylaxis or immediate reactions to radiographic contrast material. In the latter case, pretreatment of at-risk patients with prednisone at 50 mg orally at −13, −7, and −1 hour along with diphenhydramine at 50 mg at −1 hour before radiographic contrast material infusion has reduced the incidence of repeated anaphylactic reactions to −0.5%.

It is advisable that many patients who experience anaphylaxis be evaluated by an allergist–immunologist. Some specific areas of expertise include the confirmation of the diagnosis and determination of the level of risk of future episodes, advice on avoidance and cross-reacting allergens, reassurance and teaching on when to self-inject epinephrine, clarification if immunotherapy for stinging or biting insect anaphylaxis is indicated, recommending empiric treatment of patients with idiopathic anaphylaxis, and being a resource for patients who otherwise may live in fear of the next episode.

**CLINICAL PEARLS**

- An anaphylactic reaction should be suspected, diagnosed, and treated with epinephrine (for adults, 0.3–0.5 mg; for children, 0.01 mL/kg up to 0.3 mg) i.m. to prevent further clinical deterioration.
- A detailed history is important in attempting to identify the cause of anaphylaxis. If a cause is found, the agent can be avoided.
- An emergency regimen including self-injectable epinephrine, prednisone, and cetirizine should be carried by patients.
- An atopic history is associated with increased risk of anaphylaxis from latex, exercise, radiographic contrast media, foods, and that which is idiopathic. (Note absence of penicillin and stinging insects.)

**IMMUNOLOGY**

- The preformed mediators of anaphylaxis include neutral proteases, some of which activate other inflammatory cascades such as the kinin system, chemotactic factors, histamine, and proteoglycans (heparin).
- Newly synthesized mediators include prostaglandin D2, leukotriene D4, and platelet-activating factor. These are derived from lipids such as arachidonic acid. Cytokines that are newly generated include TNF-α.
- Susceptibility factors for anaphylaxis may include decreased levels of platelet-activating factor acetylhydrolase, increased baseline histamine concentrations, and low serum angiotensin-converting enzyme activity.

**REFERENCES**

Chapter 25

Idiopathic anaphylaxis

Karen Hsu Blatman, M.D., and Anne Marie Ditto, M.D.

ABSTRACT

Idiopathic anaphylaxis (IA) is defined as anaphylaxis without any identifiable precipitating agent or event. The clinical manifestations of IA are the same as allergen-associated (immunologic) anaphylaxis and include urticaria, angioedema, hypotension, tachycardia, wheezing, stridor, pruritus, nausea, vomiting, flushing, diarrhea, dysphagia, light-headedness, and loss of consciousness. Patients usually tend to have the same manifestations on repeated episodes. IA is a prednisone-responsive disease that is ultimately a diagnosis of exclusion. Approximately 40% of patients are atopic. Serum tryptase (or urine histamine or its metabolite) will be elevated acutely but if elevated in the absence of anaphylaxis, should suggest alternative diagnoses including indolent systemic mastocytosis. A focused history, examination, and follow-up will dictate whether a patient’s symptoms may be attributable to disorders that mimic anaphylaxis, such as indolent systemic mastocytosis, carcinoid syndrome, pheochromocytoma, hereditary angioedema acquired C1 esterase inhibitor deficiency, or panic attacks. The presence of urticaria may help limit the differential because they do not usually accompany any of the aforementioned disorders, except for indolent systemic mastocytosis. IA is classified according to the symptoms as well as the frequency of attacks. Patients who experience six or more episodes in a year or two or more episodes in 2 months are classified as IA-frequent (IA-F). Patients who experience fewer episodes are classified as IA-infrequent (IA-I). This distinction is important because IA-F patients initially will require prednisone as disease-modifying therapy whereas most IA-I patients will not. Patients with IA must carry and know when and how to self-administer epinephrine.


Idiopathic anaphylaxis (IA), defined as anaphylaxis without any identifiable precipitating agent or event, was first described in 1978 by Bacal et al. who reported 11 patients whose episodes of anaphylaxis could not be explained.1 This series has been expanded to include >335 patients who have been followed for over 1100 patient years without an external allergen being implicated.2 Despite the fact that much is still unknown regarding the etiology of IA, treatment is associated with good prognosis.

Multiple theories on the pathogenesis of IA have been proposed, but none have successfully explained why these patients experience episodic release of bioactive mediators from mast cells and basophils.3 To date, studies have not shown that basophils or mast cells exhibit a lower response threshold when releasing histamine or other mediators. No hidden culprit allergens have been found despite investigations into meta-bisulfit (a common food additive/ preservative) or progesterone sensitivity. Although anti-IgE autoantibodies have been shown to play a role in idiopathic urticaria—by activating mast cells via cross-linking surface IgE (or FcεRI)—preliminary studies at Northwestern University were unable to detect any significant differences in anti-IgE levels between IA patients and controls.4 Grammer et al. published data to show that IA patients displayed more activated B cells in their peripheral blood than controls and that symptomatic IA patients showed a higher percentage of activated T lymphocytes than IA patients in remission.5 The role of these activated T and B cells in the pathogenesis of IA still has to be determined.

The clinical manifestations of IA are the same as allergen-associated (immunologic) anaphylaxis and include urticaria, angioedema, hypotension, tachycardia, wheezing, stridor, pruritus, nausea, vomiting, flushing, diarrhea, dysphagia, light-headedness, and loss of consciousness.6 Patients may experience different combinations of the mentioned symptoms but usually tend to have the same manifestations on repeated episodes. Progression from hives and pruritus to the life-threatening symptoms of syncope, wheezing, and laryngeal edema may vary from 10 minutes to hours, depending on the individual.

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IA is classified according to the symptoms as well as the frequency of attacks. Patients who experience six or more episodes in a year or two or more episodes in 2 months are classified as IA-frequent (IA-F). Patients who experience fewer episodes are classified as IA-infrequent (IA-I). This distinction is important because IA-F patients initially will require prednisone as disease-modifying therapy whereas most IA-I patients will not. Those patients who experience obstructive upper airway angioedema without other systemic signs/symptoms of anaphylaxis are described as IA-angioedema (IA-A) whereas those who experience hypotension, bronchospasm, cardiovascular collapse, or gastrointestinal symptoms are classified as IA-generalized (IA-G). There are four ultimate combinations: either IA-G-F, IA-A-F, IA-G-I, and IA-A-I. Several sub classifications of IA also exist (Table 1).7

IA remains a diagnosis of exclusion after eliminating other causes. It should be considered after a thorough history, physical, and review of the medical records, especially those records from the emergency department where documented blood pressures, heart rates, and oropharyngeal examinations will help contextualize a patient’s subjective report of light-headedness or throat tightening, because vocal cord dysfunction, panic attacks, or undifferentiated somatoform anaphylaxis can also mimic IA. Physical exam findings in the acute setting will help guide laboratory work and testing for the more common causes of anaphylaxis including food, medications, insect stings, latex, and exercise. Although exercise testing is not commonly performed, skin testing is performed for penicillin, latex, venom, and food allergy when clinically relevant. If skin tests are not available for a culprit medication, test dosing may be accomplished in a monitored setting in an effort to exclude a suspected medication. This should only be done if the pretest probability for a medication is low and the issue needs to be clarified. In 2009, Commins et al. reported a novel food allergy related to IgE antibodies to the carbohydrate galactose-H9251-1,3-galactose from patients who experienced delayed symptoms of anaphylaxis, angioedema, or urticaria 3–6 hours after ingestion of beef, pork, or lamb. Of 60 patients from Virginia, Tennessee, and western Australia initially diagnosed with IA, Commins found 25 with elevated IgE antibodies to galactose-H9251-1,3-galactose; however, it remains unclear if it the antibodies are responsible for the symptom manifestations.8

A focused history also will dictate whether a patient’s symptoms may be attributable to disorders that mimic anaphylaxis, such as indolent systemic mastocytosis, carcinoid syndrome, pheochromocytoma, hereditary acquired C1 esterase inhibitor deficiency, or panic attacks. The presence of urticaria may help limit the differential because they do not usually accompany any of the aforementioned disorders, except for indolent systemic mastocytosis. Nevertheless, urine studies for 5-HIAA or metanephrines may be ordered if carci-

Table 1  Classification of IA

<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of episodes</td>
<td>More than six times per year or more than once in 2 mo: frequent</td>
</tr>
<tr>
<td></td>
<td>Less than six times per year or less than once in 2 mo: infrequent</td>
</tr>
<tr>
<td>Generalized</td>
<td>Urticaria or angioedema with bronchospasm, hypotension, or syncope</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Angioedema with upper airway compromise (laryngeal, pharyngeal, and tongue)</td>
</tr>
<tr>
<td>Corticosteroid-dependent IA</td>
<td>Used when a patient has recurrent IA symptoms below a threshold dose of prednisone</td>
</tr>
<tr>
<td>Malignant IA</td>
<td>Used when a patient requires high doses of prednisone for disease suppression, arbitrarily set at 30 mg/day or 60 mg every other day</td>
</tr>
<tr>
<td>IA-questionable</td>
<td>Used when a patient has possible IA but where documentation of objective findings is lacking and/or lack of response to medications</td>
</tr>
<tr>
<td>IA-variant</td>
<td>Used when symptoms of IA vary from classic IA; diagnosis may eventually be changed to IA-A, IA-G, IA-Q, undifferentiated somatoform IA</td>
</tr>
<tr>
<td>Undifferentiated somatoform IA</td>
<td>Used when stated symptoms mimic IA but no objective findings can be documented; should be suspected when the symptoms do not respond to treatment regimen and lack of objective findings should be documented, differentiating this from IA-Q</td>
</tr>
</tbody>
</table>

Source: Adapted with permission from Ref. 7.

IA = idiopathic anaphylaxis; A = angioedema; F = frequent; G = generalized; I = infrequent; Q = questionable.
noid or a pheochromocytoma is suspected, respectively. Skin or bone marrow biopsies may be needed to confirm a diagnosis of mastocytosis, especially if a total tryptase concentration is >20 ng/mL. A tryptase concentration also may be ordered to help confirm that a patient’s symptoms are truly caused by anaphylaxis and mast cell release. Given that peak tryptase concentrations occur about 2 (to 4) hours after an episode and decrease thereafter, optimal timing for drawing a tryptase concentration would be 1–2 hours after the event and not beyond 6 hours. Other laboratory work would include complete blood count, kidney panel, liver functions, and complement levels (C4 as screening to exclude hereditary angioedema or acquired C1 inhibitor deficiency).

In 15 patients with indolent systemic mastocytosis compared with 15 patients with IA, Koterba and Akin reported that the baseline tryptase concentrations were higher in the patients with indolent systemic mastocytosis and all bone marrow examinations displayed markers of clonal mast cell disease (CD25, c-kit D816V mutation). None of the indolent systemic mastocytosis patients experienced urticaria during their anaphylactic episodes, whereas those with IA reported urticaria frequently.

**Figure 1. Algorithm for the management of idiopathic anaphylaxis (IA).**
Although treatment for IA patients should be individualized, there are some guidelines that may be applied (Figure 1). All IA patients should be educated about their disease and taught how to manage an acute attack. At the first signs of anaphylaxis, adult patients should inject 0.3 mL (1/1000) of aqueous epinephrine intramuscularly followed by oral intake of prednisone at 50–60 mg and either cetirizine at 10 mg or hydroxyzine at 25–50 mg. In cases where a patient has a prodrome, e.g., where lip tingling precedes lip and pharyngeal angioedema, the patient may take an antihistamine immediately and be prepared to self-administer epinephrine. The emergency kit should be carried on the person at all times and occasionally monitored for expiration. All patients who use epinephrine should go immediately to the nearest emergency department for further evaluation.

Patients with IA-F need to be started on disease-modifying suppressive therapy, which should include 40–60 mg of prednisone daily as well as an antihistamine, either cetirizine at 10 mg or hydroxyzine at 25–50 mg daily. Patients should be given at least 1 week of daily prednisone although some may require 2 weeks. It is so rare that IA does not respond to daily systemic steroids that the diagnosis should be called into question if a patient is not controlled after 2–3 weeks of daily prednisone or is having symptoms (hypotension, upper airway angioedema, or generalized urticaria) on higher doses of prednisone, e.g., 40–60 mg daily after 2 weeks. Once symptoms resolve for 7 days, patients may be tapered to every-other-day dosing. If no relapses occur, the patient may be further weaned by 5 mg every other day every 1–2 weeks. The antihistamines may be tapered once the prednisone is discontinued but patients are usually maintained on a daily antihistamine, preferably nonsedating, for at least a year.

Steroid-dependent IA, requiring at least 30 mg of prednisone daily or 60 mg every other day is uncommon but alternative medications such as ketotifen, oral cromolyn, oral albuterol, or montelukast can be tried in those patients for whom prednisone cannot be discontinued. To avoid complex and costly medication regimens, these second-line agents should be discontinued if they do not clearly decrease the patient’s prednisone requirement. There have been case reports of successful anti-IgE therapy with omalizumab for IA. However, if a patient is not responsive to prednisone or cannot be tapered, diagnosis of IA should be reconsidered.

Patients with IA should be offered a Medic Alert bracelet that states their diagnosis. They should also be educated and frequently reminded about how to administer their epinephrine, prednisone, and antihistamine. Although the potential life-threatening nature of their disease should be reinforced, physicians should reassure their patients that compliance with the prescribed regimen offers a remission rate in excess of 80%.2

**IMMUNOLOGY**

- Symptoms of IA occur as a result of episodic activation of mast cells and basophils via an unknown mechanism.
- IA patients display more activated B cells in their peripheral blood.
- IA patients experiencing an acute episode display a higher percentage of activated T lymphocytes than those patients in remission.
- It is uncertain whether anti-IgE autoantibodies play a role in the pathogenesis of IA.

**CLINICAL PEARLS**

- IA is a steroid-responsive disease that is ultimately a diagnosis of exclusion.
- Its underlying pathogenesis is unknown but may be autoimmune in nature.
- All IA patients should carry an emergency kit that includes epinephrine.
- If symptoms are not responsive to systemic steroids administered over several weeks, one should reconsider the diagnosis of IA.
- Serum tryptase (or urine histamine or its metabolite) will be elevated acutely but if elevated in the absence of anaphylaxis, should suggest alternative diagnoses including indolent systemic mastocytosis.

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Eosinophilic esophagitis (EoE) is a clinicopathological disease characterized by esophageal eosinophilia. EoE was first described in 1977 by Dobbins et al. as a variant of eosinophilic gastroenteritis. The esophagus is normally devoid of eosinophils and their presence in the esophagus was previously thought to be primarily related to gastroesophageal reflux disease (GERD). In 1993, EoE became recognized as a separate clinicopathological entity when 11 of 12 adults presenting with dysphagia and eosinophils in their esophageal biopsy specimens (>20 eosinophils/high-power field) were found to have normal esophageal acid exposure on 24-hour pH monitoring. Esophageal manometry showed a nonspecific motility disturbance in 10 of them. EoE is now generally distinguished from GERD by persistent esophageal eosinophilia despite medical therapy with proton-pump inhibitors. Since recognized, the incidence of EoE has increased, and this is not explained by increased awareness alone.

EoE has a male predilection and affects both children and adults although many of the clinicopathological features differ between these two age groups including age at presentation and symptoms. Most adults do not come to clinical attention until the third decade of life, presenting most commonly with dysphagia, food impaction, heartburn, or chest pain. Although adolescents often present with similar symptoms, infants and toddlers present with feeding difficulties, failure to thrive, food aversion, and regurgitation. School-age children often present with vomiting and abdominal pain. In a case series of 103 pediatric patients, symptoms varied by age groups. These included feeding disorders (median age, 2.0 years), vomiting (median age, 8.1 years), abdominal pain (median age, 12.0 years), dysphagia (median age, 13.4 years), and food impaction (median age, 16.8 years).

The most common endoscopic features in adults with EoE include linear furrows (creases that orient longitudinally), mucosal rings (esophageal “trachealization”), small-caliber esophagus, white plaques or exudates (which are microabscesses of eosinophils), and strictures. Children often present with similar endoscopic features, but the findings may be more subtle, and one-third of pediatric patients with EoE have a
Topical corticosteroids improve esophageal eosinophilia and symptoms and have become the “gold standard” of therapy. Studies have used either “puff and swallow” aerosolized fluticasone propionate or swallowed budesonide suspension respules mixed with sucralose (Splenda [Tate & Lyle PLC, London, United Kingdom]). There is no recommended length of time to treat before discontinuing therapy. Symptom recurrence often is reported after topical steroids are discontinued. Side effects include esophageal candidiasis and unpleasant taste of budesonide with sucralose.

Removal of food antigens has been shown to improve symptoms in patients with EoE. Consultation with a dietician is recommended. An elemental/amine acid–based formula diet has shown to be effective but may not be well tolerated by adults because of taste and volume. Food elimination diets may be empiric elimination diets, often referred to as the six-food elimination diet (SFED), which entails avoiding the eight most common allergenic foods (milk, wheat, eggs, soy, peanuts, tree nuts, shellfish, and fish), or may be directed by allergy testing. Other interventions include endoscopic esophageal dilation for adults with EoE who present with strictures. Although dilation is highly effective in providing symptom relief and can be performed safely, it does not change the underlying inflammation.

EoE is an emerging disease. The understanding of the etiology, natural history, diagnosis, and management will continue to evolve. More long-term studies are needed to determine the efficacy of treatment.

**IMMUNOLOGY**

- Patients with EoE have marked up-regulation of the gene expression of eotaxin-3, a chemokine important in eosinophil migration.
- Mucosa from patients with EoE have increased Th2 proinflammatory cytokines such as IL-5.
- Mucosa from patients with EoE have increased mast cell infiltration.
- Mast cell associated genes were up-regulated in esophageal tissue and responded to both corticosteroids and diet.

**CLINICAL PEARLS**

- In adults, EoE often presents as dysphagia or food impaction.
- In children, EoE often presents with failure to thrive, reflux, vomiting, or abdominal pain.
- EoE has an association with a personal or family history of atopy.
- The majority of patients have evidence of either aeroallergen and/or food sensitization. Isolated esophageal eosinophilia is inadequate for the diagnosis of EoE. Other causes, such as GERD, must be
excluded and EoE should be associated with clinical symptoms.

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Chapter 27

Approach to primary immunodeficiency

Ashraf Uzzaman, M.D., and Ramsay L. Fuleihan, M.D.

ABSTRACT

Primary immunodeficiency diseases (PID) are inherited defects of the innate or adaptive arms of the immune system that lead to an increase in the incidence, frequency, or severity of infections. There may be defects in the adaptive arm of the immune system that include combined immunodeficiency and antibody deficiency syndromes or by abnormalities in innate immunity such as disorders of phagocytes, the complement pathway, or Toll-Like receptor (TLR) mediated signaling. Recurrent sinopulmonary infections with encapsulated bacteria such as Haemophilus influenza type B or Streptococcus pneumoniae may be characteristic of an IgG antibody deficiency or dysfunction. Frequent viral, fungal, or protozoal infections may suggest T lymphocyte dysfunction. Multiple staphylococcal skin infections and fungal infections may imply neutrophil dysfunction or the hyper-IgE syndrome, and recurrent neisserial infection is a characteristic manifestation of late complement component (C5–9, or the membrane attack complex) defects. Recurrent viral or pyogenic bacterial infections often without the presence of a significant inflammatory response suggest a defect in TLR signaling. Mycobacterial infections are characteristic of defects in interleukin (IL)-12, interferon (IFN) gamma, or their receptors. Screening of newborns for T-cell lymphopenia using a polymerase chain reaction to amplify T-cell receptor excision circles (TRECs), which are formed when a T cell rearranges the variable region of its receptor, serves as a surrogate for newly synthesized naïve T cells. Because of very low numbers of TRECs, severe combined immunodeficiency, DiGeorge syndrome, and other causes of T-cell lymphopenia have been identified in newborns.

Primary immuno-deficiency diseases (PID) are inherited defects of the innate or adaptive arms of the immune system that lead to an increase in the incidence, frequency, or severity of infections.1–3 In general, PIDs are uncommon, but the associated morbidity and mortality may be high. The overall prevalence of PID is not known but is estimated to be 1:10,000 live births. However, IgA deficiency occurs more frequently; as many as 1:333 individuals may be affected. An early diagnosis of PID is essential because prompt treatment may help prevent associated morbidity and mortality.

PRIMARY IMMUNE DEFICIENCY DISEASES

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B-cell activation and immunoglobulin isotype switching and affinity maturation requires interaction of CD40 ligand (CD40L), which is expressed on activated CD4 T cells and CD40, which is present on B cells, monocytes, and other antigen-presenting cells. A mutation in CD40L causes X-linked hyper-IgM syndrome with normal or increased IgM but decreased or absent levels of other immunoglobulin isotypes. Patients are at risk for opportunistic infection such as *P. jiroveci* pneumonia and cryptosporidium, may have neutropenia, and have a higher incidence of liver disease, sclerosing cholangitis, and tumors of the liver and biliary tree. A rapidly progressive incidence of liver disease, sclerosing cholangitis, and *toxoplasmosis* may have neutropenia, and have a higher susceptibility to opportunistic infections but develop lymphoid hyperplasia and may be more susceptible to autoimmune disease.

Antibody deficiency syndromes may result from defects in B-cell development, maturation, or function. An arrest in the development of pro- to pre-B cells in the bone marrow may be caused by a defect in the pre-B-cell receptor or by defects in the pre-B-cell receptor-associated intracytoplasmic proteins such as B-cell linker protein (BLNK) or Bruton tyrosine kinase (BTK). Defects in BTK lead to X-linked agammaglobulinemia (XLA), the most commonly observed early onset agammaglobulinemia. These defects manifest a characteristic absence (<1%) of B cells in the peripheral blood. XLA patients may have a small number of mature B cells. Individuals with antibody deficiency syndromes are susceptible to infection by encapsulated bacteria and suffer recurrent otitis media, sinusitis, and pneumonia. They are also at risk for enteroviral infections, which may lead to meningoccephalitis, vaccine-associated poliomyelitis, and infection by mycoplasma, which may cause arthritis.

Common variable immune deficiency (CVID) is characterized by impaired antibody production in response to vaccinations and infections and low concentrations of IgG and one or more other immunoglobulin isotypes. The diagnosis is usually not entertained in children <2–4 years of age. Most individuals suffer recurrent episodes of otitis media, sinusitis, and pneumonia by encapsulated bacterial organisms, and some may have an increased incidence of lymphoid hyperplasia, granulomatous lesions, lymphoma, and autoimmune manifestations such as cytopenias and inflammatory bowel disease. CVID may be several clinically distinct subtypes, and the genetic cause in most patients remains unknown. Selective IgA deficiency is the most common asymptomatic PID; however, a small number may manifest recurrent sinopulmonary infections, autoimmunity, and allergy. A number of individuals may have associated IgG subclass deficiency, most commonly of IgG2. IgG subclass deficiency also is known to occur independent of IgA deficiency and may be associated with recurrent infections, especially if associated with a specific antibody deficiency usually to polysaccharide antigens such as *Streptococcus pneumoniae*. Specific antibody deficiency is characterized by normal level of B cells and immunoglobulins associated with impaired antibody production to polysaccharide antigens.

Transient hypogammaglobulinemia of infancy is characterized by low-serum IgG concentration with good antibody responses to protein antigens such as tetanus and spontaneous resolution of the hypogammaglobulinemia, sometime after 2 years of age. Although, most children remain asymptomatic, some may have recurrent upper respiratory tract viral infections.

A defect in phagocyte numbers or function may cause recurrent bacterial and fungal infections. Recurrent oral stomatitis and infections of the respiratory tract and skin and deep-seated abscesses commonly are observed. Chronic granulomatous disease (CGD) results from a defect of phagocyte function. Reduced levels of nicotinamide adenine dinucleotide phosphate oxidase complex in phagocytes leads to defective killing of catalase-positive bacteria and fungi. The chronic inflammatory response to the presence of these organisms leads to granuloma formation especially in hollow organs, which may cause outlet obstruction in the gastrointestinal and urinary tracts.

Impaired trafficking of phagocytes from the circulation into the tissues results in leukocyte adhesion defect (LAD). Clinical and laboratory manifestations of an LAD include delayed umbilical cord separation >4–6 weeks and a very elevated white blood cell count of neutrophils (up to 100,000/µL during an infection). Defects in proteins that comprise the complement system also lead to disease. Lack of early complement components C2 and C4 predispose to autoimmune diseases such as systemic lupus erythematosus. A deficiency in C2 and C3 may lead to an increased risk of infection by encapsulated bacteria. Recurrent and invasive neisserial infections occur in individuals with defects in the terminal components of the complement pathway, C5-C9. Absence of alternate complement pathway factors such as factor D and properdin may result in a similar increase in risk of neisserial infections. Recurrent bacterial infections in early life may result from a defect in the mannose binding lectin, a
component of the mannose binding lectin complement pathway.

TLRs, which are present on cell surface and intracellularly on endosomal membranes, recognize pathogen-associated molecular patterns, which are present on bacteria and viruses such as lipopolysaccharide on Gram-negative bacteria and single- or double-stranded RNA on viruses. A defect in TLR-mediated signaling leads to reduced production of proinflammatory cytokines such as interleukin (IL)-1, IL-6, TNF-α, and IL-12 and results in an increased risk of severe and recurrent viral or pyogenic bacterial infections often without the presence of a significant inflammatory response.

**APPROACH TO DIAGNOSIS**

The diagnosis of a PID must be entertained when an individual has a family history of PID or a history of severe, unusual, frequent, or difficult-to-treat infections. A detailed history of infections should be explored including the sites and frequency of infections as well as the organisms involved. Recurrent sinopulmonary infections with encapsulated bacteria such as *Haemophilus influenza* type B or *S. pneumoniae* may be characteristic of an antibody deficiency.5 Frequent viral, fungal, or protozoal infections may suggest T-lymphocyte dysfunction. Multiple staphylococcal skin infections and fungal infections may imply neutrophil dysfunction or the hyper-IgE syndrome, and recurrent neisserial infection is a characteristic manifestation of late complement component (C5–9, or the membrane attack complex) defects. Recurrent viral or pyogenic bacterial infections often without the presence of a significant inflammatory response suggest a defect in TLR signaling. Mycobacterial infections are characteristic of defects in IL-12, interferon γ, or their receptors.

The age of onset of infections is also important. CID diseases commonly cause symptoms before 6 months of age, whereas B-cell dysfunction often becomes symptomatic between 6 and 12 months of age when maternal antibody has waned. Delayed umbilical cord separation, >4–6 weeks and a very elevated white blood cell count may indicate a LAD. X-linked recessive diseases should be considered in male patients, whereas autosomal recessive conditions affect male and female patients equally and should be entertained when consanguinity is present.

The physical exam should begin with assessment of growth parameters. Some infants with SCID may present with failure to thrive. The exam might be significant for sequelae of recurrent infections such as digital clubbing, wheezing, or rhonchi as signs of pulmonary injury. Certain immunodeficiencies are associated with specific findings on physical exam. Patients with Di-George syndrome may have facial dysmorphisms and may present with congenital heart disease. Patients with Chédiak-Higashi may have partial albinism. The skin exam may reveal multiple telangiectasias on the skin and bulbar conjunctiva in ataxia-telangiectasia. A severe eczematous rash may occur as part of hyper-IgE syndrome or Wiskott-Aldrich syndrome (WAS). Attention to the presence or absence of lymphoid tissue may help to narrow the diagnosis. Patients with XLA may lack lymph nodes revealed by absent tonsils on physical exam, whereas autosomal recessive hyper-IgM is associated with lymphoid hyperplasia.

Laboratory testing should be ordered and interpreted within the context of the individual patient’s history and physical exam. Normal ranges are usually age specific, and age-adjusted norms must be used; results may be affected by current infections, medications, and flares of autoimmune diseases. A complete blood count with differential can show lymphopenia in SCID, elevated white cell counts in LAD even in the absence of infection, or thrombocytopenia in WAS or as a complication of autoimmune in CVID or IgA deficiency. Neutropenia is found in primary neutropenia as a manifestation of autoimmune disease or in association with the X-linked hyper-IgM syndrome. Morphological exam of neutrophils can be helpful because it may reveal giant granules in Chédiak-Higashi syndrome.

Antibody deficiency is assessed with quantitative serum immunoglobulin concentrations and the functional adequacy of humoral immunity is determined by serum antibody concentrations to common vaccines such as tetanus, *H. influenza* type B, and pneumococcal vaccination, which evaluate antibody responses to protein, conjugate, and polysaccharide antigens, respectively. Flow cytometry is used to enumerate B-cell numbers, which are absent or severely reduced in agammaglobulinemia and some forms of SCID, and memory B cells, which are reduced in CVID and hyper-IgM syndrome.

T-cell numbers and subsets are enumerated by flow cytometry. T cells are absent in SCID and the presence or absence of B cells and NK cells helps differentiate different causes of SCID. In addition, flow cytometry can identify naive and memory T cells and activation markers on the T-cell surface as well as intracellular proteins such as WASP in WAS, FoxP3 in regulatory T cells, and cytokines in different effector T-cell populations. The ability of T cells to proliferate in response to mitogens helps rule out SCID and shows normal signaling pathways including the production of IL-2 and the expression of the IL-2 receptor on T cells. *In vitro* functional competence of T cells is assessed by their proliferative response to commonly encountered antigens such as *Candida* or tetanus antigens, indicating the presence of antigen-specific memory T cells. A normal antibody response to protein antigens such as tetanus
Phagocyte function may be assessed with flow cytometry. The diagnosis of LAD-1 may be confirmed by the absence of CD11b/C18 marker on leukocytes. CGD is best diagnosed by fluorescent detection of the oxidative burst using flow cytometry. This assay uses a small dye called dihydrorhodamine that fluoresces when exposed to reactive oxygen species.

An initial evaluation of complement components is performed with a CH50 level for the classic complement pathway and an AP50 level for the alternate pathway. If low, individual complement levels must then be evaluated. The TLR signaling pathways can be assessed by responses to engagement by a variety of TLR ligands.

A further review of laboratory testing to assess the immune system is discussed in another article in this journal.6

**TREATMENT**

Treatment of immunodeficiency should begin quickly and aggressively after the diagnosis is made to prevent complications from infections. Humoral immunity disorders require treatment with immunoglobulin replacement i.v. at doses of 400–600 mg/kg per month or subcutaneously at 100–200 mg/kg per week,7 avoidance of live polio vaccine, and may require antibiotic prophylaxis. Milder cases of humoral immunodeficiency such as specific antibody deficiency syndrome may be managed with antibiotic prophylaxis. Cellular disorders such as SCID require prompt evaluation for a stem cell transplant,8 avoidance of live viral vaccines including rotavirus, and any blood product transfusion needs to be irradiated, leukoreduced, and CMV-. X-linked hyper-IgM, WAS, and other severe immunodeficiency diseases also can be treated with stem cell transplantation. X-linked SCID, adenosine deaminase (ADA)–deficient SCID, and WAS can also be treated by gene therapy, especially if the patient does not have a matched donor for stem cell transplantation.9 ADA-deficient SCID may be treated with enzyme replacement with PEG-ADA. Patients with complete DiGeorge syndrome may benefit from thymic transplant. Prophylaxis against infections with antibiotics (trimethoprim/sulfamethoxazole and itraconazole) and interferon γ may be used in patients with CGD. It is important to keep in mind that patients with an underlying immunodeficiency may require prolonged and aggressive therapy for infections.

**NEWBORN SCREENING**

Newborn screening for T-cell lymphopenia has been initiated in Wisconsin and in other states using a polymerase chain reaction to amplify T-cell receptor excision circles, which are formed when a T cell rearranges the variable region of its receptor and serves as a surrogate for newly synthesized naïve T cells. SCID, DiGeorge syndrome, and other causes of T-cell lymphopenia have been identified in the newborn period allowing curative treatment by stem cell transplantation before the development of serious and life-threatening infections and complications.

**SUMMARY**

In summary, although immunodeficiency disorders are uncommon, physicians must remain suspicious in the setting of frequent severe infections or infections by unusual organisms. Prevention of associated morbidity and mortality is dependent on early diagnosis and treatment.

**IMMUNOLOGY**

- B-cell disorders are characterized by decreased numbers of B cells and low-serum quantitative immunoglobulins and poor response to polysaccharide antigens.
- Bruton’s agammaglobulinemia, an example of a B-cell disorder, is caused by a defect in B-cell tyrosine kinase, which results in decreased serum immunoglobulins.
- T-cell disorders are characterized by decreased numbers of T cells and/or decreased T-cell function. An example is SCID, which may be caused by number of genetic defects.
- Defects of innate immunity also cause severe, recurrent, and life-threatening infections and can be caused by defects in complement proteins, phagocytic cells, or signaling defects in TLRs.

**CLINICAL PEARLS**

- Immunodeficiency should be suspected in patients with recurrent, unusual, or difficult-to-treat infections or with a family history of immunodeficiency.
- Consider humoral immunity defect in patients with recurrent encapsulated bacterial infections.
- Consider T-cell defects in patients with frequent viral, fungal, or protozoal infections or recurrent infections and failure to thrive.
- In patients with recurrent neisserial infections, a late complement defect should be considered.
- Newborn screening can identify patients with T-cell lymphopenia before recurrent infections develop.
- Early and aggressive therapy can reduce morbidity and mortality and result in an improved outcome.
REFERENCES
Classification of hypersensitivity reactions

Ashraf Uzzaman, M.D., and Seong H. Cho, M.D.

ABSTRACT

The original Gell and Coomb’s classification categorizes hypersensitivity reactions into four subtypes according to the type of immune response and the effector mechanism responsible for cell and tissue injury: type I, immediate or IgE mediated; type II, cytotoxic or IgG/IgM mediated; type III, IgG/IgM immune complex mediated; and type IV, delayed-type hypersensitivity or T-cell mediated. The classification has been improved so that type IIa is the former type II and type IIb is antibody-mediated cell stimulating (Graves Disease and the “autoimmune” type of chronic idiopathic urticaria). Type IV has four major categories: type IVa is CD4+Th1 lymphocyte mediated with activation of macrophages (granuloma formation and type I diabetes mellitus); type IVb is CD4+Th2 lymphocyte mediated with eosinophilic involvement (persistent asthma and allergic rhinitis); type IVc is cytotoxic CD8+ T lymphocyte with involvement of perforin-granzyme B in apoptosis (Stevens-Johnson syndrome and toxic epidermal necrolysis); type IVd is T-lymphocyte–driven neutrophilic inflammation (pustular psoriasis and acute generalized exanthematous pustulosis). Some diseases have multiple types of immunologic hypersensitivity.

Although, the immune system is primarily used to protect against microbes such as bacteria, viruses, and fungi, unexpected excesses of the immune response may lead to disease states. The excessive immune responses are usually referred to as hypersensitivity reactions. The original Gell and Coomb’s classification categorizes hypersensitivity reactions into four subtypes according to the type of immune response and the effector mechanism responsible for cell and tissue injury: type I, immediate or IgE mediated; type II, cytotoxic or IgG/IgM mediated; type III, IgG/IgM immune complex mediated; and type IV, delayed-type hypersensitivity or T-cell mediated. In clinical practice, however, patients often display a constellation of symptoms that usually overlap several of these mechanisms. For example, individuals who are allergic to penicillin may exhibit symptoms that suggest a type I or IgE-mediated reaction such as anaphylaxis; they may also exhibit a serum sickness such as a disease that suggests a type III or an IgG/IgM immune complex–mediated reaction (Table 1).
caused by repeated immediate hypersensitivity and late-phase reactions in the lung tissue; and skin manifestations such as urticaria, which is a wheal and flare (erythema) reaction.

**TYPE II—CYTOTOXIC OR IgG/IgM-MEDIATED REACTIONS**

Immune responses that usually afford protection against infections and eradication of malignant cells may sometimes cause damage to tissues. The immune responses commonly involve IgG and IgM and, to a lesser extent, IgA antibodies. The antibodies usually are directed against cell surface antigens such as those present on red blood cells, neutrophils, and platelets; those present on epithelial cells of glandular and mucosal surfaces; or against those present on tissues such as basement membranes. Three underlying mechanisms commonly account for the tissue damage. First, antibodies may directly coat or opsonize cells or they may activate the complement system, which leads to the production of activated complement components that may then coat or opsonize the cells. These opsonized cells are phagocytosed and are destroyed by phagocytes that express receptors for antibodies and complement proteins. The underlying mechanism in autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura is an example. Second, antibodies deposited in tissues subsequently recruit neutrophils and macrophages, which leads to tissue injury and inflammation. This is the mechanism of injury in antibody-mediated glomerulonephritis. The third mechanism of immune response is antibody-dependent cell-mediated cytotoxicity, which occurs when eosinophils bind to IgE-bound helminths and release their granule components. Type II reactions can also be divided into two different subtypes. Type IIa reactions are characterized by cytolytic reactions produced by antibodies causing autoimmune hemolytic anemia, whereas type IIb reactions are characterized by cell-stimulating antibodies in patients with Graves disease (a long-acting thyroid stimulator, thyroid-stimulating hormone receptor antibodies) or antibodies to the high-affinity mast cell receptor (FcεRIa) or IgE in chronic idiopathic urticaria.

**TYPE III—IgG/IgM IMMUNE COMPLEX MEDIATED**

In type II immune response, the mechanism of tissue injury involves the formation of IgG or IgM antibodies to self or foreign antigens and then the formation of complexes. The complexes deposit and activate the complement pathway, with concomitant fall in serum complement levels. The activated complement components recruit and activate neutrophils, which results in inflammation and tissue injury. The constellation of symptoms is determined by the site of immune complex deposition and not by the source of the antigen. The antigen–antibody complexes are usually deposited in small arteries, renal glomeruli, and synovial joints and the symptoms usually are vasculitis, nephritis, and arthritis, respectively. One example is serum sickness-like disease, which may be acute or may have a prolonged or chronic course. This prototypical immune

**Table 1  Classification of hypersensitivity reactions**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Immunoreactants</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Mast cell mediated, IgE dependent (anaphylactic, and IgE independent)</td>
<td>Anaphylaxis, urticaria, angioedema, asthma, and allergic rhinitis</td>
</tr>
<tr>
<td>Type IIa</td>
<td>Antibody-mediated cytotoxic reactions (IgG and IgM antibodies complement often involved)</td>
<td>Immune cytopenias</td>
</tr>
<tr>
<td>Type IIb</td>
<td>Antibody-mediated cell-stimulating reactions</td>
<td>Graves disease and chronic idiopathic urticaria</td>
</tr>
<tr>
<td>Type III</td>
<td>Immune complex–mediated reactions complement involved</td>
<td>Serum sickness and vasculitis</td>
</tr>
<tr>
<td>Type IVa</td>
<td>Th1 cell-mediated reactions macrophage activation</td>
<td>Type 1 diabetes and contact dermatitis (with IVc)</td>
</tr>
<tr>
<td>Type IVb</td>
<td>Th2 cell–mediated reactions eosinophilic inflammation</td>
<td>Persistent asthma and allergic rhinitis</td>
</tr>
<tr>
<td>Type IVc</td>
<td>Cytotoxic T cell-mediated (perforin/granzyme B involved)</td>
<td>Stevens-Johnson syndrome and TEN</td>
</tr>
<tr>
<td>Type IVd</td>
<td>T-cell-mediated neutrophilic inflammation</td>
<td>AGEP and Behcet disease</td>
</tr>
</tbody>
</table>

*Source: Adapted from Ref. 2.*

AGEP = acute generalized exanthematous pustulosis; TEN = toxic epidermal keratinocytes.
complex–mediated disease, however, was first observed in individuals with diphtheria infections. These individuals were being treated with sera containing antibodies to diphtheria antitoxin (passive immunization) from horses that had been immunized with the diphtheria toxin. A number of autoimmune diseases may also be caused by tissue deposition of antigen–antibody complexes. Systemic lupus erythematosus is an autoimmune disease in which a large number of antibodies to DNA and nucleoproteins are produced, which complex with antigens and then deposit in the tissues and lead to an inflammatory response.

**TYPE IV—DELAYED-TYPE HYPERSENSITIVITY OR T-CELL MEDIATED**

Type IV reactions involve sensitized T cells. The type IV reaction that Gell and Coombs described, also called delayed-type hypersensitivity, is mediated by CD4+ T helper cells and is a Th1 type of response.2 This response is currently called type IVa. The tissue injury is primarily caused by lysosomal enzymes, reactive oxygen intermediates, nitric oxide, and proinflammatory cytokines that are secreted by activated macrophages. The secretion of cytokines and growth factors often lead to tissue fibrosis. A delayed hypersensitivity response may be involved in the pathogenesis of a number of diseases. Examples include, type I diabetes, in which destruction of insulin-producing islet cells may be affected by lymphocytes and macrophages; multiple sclerosis, an autoimmune disorder affecting the central nervous system, in which T cells react against myelin antigens; and rheumatoid arthritis, in which a T-cell–mediated inflammation is suspected.

Enumeration of the T-cell subsets has allowed further categorization of the type IV immune responses. This categorization into four subtypes—type IVa, IVb, IVc, and IVd—is based on the distinct cytokine profile, types of cells involved, and pathogenesis.11 An example of type IVa response is contact dermatitis due to poison ivy Rhus antigen. This reaction involves Th1 type T cells that activate macrophages by secreting large amounts of cytokines such as interferon-γ and tumor necrosis factor-α. Type IVb reactions follow a Th2 type immune response. CD4+ Th2 cells produce IL-4, IL-5, and IL-13, which promote IgE production from B cells, deactivation of macrophage, and mast cell and eosinophil responses. Type IVb reactions may be involved in the late-phase allergic inflammations of the bronchi or nasal mucosa (i.e., asthma and allergic rhinitis). Type IVc reactions are mainly mediated by cytotoxic CD8+ T cells. Type IVc reactions seem to be the major mechanism of bullous skin reactions such as Stevens-Johnson’s syndrome and toxic epidermal necrolysis, where activated CD8+ T cells induce apoptosis or necrosis of keratinocytes. Type IVd reactions are neutrophilic inflammation via T lymphocytes. Sterile neutrophilic inflammation of the skin in acute generalized exanthematous pustulosis is a typical example. Acute generalized exanthematous pustulosis is characterized by appearance of superficial pustules after drug ingestion or infection. In this disease, T-cell–derived CXCL-8 recruits neutrophils to the lesion and granulocyte monocyte colony-stimulating factor from T cells prevents apoptosis of the recruited neutrophils. In addition, IL-17 and IL-22 stimulate production of IL-8, which supports the accumulation of neutrophils in lesions. Behcet disease and pustular psoriasis are other examples of type IVd reactions.

**IMMUNOLOGY**

- Type I reactions are effected by mediators released from mast cells and basophils.
- Type II reactions result from formation of antibodies that are usually directed against cellular or matrix antigens and lead to localized disease.
- Type III reactions result from the deposition of antigen-antibody complexes that activate the complement pathway and then recruit and activate neutrophils and result in tissue injury.
- Type IV reactions are mediated by T lymphocytes; there are four subtypes. Some conditions involve more than one subtype.

**CLINICAL PEARLS**

- Penicillin can cause all types of reactions; type I, anaphylaxis and urticaria; type II, hemolytic anemia; type III, serum sickness-like reaction; and type IV, delayed type drug rash or contact dermatitis.
- An anaphylactic reaction to radiocontrast media is non-IgE–mediated hypersensitivity reaction and can be prevented by pretreatment with corticosteroid and antihistamine, whereas IgE-mediated anaphylaxis is not blocked by corticosteroid pre-treatment.

**REFERENCES**

Unproved and controversial methods and theories in allergy–immunology

Rachna Shah, M.D., and Paul A. Greenberger, M.D.

ABSTRACT

Unproved methods and controversial theories in the diagnosis and management of allergy–immunology are those that lack scientific credibility. Some definitions are provided for perspective because in chronic medical conditions, frequently, nonscientifically based treatments are developed that can have a very positive psychological effect on the patients in the absence of objective physical benefit. Standard practice can be described as “the methods of diagnosis and treatment used by reputable physicians in a particular subspecialty or primary care practice” with the understanding that diagnosis and treatment options are consistent with established mechanisms of conditions or diseases. Conventional medicine (Western or allopathic medicine) is that which is practiced by the majority of MDs, DOs, psychologists, RNs, and physical therapists. Complementary medicine uses the practice of conventional medicine with complementary and alternative medicine such as using acupuncture for pain relief in addition to opioids. Alternative medicine implies use of complementary and alternative practices in place of conventional medicine. Unproved and controversial methods and theories do not have supporting data, validation, and sufficient scientific scrutiny, and they should not be used in the practice of allergy–immunology. Some examples of unproven theories about allergic immunologic conditions include allergic toxemia, idiopathic environmental intolerance, association with childhood vaccinations, and adrenal fatigue. Unconventional (unproved) diagnostic methods for allergic–immunologic conditions include cytotoxic tests, provocation–neutralization, electrodermal diagnosis, applied kinesiology assessments, and serum IgG or IgG4 testing. Unproven treatments and intervention methods for allergic–immunologic conditions include acupuncture, homeopathy (“likes cure likes”), halotherapy, and autologous urine injections.

Unproved methods and controversial theories in the diagnosis and management of allergy–immunology are those that lack scientific credibility. There continues to be widespread interest in “alternative or complementary medicine” with estimates of 34–40% consumption of alternative medicine/products in the United States. These methods and treatments may not be based on scientific evidence or controlled trials; in fact, when trials are performed, the results are not supportive for efficacy or diagnostic usefulness. To put unproved and controversial methods and theories in context, some definitions are provided. Standard practice can be described as “the methods of diagnosis and treatment used by reputable physicians in a particular subspecialty or primary care practice” with the understanding that diagnosis and treatment options are consistent with established mechanisms of conditions or diseases. These methods and treatments have “stood the test of time” through studies of efficacy and safety. It should be mentioned that standard practice may change from information learned from scientific studies or expert opinion. Conventional medicine (Western or allopathic medicine) is that which is practiced by the majority of MDs, DOs, psychologists, RNs, and physical therapists. Complementary medicine uses the practice of conventional medicine with complementary and alternative medicine such as using acupuncture for pain relief in addition to opioids. Alternative medicine implies use of complementary and alternative practices in place of conventional medicine. The following unproved and controversial (“alternative and complementary”) methods and theories do not have supporting data, validation, and sufficient scientific scrutiny. Thus, they should not be used in the practice of allergy–immunology.

UNPROVEN THEORIES ABOUT ALLERGY-IMMUNOLOGY

Allergic Toxemia

Allergic toxemia has also been referred to as “cerebral allergy” or allergic tension fatigue syndrome. It is
based on a theory that allergies to environmental or food allergens can cause weakness, fatigue, lethargy, irritability, myalgias, arthralgias, and confusion in patients without any evidence of allergic disease on physical exam. Patients are instructed to avoid the food or chemical that they are "allergic" to with the goal of improving symptoms. Allergic toxemia has also been promoted to explain psychiatric illness such as attention deficit hyperactivity disorder and adult schizophrenia. Literature on this subject is anecdotal.

Idiopathic Environmental Intolerance

Idiopathic environmental intolerance, once known as clinical ecology or multiple chemical sensitivities, is based on the theory that disease results from the failure of human adaptation to synthetic chemicals. Patients are described as having symptoms consistent with conversion reactions, anxiety, depression, and psychosomatic illness. Patients do not have abnormal physical findings on exam. Neutralization (described later) and avoidance of foods and chemicals are the common modes of treatment. There is no basis for this theory. In a retrospective study analyzing the claims of “environmental illness” of 90 workers, when records were examined by physicians who were not clinical ecologists, there was presence of psychological illnesses without objective evidence of disease.

Childhood Vaccination

A theory regarding the role of childhood vaccinations increasing prevalence of allergic disease and autoimmunity remains popular in the public and is promoted by anti-vaccination advocates. A meta-analysis exploring the role of vaccination practices and development of atopy has shown no conclusive evidence of vaccinations resulting in increased development of atopy.

Adrenal Fatigue

Underproduction of hormones produced by the adrenal gland, known as “adrenal fatigue,” has been reported as a possible cause of food allergies, rashes, chronic low blood pressure, and mild depression. This theory is based on the concept that the stresses of modern life can “wear down” the adrenal gland resulting in illness. Stresses include serious illnesses, allergies, and experiencing prolonged physical and/or emotional stress. Baseline serum cortisol concentrations are normal in these patients. Treatment is based on lifestyle changes and homeopathic medications. There is no scientific basis for the existence of this disorder and no conclusive method for diagnosis.

UNCONVENTIONAL DIAGNOSTIC METHODS

Cytotoxic Test

The cytotoxic test is also known as the leukocytotoxic test or Bryan’s test. In this test, the buffy coat from whole blood is placed on a slide coated with dried extract of food or aeroallergen. The slide next is examined under the microscope for vacuolation, crenation, lack of movement, and fragmentation. If these changes are present, the test is considered positive for the patient having an allergy to the tested allergen. This test has not been standardized and is not reproducible based on clinical trials.

Antigen Leukocyte Cellular Antibody Test

Antigen leukocyte cellular antibody test is a test that claims to diagnose allergy based on measuring the size of white blood cells before and after incubation with a gel containing the allergen. If the change is large, then an allergy to the tested allergen can be diagnosed. There have been no controlled trials establishing that the antigen leukocyte cellular antibody test is a diagnostic test.

Provocation–Neutralization

The provocation–neutralization test has been advocated for the diagnosis and management of allergies to foods, inhalants, hormones, and environmental chemicals. In this test, the patient is exposed to a test dose of the extract by subcutaneous injection, intradermal injection, or sublingual drops. Concentration of the extract is increased until any subjective symptom occurs. When a subjective symptom occurs, the test is considered positive and the patient is deemed allergic to the tested substance. After symptoms arise, the patient is advised to use progressively lower doses until the symptoms have resolved or decreased. This is considered the “neutralization” dose. This dose is prescribed to the patient to take prophylactically to the offending food or inhalant to eliminate symptoms. This test has been reported with various methodologies, symptom reports, and variable criteria for a positive result. Based on current knowledge of immunology, there remains no basis for this mode of diagnosis.

Electrodermal Diagnosis

Changes in skin resistance after exposure to an allergen are the basis of electrodermal diagnosis of allergies. A glass vial containing the allergen extract is placed in an electrical circuit between the patient’s skin and a galvanometer. If there is a decrease in electrical resistance, the patient is reported as being allergic to the allergen. This method has no scientific basis and has not been established to be an effective diagnostic tool.
Applied Kinesiology
This approach involves evaluating subjective changes in muscle strength before and after exposure to an allergen. Exposure to the allergen is performed by sublingual administration or holding a glass vial containing the allergen. If the patient feels that muscle strength has decreased after exposure, the patient is reported as being allergic to the allergen. No scientific data support the use of this test.

Serum IgG or IgG₄ Testing
Serum IgG₄ testing is the most common unconventional diagnostic test performed in the United States to diagnose allergies. IgG₄ to a variety of foods and allergens can be measured, but the presence or absence is not involved with the known immunologic mechanism of atopic disease. IgG to certain foods is a common postprandial finding and can not be used to diagnose allergy. (In making the diagnosis of food allergy, one uses the history and demonstration of anti-food IgE antibodies.) In contrast, detecting serum IgG antibody to the relevant antigen may be supportive for those immune complex diseases where the immunogenic antigen is known or suspected, i.e., serum sickness or allergic bronchopulmonary aspergillosis.

UNPROVEN TREATMENTS

Acupuncture
Acupuncture has been used for the relief of allergic rhinitis, asthma, and allergic skin conditions. Patients may perceive temporary relief of symptoms. Some acupuncture treatments rely on the concept of energy fields and place the physical allergen or a digital picture of the allergen within the energy field while acupuncture is being performed. Because of the diversity of acupuncture points, different periods of stimulation, and different methods of needle insertion, studies have been difficult to interpret.

Homeopathy
Homeopathic medication is based on the theory of treating a disease by giving small amounts of the causative agent such that “likes cure likes.” These medications are made by using extracts from flower, plants, insects, and animals. Homeopathic medications are used on a daily basis by placing the tablets under the tongue. The effectiveness of these medications has not shown substantial benefit in the treatment of allergies.

Halotherapy
Halotherapy, or salt cave based on speleotherapy, is an approach that claims to improve symptoms and reduce airway obstruction of asthma. Rooms are coated with a thick layer of salt, and dry sodium chloride is aerosolized in the room. Patients undergo treatment in these rooms for 1–2 hours/day. Although already popular in eastern Europe, salt caves are increasing in popularity in the United States. At this time, no randomized control trial has been reported (in English) establishing the effectiveness of this treatment for asthma although an observational report describes some benefits.

Urine Injections
Intramuscular injections of human (autologous) urine have been advocated as a therapy for allergic diseases. Injections of autologous urine containing “chemicals” have been claimed to neutralize or prevent future allergic reactions. Urine immunization is not supported by scientific evidence or case reports. Urine injections also are associated with side effects, including nephritis. Heterologous (from pregnant women) urine injections have been promoted for weight loss.

CLINICAL PEARLS
• The physician and health care professionals must be educated and critical of methods and concepts that are trusted in the practice of medicine without having shown clinical efficacy and safety. Some unproven and controversial methods can cause harm to the patient.
• In chronic medical conditions requiring long-term management, frequently, nonscientifically based treatments are developed that can have a very positive psychological effect on the patients in the absence of objective physical benefit.
• If a patient is not improving, reconsider all therapies that are being used. Be cognizant that many patients will not report unproved and controversial treatments to physicians and health care professionals who practice conventional medicine.

REFERENCES
Drug allergy
describes clinical adverse reactions that are proved or presumed to be immunologically based. Some examples include anaphylaxis, urticaria, angioedema, pruritic rashes, blistering rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, wheezing and/or dyspnea, shock (drop of systolic blood pressure of 30 mmHg in adults), hepatitis, nephritis, arthralgias or arthritis, and hematologic conditions such as leukopenia and thrombocytopenia. Allergic drug reactions do not resemble pharmacologic actions of the incriminated drug and may occur at fractions of what would be the therapeutic dosage. Allergic drug reactions are unpredictable; nevertheless, there is increased risk of drug hypersensitivity in (1) patients with cystic fibrosis who receive antibiotics; (2) patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) who receive trimethoprim/sulfamethoxazole or if HLA-B*5701 and receive the antiretroviral agent, abacavir; (3) other genetically susceptible populations such as Han-Chinese who are HLA-B*1502 who develop Stevens-Johnson syndrome and toxic epidermal necrolysis from carbamazepine or if HLA-B*5801 are at increased risk for such reactions from allopurinol; and (4) patients with a history of previous compatible allergic reaction to the same medication, similar class, or potentially unrelated medication. Specific patient groups at higher risk for drug allergy include those with Epstein-Barr virus infection, chronic lymphatic leukemia, HIV/AIDS, cystic fibrosis, patients with seizures being treated with antiepileptic medications, and patients with asthma (especially severe asthma) who are at increased risk of anaphylaxis from any cause including drugs compared with patients without asthma. In patients with a history of penicillin allergy, skin testing helps clarify the current level of risk for anaphylaxis by using the major (penicilloyl-polylysine) and minor penicillin determinants where sensitivity is 99%. If penicilloyl-polylysine and penicillin G are used for skin testing, the sensitivity is ~85%. When skin tests are negative, graded challenges are performed to administer optimal or truly essential antibiotics.

CLASSIFICATION BY IMMUNOLOGIC HYPERSENSITIVITY

It is useful to classify drug allergy based on modifications of the Gell and Coombs classification of hypersensitivity reactions. The classification of hypersensitivity disorders is the focus of another article in this journal. For example, type I hypersensitivity includes anaphylaxis whether IgE mediated or IgE independent resulting in acute urticaria, bronchoconstriction, shock, or angioedema. IgE independent refers to what formerly was designated anaphylactoid or pseudoallergic such as with radiocontrast material–induced acute urticaria and hypotension. Type IIa allergic drug reactions are IgG and/or IgM antibody mediated such as drug-induced thrombocytopenia. Type III reactions are those characterized by immune complex–mediated reactions resulting in serum sickness or vasculitis such as from antithymocyte heterologous sera being injected.
ADVERSE DRUG REACTIONS

In contrast to drug allergy where the clinical reaction is compatible with a proven or presumed immunologic reaction, the differential diagnosis of drug allergy includes the much larger category of adverse drug reactions. If possible, the health record should contain the specifics of the patient’s drug “allergy” so that physicians and other health professionals can determine if there was a true allergic drug reaction or other untoward, noxious effect. Adverse drug reactions may be separated into predictable reactions occurring in normal subjects and unpredictable reactions occurring in susceptible subjects. For example, predictable reactions include (1) toxic or untoward effects from overdosage, (2) side effects, (3) drug-drug or drug-disease interactions, and (4) indirect or secondary effects that may be drug related or disease related. Two examples of disease-related indirect effects are the high incidence of maculopapular skin rashes when ampicillin is administered to patients with underlying Epstein-Barr virus infection and the intensification of skin lesions, fever, myalgia, and, rarely, hypertension followed by hypotension when patients with primary or secondary syphilis are treated with high-dose penicillin (Jarisch-Herxheimer reaction). In the Jarisch-Herxheimer reaction, the death of spirochetes releases microbial antigens and endotoxins that trigger this mimic of an allergic reaction that occurs within 2–3 hours of administration of penicillin. Elevated concentrations of TNF-α, IL-6, and IL-8 have been established. Other examples of the Jarisch-Herxheimer reaction occur after treatment of tickborne disease (borreliosis), leptospirosis, typhoid fever, and brucellosis. Unpredictable adverse reactions that occur in susceptible subjects include allergic drug reactions (comprising terminology of hypersensitivity, pseudoallergic, and anaphylactoid), intolerance, and idiosyncrasy. Intolerance is a characteristic (pharmacologic) effect of a medication that occurs at a small dose of the medication and may be explained genetically or by enzymic differences from the large proportion of patients who do not suffer such an adverse effect. Explained differently, intolerance is a quantitatively increased pharmacologic effect in susceptible individuals such as tinnitus from a low dose of aspirin or an elderly patient developing hypotension and “shock” from 20 mg of furosemide. Idiosyncratic reactions are qualitatively unexpected, abnormal reactions and can resemble hypersensitivity because of the rapidity or severity of the adverse effect. Pharmacogenetic abnormalities causing extremes in enzymic activity may result in harm when a particular medication is administered. One example is glucose-6-phosphate deficiency (G6PD)-associated hemolytic anemia in white Americans (of Mediterranean origin) that can cause hemolytic anemia to as many as 50 different medications. To detect susceptible patients ahead of time, measurement of G6PD activity is an available laboratory test. The differences in therapeutic dosages of warfarin are another example because some patients require not >2 mg daily whereas others require 12 mg daily to achieve an INR of 2–3. For perspective, the representative patient requires 5 mg daily. In measuring activity of the vitamin K epoxide reduc- tase complex subunit 1 (VKORC1) and its polymorphisms, the low-dose haplotype patients (typically Asian Americans) and high-dose haplotypes (typically black Americans) have polymorphisms that make the former patients anticoagulated with low doses of warfarin and the latter patients appear to be resistant to warfarin. With advancement of the field of pharmacogenetics of adverse drug reactions, “pop-up” alerts in electronic order entry, and more widespread testing, it is hoped that there will be fewer patients experiencing idiosyncratic adverse reactions.

COINCIDENTAL AND UNUSUAL REACTIONS

When a known pharmacologic effect of a medication produces a larger than usual response, the patient may be labeled “allergic” when the reaction should be considered “intolerance.” Coincidental reactions are those that appear to be related to the medication, immuniza-
severe asthma) are at increased risk of anaphylaxis and patients with seizures being treated with antiepileptic medications. Patients with asthma (especially those with Ebstein-Barr virus infection, chronic lymphatic leukemia, human immunodeficiency virus/acquired immunodeficiency syndrome, cystic fibrosis, and patients with seizures) are at increased risk of anaphylaxis to eight different classes of medications. Some patients express excessive somatoform symptoms when no objective findings can be identified and thus have a list of drug allergies that are psychological in etiology. Rarely, a patient self-induces a serious allergic reaction as a manifestation of Munchausen syndrome, such as the deliberate ingestion of aspirin or a nonselective anti-inflammatory drug in and by a patient with aspirin-induced anaphylaxis or aspirin-exacerbated respiratory disease. In contrast to a patient with somatoform symptoms of drug allergy, a Munchausen patient produces true anaphylaxis or severe wheezing dyspnea.

TIPS TO HELP SUSPECT AND CONFIRM DRUG ALLERGY

Patient groups at higher risk for drug allergy include those with Ebstein-Barr virus infection, chronic lymphatic leukemia, human immunodeficiency virus/acquired immunodeficiency syndrome, cystic fibrosis, and patients with seizures treated with antiepileptic medications. Patients with asthma (especially severe asthma) are at increased risk of anaphylaxis from any cause including drugs compared with patients without asthma. On an individual level, patients who have experienced a convincing allergic drug reaction are at increased risk of a future reaction to the same medication and to some medications in the same class (amoxicillin or piperacillin in a patient allergic to penicillin) or related class (the first-generation cephalosporin, cephalaxin, in a patient allergic to penicillin). Exceptions apply, but caution is advised in readministration of necessary medications. When anaphylaxis occurs, the culprit medication or diagnostic agent (radiocontrast material) is either being administered when the symptoms begin or within an hour of completion of the i.v. infusion or 2 hours of the oral ingestion. When anaphylaxis is fatal, often the time of onset of symptoms and signs to death is no more than 1 hour. Some patients develop anaphylaxis after tolerating a medication for 3 days and then experience explosive onset of generalized urticaria with severe wheezing and stridor. Anaphylactic shock can result from nonparental routes of drug exposure such as from bacitracin occurring 5–15 minutes after beginning the irrigations. Serum sickness reactions, consisting of generalized urticaria and painful arthralgias occur classically by 7–10 days after administration of a medication such as penicillin, heterologous or humanized antibody. When a maculopapular rash appears and the possibility of drug allergy is considered, consider the “suspects” as those medications currently being ingested or infused and any medication in which the course of treatment has been completed for the previous 7 days. The very serious conditions, Steven-Johnson syndrome and toxic epidermal necrolysis, often have their onset from 7 to 21 days to 2 months after the culprit medication has been initiated. Notably, when a patient with a previous diagnosis of either of those conditions receives the incriminated medication in the future, the reexposure can precipitate Stevens-Johnson syndrome or toxic epidermal necrolysis within 1–2 days. Regrettably, some such reexposures have produced fatalities.

To help confirm a diagnosis of drug allergy, discontinuation of the incriminated medication with resolution of the allergic reaction helps to support the suspect medication as the culprit. Deliberate rechallenge with the suspect medication carries high risk (and should have specialty expertise and a very strong indication) and although theoretically helpful to confirm drug allergy, carries significant risk and should be considered only after other options have proved ineffective and the patient agrees to a challenge. Another helpful aid to confirm a diagnosis of drug allergy includes skin testing, such as with penicillin reagents, which can help establish antipenicillin IgE antibodies that are used as evidence to support the penicillin (or β-lactam antibiotic) as the cause of the drug reaction as opposed to other concurrently administered medications. A graded challenge (test dosing) with the incriminated medication may be necessary in some patients and although it is hoped that the challenge would not result in a serious allergic drug reaction, evidence of a mild allergic reaction such as limited urticaria or a macular rash would confirm the incriminated medication as the culprit. (Such a graded challenge should be differentiated from true desensitization where the stepwise administration of the incriminated medication is better termed, “controlled anaphylaxis” or “induction of tolerance,” depending on the type of allergic drug reaction.) Finally, laboratory tests may provide supportive evidence for drug allergy such as serum tryptase for anaphylaxis, peripheral blood eosinophilia for skin reactions, drug reaction with eosinophilia and systemic symptoms, blistering rashes such as Stevens-Johnson syndrome, drug-induced liver injury with hypersensi-
tivity, and interstitial nephritis, and complement (C3 and C4) in serum sickness, and demonstration of anti–penicilloyl penicillin (major determinant) IgE antibodies for penicillin allergy. The presence of a positive polymerase chain reaction for human herpesvirus 6 can be supportive of drug hypersensitivity. Skin biopsies can help differentiate conditions such as IgA linear dermatosis from vancomycin from a Stevens-Johnson syndrome or toxic epidermal necrolysis.

**SPECIFIC EXAMPLES OF DRUG ALLERGY AND APPROACHES**

**Penicillin and Other β-Lactam Antibiotics**

For detection of risk of anaphylaxis, demonstration of presence or absence of antipenicillin IgE antibodies provides the most optimal assessment of current risk. Penicillin quickly transforms after administration, and IgE antibodies recognize what are designated as transformation products of penicillin. The most helpful testing is skin testing (prick and intradermal) with the major determinant, benzyl penicilloyl-polylysine (Pre-Pen; Aller-Quest, Plainville, CT) and several minor determinants including penicillin G (tested with 6000–10,000 U/mL). When these tests are negative, the negative predictive value approaches 99% on administration of penicillin and other β-lactam antibiotics. If the major determinant and penicillin G are used without the minor determinants, then the negative predictive value for penicillin administration is ~85–88% because most, currently allergic, patients have IgE antibodies that react with the major determinant, penicilloyl-polylysine, or penicillin G.10 These two products are available commercially in the United States. If the skin tests are positive, the risk of anaphylaxis from a deliberate, unmodified infusion of penicillin administered is at least 67%, a very high incidence. Alternatively, if the penicillin is administered in a sequential process called desensitization, (to consume free antipenicillin IgE antibodies), the incidence of anaphylaxis in skin-test-positive patients can be reduced significantly and managed safely.

**Cephalosporins**

Allergic reactions to cephalosporins are more likely to occur in penicillin-allergic patients but the overall risk decreases from first generation (cephalexin, ~5–16.5%), second generation (up to 10%), and third generation (2–3%).10 Alternatively, if a patient is known to be allergic to a cephalosporin, they have an ~50% incidence of experiencing an allergic reaction to a penicillin. Skin testing with penicillin determinants is advised in anticipation of administration of cephalosporins to reduce the risks and uncertainties involved. If skin testing is not available, then cautious (graded) administration is advised, especially if first- or second-generation cephalosporins are required.

**Other Antibiotics with β-Lactam Rings**

The carbapenems (imipenem, meropenem, and ertapenem) possess β-lactamases, which allow them to have broad antimicrobial activity. There is little “cross-reactivity” between penicillin and carbapenems. When indicated, graded challenges can be performed unless penicillin skin tests are available and are proven to be negative. For penicillin-allergic patients who require the monobactam, aztreonam, this antibiotic can be administered without skin testing or test dosing for most patients because the incidence of anaphylaxis is very low in penicillin-allergic patients.

**Sulfonamides or Sulfamethoxazole/Trimethoprim**

Drug allergy can manifest as cutaneous eruptions from urticaria or maculopapular rash to life-threatening blistering conditions. Skin-test reagents are not available. Should a “sulfa”-allergic patient truly require a sulfonamide (antibiotic) or sulfamethoxazole-trimethoprim, with the patient’s approval, a graded challenge should be performed. In contrast, the data have been published that patients reporting “sulfa or sulfonamide allergy” are not at increased risk for allergic reactions to nonantibiotic sulfonamides such as diuretics and sulfonyleureas.

**Summary Points Regarding Testing, Graded Challenges, and Desensitizations**

Skin testing to detect the presence of or show absence of anti–drug IgE antibodies is not useful and should not be performed if the patient has experienced Stevens-Johnson syndrome or toxic epidermal necrolysis, interstitial nephritis, or hematologic reactions such as thrombocytopenia or leukopenia because potential harms outweigh likely benefits. Risk assessment, testing, and challenges ideally should be performed by in consultation with an allergist–immunologist who has the most professional expertise in diagnosis and management of drug allergy. In at least one study of patients reporting maculopapular rashes from penicillin, 25% of the patients were found positive on testing with major and minor penicillin determinants, identifying a much higher current risk than some might suspect based on the history itself. Finally, although perhaps 85% of patients reporting a history of penicillin allergy will be found to be skin-test negative to major and minor determinants implying a very low current risk of anaphylaxis to penicillin and other β-lactams, when the 15% of patients who were skin-test positive had their reports of penicillin allergy assessed, about one-third of such patient’s histories of penicillin allergy were considered vague! Thus, caution is required.
when a patient reports a drug allergy and the incriminated drug is thought to be indicated.

**IMMUNOLOGY**

- The use of the major determinant, benzyl penicilloyl-polylysine, and a minor determinant mix for skin testing patients with penicillin allergy produces sensitivity of ~99%, and the sensitivity is ~85% if the major determinant and penicillin G are used together without a minor determinant mix.
- **Biological modifiers, humanized antibodies, and even fragments of antibodies (papain treatment of IgG producing noncomplement fixing Fab fragments) based treatments can produce anaphylaxis, serum sickness, and blistering rashes despite their “customized” characteristics.
- **Keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis is attributable to effects of granulysin, perforin, granzyme B, and FAS ligand (CD95L) with involvement by cytotoxic lymphocytes.**

**CLINICAL PEARLS**

- **Penicillin allergy appears to be misdiagnosed initially or lost over a period of years, and skin testing with major and minor determinants can help clarify the current risk of anaphylaxis.**
- **Allergy to sulfonamide antibiotics does not imply a high-risk status for administration of nonantimicrobial sulfonamides (sulfonylureas and diuretics) and medications that contain a S moiety in their chemical structure.**
- **Genetic susceptibility for developing serious allergic reactions include patients expressing HLA-B*1502 for carbamazepine and HLA-B*5801+ for allopurinol.**

**REFERENCES**

Chapter 31

Common in vitro tests for allergy and immunology

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ABSTRACT

Allergen-specific IgE antibody is the most commonly ordered in vitro test in the practice of allergy and is used to diagnose type I hypersensitivity reactions to foods or reactivity to aeroallergens in patients with relative contraindications to skin-prick testing such as dermatographism. The Phadebas radioallergosorbent test (RAST; Pharmacia, Uppsala, Sweden) was the first assay reported for the detection of the allergen-specific IgE antibody. In a RAST, antigen (allergen) is bound to a solid phase, such as a paper disk, and then incubated with human serum. A buffer wash removes unbound serum proteins, and radiolabeled anti-human IgE is added to detect bound IgE, if present. The results are reported in arbitrary units of IgE per milliliter of serum. The term RAST was originally a brand name but it is now often used colloquially (and incorrectly) to describe any in vitro assay for allergen-specific IgE. Total serum IgE can be measured and is helpful in determining atopic presentations such as in allergic bronchopulmonary aspergillosis or in patients with persistent asthma who are candidates for monoclonal anti-IgE antibody therapy with, omalizumab. In patients with recurrent bacterial infections of the sinopulmonary tract, the basic humoral immune system testing includes measuring quantitative immunoglobulins (IgG, IgA, and IgM) and comparing them to age-matched normal ranges. Most clinical laboratories use nephelometry to measure immunoglobulin levels quantitatively. Nephelometry detects either the rate or the end point of soluble immune complex formation (the IgG in sera complexes with an anti-IgG antibody forming a classic immunoprecipitation reaction) by monitoring the scatter of transmitted light. The most common method for the screening of cellular immunodeficiency involved the measurement of the absolute and relative representation of the major lymphocyte subsets, T-cells, T-helper cells, T-cytotoxic cells, B-cells and NK-cells.

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In vitro tests are very helpful in the diagnosis of both allergic and immunologic diseases. There have been several important technological advancements in recent years that have led directly to new and improved laboratory tests. Although in vitro testing can be extremely helpful, especially in the diagnosis of immunodeficiency, no single laboratory test is pathognomonic of an allergy (e.g., see food allergy diagnostic guidelines). Of the many tests available, this summary includes details of the tests most commonly used by clinical allergists and immunologists.

Testing for Allergic Disease

Allergen-specific IgE antibody is the most commonly ordered in vitro test in the practice of allergy and is used to diagnose type I hypersensitivity reactions to foods or reactivity to aeroallergens in patients with contraindications to skin-prick testing such as dermatographism. The Phadebas radioallergosorbent test (RAST; Pharmacia, Uppsala, Sweden) was the first assay reported for the detection of the allergen-specific IgE antibody. In a RAST, antigen (allergen) is bound to a solid phase, such as a paper disk, and then incubated with human serum. A buffer wash removes unbound serum proteins, and radiolabeled anti-human IgE is added to detect bound IgE, if present. The results are reported in arbitrary units of IgE per milliliter of serum. The term RAST was originally a brand name but it is now often used colloquially (and incorrectly) to describe any assay for allergen-specific IgE.

Over the years, a newer group of second-generation, allergen-specific IgE antibody clinical assays has been developed, which are more sensitive and specific than earlier methods. These tests are also more quantitative, reproducible, and automated in comparison with their predecessors. Multiple assays exist, although none has been adopted as the industry standard. There are now completely automated systems that include several Food and Drug Administration (FDA) labeled (in the United States) for in vitro diagnostic use allergen-
specific IgE tests. Currently, the ImmunoCap System™ (Thera Fisher, Upsala, Sweden) is regarded by many allergists and laboratories as the method of choice. It uses a cellulose sponge (instead of a paper disk) to enhance the binding capacity to allergens and uses fluorescent anti-IgE in a quantitative fluorescence enzyme immunoassay. Results are reported quantitatively (<0.10 to >100 kU/L) as well as by classes (0–VI), although the class system is rarely used in allergy practice. For assessing children with food allergy, 95% cutoff levels for allergen-specific IgE have been established for predicting clinical reactivity to eggs, milk, peanuts, and fish using the Immunocap system. Of note, there is a definite trend for allergen-specific IgE assays that are currently labeled as “research use only” to be cleared by the FDA as in vitro diagnostic use for the diagnosis (at least a component of the diagnosis) of allergies. Recently, the FDA has approved allergen component testing using the Immunocap system (Phadia Immunology Reference Library PiRL, Phadia US, Inc., Portage, MI). This testing can be used for both food and aeroallergen protein components. Knowledge of allergen component sensitizations may help differentiate between severe/anaphylactic allergy and other allergic diseases such as oral allergy syndrome.

Pitfalls of the in vitro allergen-specific IgE testing include false positives in patients with a high total IgE level (because of nonspecific binding of allergen to some immunosorbents) and falsely low results in patients with high levels of IgG antibody. Moreover, the quantity of allergen-specific IgE may not directly reflect the biologically relevant mast cell-fixed antibody and severity of clinical reactions.

Total serum IgE can be measured and is helpful in determining atopic presentations. This test is useful in certain clinical scenarios including diagnosing diseases such as allergic bronchopulmonary aspergillosis or allergic bronchopulmonary mycosis. It is also tested in patients in whom the use of the humanized monoclonal anti-IgE drug omalizumab (Xolair; Genentech, Inc. [San Francisco, CA] Novartis Pharmaceuticals Corp. [East Hanover, NJ]) is being considered. The clinical usefulness is limited by age-dependent concentration and the variation between atopic and nonatopic individuals. Total serum IgE can be measured using the Immunocap™ (Thera Fisher) technology but is also measured with other technologies including enzyme-linked immunosorbent assay (ELISA). Briefly, the ELISA procedure includes, first, fixing anti-human IgE to a solid surface, such as a microtiter plate or plastic bead, and then incubating the latter with human serum. IgE from human serum binds to the anti-human IgE fixed on the plate; unbound serum components are washed away and a secondary enzyme-conjugated (often horseradish peroxidase or alkaline phosphatase) anti-human IgE antibody is added. The excess conjugate is washed out, an enzymatic substrate is added, and the colorimetric change produced by the enzymatic reaction is detected spectrophotometrically. Results are quantitated by extrapolation from a standard curve of known IgE concentration included in the same microtiter plate. Results for total IgE are usually reported in international unit per milliliter, kilounit per liter, or nanogram per milliliter (1 IU/mL = 1 kU/L = 2.4 ng/mL of IgE).

Epicutaneous skin testing remains the preferred method for detection of allergen-specific IgE antibody because it is more specific, sensitive, and rapid than its in vitro counterpart. Skin testing involves placing a drop of allergen solution on the skin and introducing it into the epidermis with a testing device. A reaction (wheat and erythema) is read 15–20 minutes after placement. Positive (histamine) and negative (saline) controls are applied together with the allergens to ensure validity and to control for problems such as premedication with antihistamines or dermatographism. The stability and concentration of allergen and technique used may limit the quality of skin testing.

Intradermal skin testing involves using a tuberculin syringe to administer allergen intracutaneously; 0.02 mL of allergen is injected and the test is read 15–20 minutes later. This is useful for drug and venom testing and is also used for aeroallergen testing if epicutaneous testing is negative.

Precipitating IgG antibodies (precipitins) are used to test patients who have hypersensitivity pneumonitis induced by chronic exposure to organic dust antigens such as molds (thermophilic actinomyces, Aspergillus species, etc.) and feces/droppings from pet birds. This test is only available in more specialized laboratories.

Mast cells have preformed mediators including tryptase, which are used by allergists and emergency department physicians to measure systemic mast cell activation. Concentrations of α-tryptase correlate with mast cell number while β-tryptase concentrations are associated with current (acute) mast cell activation. Total serum tryptase can be used to confirm a diagnosis of anaphylaxis, although samples need to be collected within 4 hours of a suspected anaphylactic reaction. β-Tryptase levels are thought to peak 30–60 minutes after a reaction with a half-life of 2 hours. Normal total tryptase ranges from 1 to 10 ng/mL of serum. If baseline tryptase is >20 ng/mL in a patient without acute symptoms of anaphylaxis, indolent systemic mastocytosis should be suspected and further evaluation sought.

The availability of skin testing as well as the increased availability of in vitro testing are extremely helpful in the diagnosis of allergic disease. The clinician must, however, perform a detailed clinical history and patient presentation to avoid unnecessary testing.
Testing for Primary Immunodeficiency

Patients with primary immune deficiencies present with recurrent or severe infections, autoimmunity, failure to thrive, diarrhea or any combination of these symptoms.\textsuperscript{11} Appropriate diagnostic testing is essential to making an early diagnosis. Immunologic testing is guided by the clinical presentation of the patient including age, sex, type and severity of infections, autoimmunity, and family history.

Several laboratory tests have been developed to assess the major components of the humoral and cellular arms of the immune system.\textsuperscript{12,13} Patients who present with recurrent bacterial infections of the sinopulmonary tract should be tested for humoral immune deficiencies. The basic humoral immune system testing includes measuring quantitative immunoglobulins (IgG, IgA, and IgM) and comparing them with age-matched normal ranges. Most clinical laboratories use nephelometry to measure immunoglobulin levels quantitatively. Nephelometry detects either the rate or the end point of soluble immune complex formation (the IgG in sera complexes with an anti-IgG antibody forming a classic immunoprecipitation reaction) by monitoring the scatter of transmitted light. Accurate measurement of antigens (in this case the antigen actually is an immunoglobulin molecule) can be made only with conditions of antibody excess. Fluorescent light sources can be used to enhance the sensitivity of this test. As a general rule, in patients with recurrent infections, an IgG concentration in serum of <300 mg/dL in adolescents or adults or values below the age-matched reference value in a child warrants further workup for humoral immune deficiency.

Further evaluation of humoral immune deficiencies include measurement of specific antibody responses to previous immunizations and isohemagglutinins (usually IgM antiblood group A or B antibodies). A patient with low levels of specific antibody can be immunized with protein (i.e., tetanus toxoid) or polysaccharide antigen (i.e., pneumococcal polysaccharide) and have antibodies measured 4–6 weeks after vaccination to confirm the ability of the patient’s B cells to make specific antibodies.

Combined immune deficiencies and T-cell immune deficiencies are evaluated initially with a white blood cell count and differential. Marked lymphopenia (<3000/\text{mm}^3) in an infant warrants immediate evaluation. Human immunodeficiency virus infection should be ruled out by appropriate antibody/antigen testing. The most common screening test for cellular immunodeficiency involves lymphocyte immunophenotyping. Flow cytometry is used to measure the relative representation and absolute numbers of the major lymphocyte subsets, i.e., B cells, T cells, NK cells, T-helper cells, and cytotoxic T cells. Lymphocyte subset numbers can be compared with age-matched reference ranges. Briefly, laser(s) within the flow cytometer is focused on a fluid stream containing cells as they pass single file. The cytometer contains photodiodes and photomultipliers that capture the scattered laser light in both a forward (roughly correlating to size) and at a right angle (roughly correlated with the internal complexity of the cell) as well as light emitted by the fluorochromes that are conjugated to antibody (usually monoclonal antibody [mAb]). The mAb are directed against specific targets (e.g., clusters of differentiation [CD4]) on specific cells (e.g., CD3\textsuperscript{+} T cells). Based on their innate physical properties lymphocytes generate specific light scatter signals that allows them to be differentiated from monocytes and granulocytes. The lymphocytes will also emit a specific fluorescence signal(s) depending on the specific mAb bound to their surface. Various panels of mAb are designed to measure specific subsets of lymphocytes based primarily on the expression of different CDs. Abnormalities in the relative representation of lymphocyte subsets are readily identified and known to be associated with specific primary immunodeficiency diseases. It is also possible to measure the expression of known antigens associated with specific primary immunodeficiency diseases (e.g., CD40 ligand, major histocompatibility complex class I, IL-2R\gamma chain, and CD3 chains); however, because of the rare incidence of many of the primary immunodeficiency diseases and the relative complex and expensive nature of these more specific flow cytometry–based tests, they are only performed in highly specialized laboratories.

Flow cytometry is extremely useful in the classification of hematopoietic malignancies. Assessment of T-cell function can be performed by stimulating T cells with mitogens (e.g., phytohemagglutinin, concanavalin A, and pokeweed mitogen) and antigens (Candida, tetanus, and others). If 22q11 deletion syndrome (DiGeorge syndrome) is suspected, fluorescence in situ hybridization for the microdeletion can be performed. Measuring the number of T-cell receptor excision circles (TRECs) in dried blood spots has recently been adopted by a few states in the United States as a newborn screen for severe combined immune deficiency. TRECs numbers also have been measured for evaluating the severity of T-cell depletion in DiGeorge patients and evaluating immune reconstitution after bone marrow transplantation although this has not been widely adopted. TRECs are circular pieces of DNA formed as T cells rearrange their T-cell receptor genes during T-cell maturation in the thymus and do not replicate; therefore, the number of TRECs correlates with the production of new T cells from the thymus. TRECs are measured using appropriate DNA primers and quantitative DNA amplification techniques.

Another more specialized test involves the assessment of the breadth of the T-cell repertoire. Certain primary immunodeficiency diseases, e.g., Omenn syndrome patients, develop only a few mature T-cell clones in the periphery, so-called oligoclonal expansion. A relatively
easy method to measure the T-cell repertoire can be performed using a panel of monoclonal antibodies directed against 24 Vβ-family–specific targets on the T-cell receptor. Each of the 24 T-cell receptor Vβ-chain families are found in healthy subjects. In patients with Omenn syndrome or atypical DiGeorge syndrome, only a few Vβ-families will be represented.

Testing for other immune deficiencies are available and include a variety of procedures designed to detect cellular targets known to be associated with specific immune abnormalities. Screening for chronic granulomatous disease is now commonly performed using a flow cytometry assay and an oxygen-sensitive dye, dihydrorhodamine 123 to measure the ability of granulocytes to exhibit an oxidative burst in vitro or can be done using the older nitroblue tetrazolium test. Leukocyte adhesion deficiency testing is also performed by flow cytometry assessment of CD11 and CD18 or CD15, adhesion molecules on neutrophils, which are absent or decreased in this disorder.

Complement deficiency screening is performed in patients with recurrent sinopulmonary infections (C2 deficiency), pyogenic infections (C3, factor I, and H), systemic lupus erythematosus-like symptoms of autoimmunity (C1q, r, s, C2, or C4 deficiencies) or susceptibility to neisserial infections (terminal complement defects C5–C9, factor D, or properdin). Testing involves complement function screening of both the classic (CH50) and the alternative (AH50) pathways and assessing specific complement component levels when function is markedly decreased. A decreased AH50 test suggests problems with factor B, D, or properdin. Decreased CH50 and AH50 suggests a defect in a shared complement component (C3–C9).

Other testing for immune deficiencies is disease specific. A few examples include ALPS (increased number CD4 and CD8 [double negative] T-cells expression the α/β-form of the T-cell receptor); IPEX (diminished or absent FOXP3 protein in the nucleus of CD4 T cells), APECED/chronic mucocutaneous candidiasis (AIRE or other genetic sequencing), or X-linked lymphoproliferative disorder presenting with hemophagocytic lymphohistiocytosis (NK-cell testing and genetic sequencing) and Toll-like receptor pathway testing for disorders such as IRAK4, MYD88, and NEMO.

As with allergic diseases, laboratory-based testing for immune deficiencies is imperative in guiding correct diagnosis and management; however, testing should be used judiciously in patients in whom a high level of suspicion is present.

**CLINICAL PEARLS**

- **In vitro** tests for anti-allergen IgE can not be used as sole evidence in the diagnosis of allergy. (high sensitivity but not high enough specificity).
- The ImmunoCAP™ System is widely regarded as the method of choice for detection of allergen-specific IgE antibody. However, the in vivo test is preferable to all in vitro methods.
- New component allergy testing is starting to be used to differentiate patients with reactivity that is associated with severe anaphylaxis.
- Total IgE is can be measured by ImmunoCAP, nephelometry, and ELISA.
- Quantitative immunoglobulins are measured by nephelometry and used to screen for humoral immune deficiencies.
- Flow cytometry is used to detect abnormalities in the major lymphocyte subsets (such as T and B cells).
- Flow cytometry also is used to identify the abnormal representation of rare lymphocyte subsets, abnormal surface marker expression, the T-cell repertoire, and specific neutrophil functions associated with known primary immunodeficiency diseases.

**REFERENCES**